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Highly Diastereoselective One-Pot Synthesis of Spiro{cyclopenta[*a*]indene-2,2′-indene}diones from 1-Indanones and Aromatic Aldehydes

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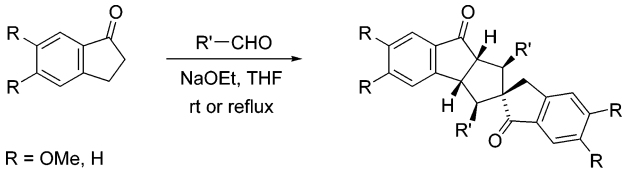

R = OMe, H

R' = 2-, 3-, and 4-pyridyl, 2-furyl, 2-thienyl, *N*-methyl-2-pyrrolyl, phenyl

Treatment of 1-indanones with aromatic aldehydes and NaOEt in THF affords complex spiropolycyclic compounds through a four-component reaction in which two molecules of each starting compound are combined with formation of four new carbon−carbon bonds, leading to the elaboration of a new five-membered ring that bears five contiguous stereogenic centers with a well-defined relative configuration. Different amounts of a minor epimer of the main product are also formed. The presence of methoxy substituents in the indanone component and the use of aldehydes derived from π-excedent heterocycles make the dimerization step a slower transformation. In these cases, better yields of spirodimers are obtained starting from the preformed enones. The reaction seems to take place by cross-aldol condensation, dehydration, and dimerization of the thus formed enones. The molecular mechanism of the dimerization reaction of enone **5g** has been studied using DFT methods at the B3LYP/6-31G* level. The dimerization takes place through a process involving a Michael addition of a carbanion, obtained by deprotonation of **5g** at the 3-position, to a second molecule of **5g**, followed by an intramolecular Michael addition in the corresponding intermediate. The final protonation of the resulting anion accounts for the formation of the cis-fused pentacyclic system.

Introduction

In connection with the synthesis of novel donepezil-based anti-Alzheimer agents, we carried out the reaction of 5,6-dimethoxy-1-indanone (**1**) with 4-pyridinecarboxaldehyde (**3a**) in the presence of a substoichiometric amount of NaOEt in THF to gain access to the key intermediate, enone **4a**[1] (Scheme 1). When this reaction was carried out at room temperature for 16 h, enone **4a** was obtained in 69% yield. Surprisingly, in an attempt to optimize the yield of this reaction by working at the reflux temperature, no enone **4a** was obtained and the complex spiropolycyclic compound **6a** was isolated instead in 76% yield, after column chromatography, whose structure was unambiguously determined on the basis of NMR correlation techniques and X-ray diffraction analysis. The formation of compound **6a** in a one-pot process in which four components (two molecules of indanone **1** and two molecules of aldehyde **3a**) react to form the product, incorporating most of the atoms of the starting materials, fulfils the requirements of a multicomponent reaction.[2]

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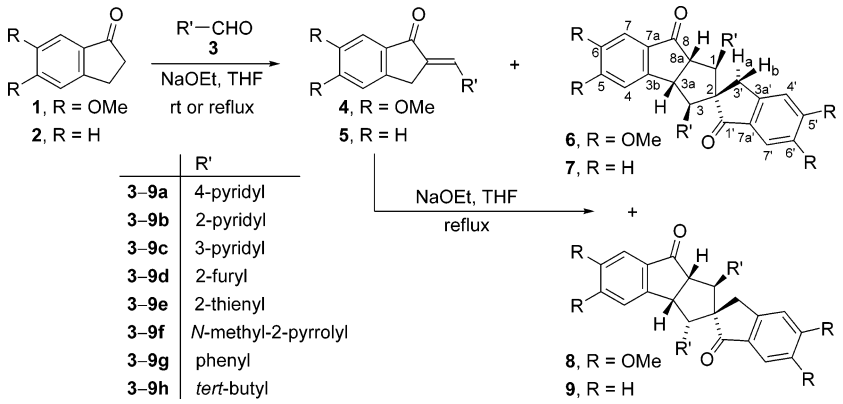
SCHEME 1. Preparation of Spirocompounds 6/7 and 8/9 from Indanones 1/2 and Aldehydes 3 or by Dimerization of Enones 4/5



Moreover, in this reaction, four new carbon−carbon bonds are formed, leading to the elaboration of a new five-membered ring that bears five contiguous stereogenic centers with a well-defined relative configuration.

After a literature search, we realized that a few examples of this kind of spiropolycyclic compounds had already been described by different groups.[3] The first reports described the formation of an unexpected high-melting compound (presumably the spirocompound **7g**) together with the expected enone **5g**, although this unexpected compound was not characterized[3a] or was incorrectly characterized.[3b] In the rest of the reports,[3c−g] the starting materials were not the indanone **2** and the aldehyde **3g**, but **5g**, which under basic conditions seemed to dimerize to the same high-melting product described in the first reports. After several attempts to elucidate the structure of this spirodimer, Leblanc and co-workers recently proposed, on the basis of COSY, HMQC, HMBC, and NOESY NMR correlation techniques, the structure of the high-melting spirodimer to be **7g** (with the same relative stereochemistry that we determined for **6a**), which was confirmed by X-ray diffraction analysis.[3f] The same group reported the formation under different reaction conditions of two other minor diastereomeric spirodimers, which were characterized only spectroscopically,[3f] and also described the synthesis of other spirodimers bearing two 4-(methylthio)-phenyl, 4-(methanesulfonyl)phenyl, methoxycarbonyl, or cyano groups instead of the two phenyl groups of **7g**, always by dimerization of the correponding 2-alkylidene-1-indanone.[3g] A double Michael reaction was proposed to explain the formation of these spirodimers from the correponding 2-alkylidene-1-indanones.[3e−g] Also, an ionic cycloaddition was suggested to explain the high level of diastereoselectivity observed in these dimerization reactions.[3g]

In summary, only a few spiropolycyclic compounds of general structure **7** and several diastereomers thereof have thus far been characterized, and in all cases they have been prepared by dimerization of 2-alkylidene-1-indanones and not by direct reaction of 1-indanones with aldehydes. The surprising outcome of the rather unexplored four-component reaction of 1-indanones with aldehydes and the structural complexity and defined stereochemistry of the resulting spiropolycyclic compounds prompted us to carry out a broader study of this reaction. In this article, we report our work on the direct reaction of 1-indanone or 5,6-dimethoxy-1-indanone with a variety of aldehydes to assess the effect of the substitution both in the indanone and in the aldehyde on the outcome of the reaction. Moreover, the mechanism for the formation of the spiropolycyclic compounds **7g** and **9g** from enone **5g** has been studied using DFT methods at the B3LYP/6-31G* level.

Results and Discussion

We have used as starting compounds 5,6-dimethoxy-1-indanone (**1**) or 1-indanone (**2**) and several aldehydes of different electronic nature: aldehydes derived from π-deficient aromatic systems such as 4-, 2-, and 3-pyridinecarboxaldehyde (**3a**−**c**), from π-excedent aromatic systems such as 2-furancarboxaldehyde (**3d**), 2-thiophenecarboxaldehyde (**3e**), and *N*-methyl-2-pyrrolecarboxaldehyde (**3f**), as well as benzaldehyde (**3g**) and pivalaldehyde (**3h**), the last one as a nonenolizable aliphatic aldehyde (Scheme 1).

As in the case of the above-mentioned reaction of indanone **1** with **3a**, the treatment of **1** with 1.2 equiv of aldehydes **3b**−**h** in the presence of 0.86 equiv of NaOEt in THF at room temperature for 16 h (method A, Table 1) led to the corresponding enones **4b**−**h** with no trace of spiropolycyclic compounds, except in the case of the reaction with aldehyde **3d**, which afforded enone **4d** (72% yield) and small amounts of spirocompound **6d** (4% yield) and byproduct **10** (7% yield) (Chart 1, Scheme 1, Table 1, entries 1, 3, 5, 7, 9, 11, 13, and 15). The product **10** presumably arises from enone **4d** by deprotonation at position 3, followed by condensation with a second molecule of aldehyde **3d**.

However, when the same reaction of indanone **1** with aldehydes **3b**−**h** was carried out in refluxing THF (method B, Table 1), spiropolycyclic compounds were formed in most cases, as previously mentioned for the reaction with **3a**, but with significant differences depending on the electronic or steric nature of the aldehyde. Thus, reaction of **1** with aldehyde **3c**, containing the π-deficient 3-pyridyl rest, afforded the spirocompound **6c** (55% yield) and minor amounts of its epimer **8c** (14% yield) and enone **4c**[2] (20% yield) (Table 1, entry 6). Unexpectedly, reaction of **1** with the more electrophilic aldehyde **3b** (relative to **3c**) led to a lower yield of spirocompound **6b** (11% yield, Table 1, entry 4), and enone **4b**[2] was the main reaction product (51% yield). Reaction of indanone **1** with the

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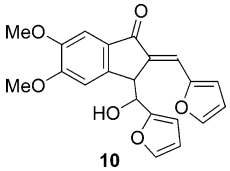
TABLE 1. Reaction of Indanones 1 and 2 with Aldehydes 3

	starting compounds			reaction products (% isolated yields)		
entry	indanone	aldehyde	method[a]	**4**/**5**	**6**/**7**	**8**/**9**
1	**1**	**3a**	A	**4a** (69%)		
2	**1**	**3a**	B		**6a** (76%)	
3	**1**	**3b**	A	**4b** (46%)		
4	**1**	**3b**	B	**4b** (51%)	**6b** (11%)	
5	**1**	**3c**	A	**4c** (74%)		
6	**1**	**3c**	B	**4c** (20%)	**6c** (55%)	**8c** (14%)
7	**1**	**3d**	A	**4d** (72%)	**6d** (4%)[b]	
8	**1**	**3d**	B	**4d** (50%)	**6d** (28%)	**8d** (21%)
9	**1**	**3e**	A	**4e** (92%)		
10	**1**	**3e**	B	**4e** (43%)	**6e** (29%)	**8e** (7%)
11	**1**	**3f**	A	**4f** (81%)		
12	**1**	**3f**	B	**4f** (92%)		
13	**1**	**3g**	A	**4g** (88%)		
14	**1**	**3g**	B	**4g** (6%)	**6g** (67%)	**8g** (23%)
15	**1**	**3h**	A	**4h** (21%)[c]		
16	**1**	**3h**	B	**4h** (20%)[d]		
17	**2**	**3a**	A		**7a** (82%)	
18	**2**	**3a**	B		**7a** (85%)	
19	**2**	**3b**	A		**7b** (72%)	
20	**2**	**3b**	B		**7b** (66%)	**9b** (4%)
21	**2**	**3c**	A		**7c** (84%)	
22	**2**	**3c**	B		**7c** (83%)	**9c** (9%)
23	**2**	**3d**	A	**5d** (22%)	**7d** (48%)	**9d** (21%)
24	**2**	**3e**	A	**5e** (6%)	**7e** (70%)	**9e** (8%)
25	**2**	**3f**	A	**5f** (88%)		
26	**2**	**3f**	B	**5f** (73%)	**7f** (27%)	
27	**2**	**3g**	A	**5g** (42%)	**7g** (32%)	**9g** (9%)
28	**2**	**3g**	B		**7g** (79%)	**9g** (20%)
29	**2**	**3h**	A	**5h** (68%)[e]		
30	**2**	**3h**	B	**5h** (94%)		

[a] All reactions were performed by stirring a mixture of the indanone, the aldehyde (1.2 equiv), and NaOEt (0.86 equiv) in THF (1.7−2.4 mL/mmol indanone) either at room temperature (method A) or under reflux (method B) for 16 h. Reaction products were isolated by column chromatography. [b] In this reaction, compound **10** (7%) was also obtained. [c] In this reaction, starting **1** (43%) was also recovered. [d] In this reaction, starting **1** (75%) was also recovered. [e] In this reaction, starting **2** (17%) was also recovered.

CHART 1. Structure of Byproduct 10



10

less electrophilic aldehydes **3d**−**f**, containing the π-excedent 2-furyl, 2-thienyl, and *N*-methyl-2-pyrrolyl rests, afforded the corresponding aldol condensation products as the main [**4d** (50% yield); **4e** (43% yield)] or sole [**4f** (92% yield)] reaction products, accompanied in the first two cases by lower amounts of spirocompounds [**6d** (28% yield) + **8d** (21% yield); **6e** (29% yield) + **8e** (7% yield)] (Table 1, entries 8, 10, and 12). No spirocompound was formed in the reaction of the most electron-rich aldehyde **3f**. Reaction of **1** with benzaldehyde (**3g**) proceeded in a way similar to that of the most reactive aldehydes, furnishing the spirocompound **6g** as the main reaction product in high yield (67% yield), together with a significant amount of its epimer **8g** (23% yield) and only traces of enone **4g** (6% yield) (Table 1, entry 14). In sharp contrast, reaction of **1** with the sterically hindered pivalaldehyde (**3h**) afforded the enone **4h** as the sole reaction product in low yield (20% yield), and most of the starting indanone was recovered unchanged (Table 1, entry 16).

The change of 5,6-dimethoxy-1-indanone (**1**) by the unsubstituted 1-indanone (**2**) led to a drastic change in the outcome of the reactions with aldehydes **3a**−**h**, probably as a consequence of the higher acidity of enones **5** as compared to enones **4**. Thus, under conditions of method A, reaction of indanone **2** with aldehydes **3a**−**c** afforded the spirocompounds of general structure **7**, having the same relative configuration as the spirocompounds **6** of the 5,6-dimethoxy series, as the sole isolated reaction products in high yields [**7a** (82% yield); **7b** (72% yield); **7c** (84% yield)] (Table 1, entries 17, 19, and 21). Similarly, the reaction of **2** with the less reactive aldehydes **3d** and **3e** also afforded spirocompounds **7d** and **7e** as the main reaction products, although in lower yields than in the reactions with **3a**−**c** (48 and 70% yield, respectively) and accompanied by significant or minor amounts of their epimers **9d** and **9e** (21 and 8% yield, respectively) and enones **5d**[4] and **5e**[4] (22 and 6% yield, respectively) (Table 1, entries 23 and 24). Aldehyde **3f** behaved as in the 5,6-dimethoxy-series, leading to the exclusive formation of the enone **5f** in high yield (88% yield) (Table 1, entry 25). Reaction of indanone **2** with benzaldehyde (**3g**) under conditions of method A also afforded some spirocompounds but in moderate to low yields [**7g**[3f] (32% yield) + **9g**[3f] (9% yield)]; in this case the enone **5g**[3a] was the main reaction product (42%) (Table 1, entry 27). As observed in the 5,6-dimethoxy series, reaction of **2** with pivalaldehyde furnished exclusively the enone **5h**,[5] although in higher yield (68%) (Table 1, entry 29).

In view of the high yield of spirocompounds **7** in most of the reactions of indanone **2** with aldehydes **3**, the corresponding reaction under conditions of method B (refluxing THF) was carried out only in several selected cases. Thus, reaction of **2** with aldehydes **3a**, **3b**, and **3c** furnished spirocompounds **7a**, **7b**, and **7c** in high yields (85, 66, and 83% yield, respectively) and, in the last two cases, minor amounts of the epimers **9b** and **9c** (4 and 9% yield, respectively) (Table 1, entries 18, 20, and 22). Aldehyde **3f**, which had failed to give any spiropolycyclic compound in any conditions by reaction with indanone **1** or by reaction with indanone **2** at room temperature, did afford spirocompound **7f** although in low yield (27%) together with enone **5f** (73% yield) on reaction with **2** in refluxing THF (Table 1, entry 26). The moderate and low yields of spirocompounds **7g** and **9g** under conditions of method A could be increased to 79 and 20% yield, respectively, when benzaldehyde (**3g**) was reacted with **2** under conditions of method B, while no trace of enone **5g** was observed (Table 1, entry 28). Finally, on treatment of indanone **2** with pivalaldehyde (**3h**) in refluxing THF no spirocompound was formed, and the enone **5h** was obtained as the sole reaction product (94% yield) (Table 1, entry 30).

To improve the yields of the spirocompounds that were obtained in low yields or that could not be obtained under conditions of methods A or B, we attempted the direct dimerization of the corresponding 2-alkylidene-1-indanones **4** or **5** in the presence of 0.86 equiv of NaOEt in refluxing THF for 16 h (method C, Table 2). Thus, all of the enones of structure **4**, derived from the less reactive 5,6-dimethoxy-1-indanone **1**, as well as enones **5f** and **5h** were submitted to these reaction conditions. In general, with the exception of enones **4h** and **5h**, which were recovered unchanged (Table 2, entries 8 and 10),

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(5) Lemke, T. L.; Sawhney, K. N.; Lemke, B. K. *J. Heterocycl. Chem.* **1982**, *19*, 363.

TABLE 2. Dimerization of Enones 4/5

entry	enone[a]	reaction products (% isolated yields) 6/7	8/9
1	**4a**	**6a** (61%)	
2	**4b**	**6b** (62%)	**8b** (29%)[b−d]
3	**4c**	**6c** (66%)	**8c** (16%)
4	**4d**	**6d** (59%)	**8d** (19%)[e]
5	**4e**	**6e** (75%)	**8e** (24%)
6	**4f**	**6f** (27%)[f,g]	
7	**4g**	**6g** (78%)	**8g** (18%)
8	**4h**	*h*	
9	**5f**	**7f** (56%)	
10	**5h**	*h*	

[a] All reactions were performed by stirring a mixture of enone and NaOEt (0.86 equiv) in THF (4.7 mL/mmol enone) under reflux for 16 h. Reaction products were isolated by column chromatography. [b] Starting **4b** (7%) was also recovered. [c] When the reaction was carried out at room temperature, enone **4b** was recovered unchanged. [d] When the reaction was carried out at room temperature using *t*-BuOK as the base, dimers **6b** and **8b** were obtained in 60 and 18% yield, respectively, and some **4b** (17%) was recovered. [e] Starting **4d** (22%) was also recovered. [f] Starting **4f** (70%) was also recovered. [g] When this reaction was carried out for 72 h, dimer **6f** was obtained in 81% yield, and starting **4f** (17%) was also recovered. [h] The starting enone was recovered unchanged.

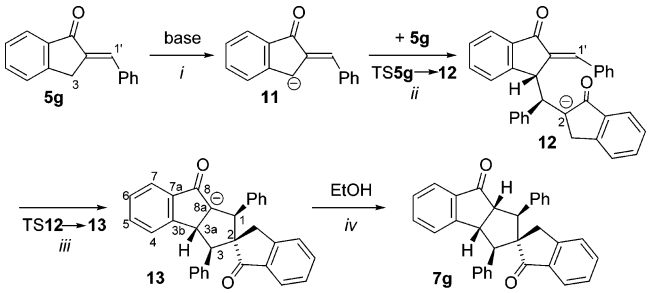
and enone **4a** (Table 2, entry 1), the dimerization of the rest of the enones afforded clearly higher yields of spirocompounds than those obtained under conditions of method B (Table 2, entries 2−7 and 9). Even the enone **4f** dimerized under conditions of method C to provide **6f** in 27% yield (Table 2, entry 6), which had not been obtained under conditions of methods A or B from indanone **1** and aldehyde **3f**. Interestingly, when the last dimerization was carried out for 72 h instead of 16 h, the yield of spirodimer **6f** increased to 81% yield.

In the direct reaction of indanones **1** and **2** with aldehydes **3** under conditions of methods A or B, the water formed during the dehydration of the aldol leading to enones **4** or **5** would react with the initial base NaOEt to give NaOH. Thus, the less basic NaOH must be the base catalyst in the subsequent reactions leading to the spirocompounds **6** and **8** or **7** and **9**. The higher basicity of NaOEt, which is always present in the dimerization of the enones **4** or **5**, relative to that of NaOH could explain the higher yields of obtention of the spirocompounds under conditions of method C. This explanation is supported by the observation that when enone **4b** was reacted with NaOEt in THF for 16 h at room temperature instead of under reflux, the starting enone was recovered unchanged, while treatment of **4b** under similar reaction conditions but using the even more basic *t*-BuOK afforded dimers **6b** and **8b** in 60 and 18% yield, respectively, and the starting enone was recovered in only 17% yield.

The possible interconversion between the spirocompounds **6**/**8** or **7**/**9** was studied. Treatment of the major diastereomers **6b**, **6g**, **7d**, and **7g**, and the minor diastereomers **8b**, **8d**, **8g**, **9d**, and **9g** with NaOEt in THF under reflux for 16−128 h left the starting compounds unchanged, thus indicating that the formation of spirocompounds **6**/**8** or **7**/**9** is kinetically controlled.

The results herein described showed that the more acidic intermediate enones, that is, those lacking the methoxy substituents on the indanone ring and derived from the more electrophilic aldehydes (**5a**−**c**,**g**), give the dimers under less drastic conditions than those required with the less acidic enones. The lack of reactivity toward dimerization of enone **5h** may be easily understood on steric grounds.

SCHEME 2. Mechanism of Formation of Spirocompound 7g by Dimerization of Enone 5g



All of the new compounds were fully characterized through their spectroscopic data and elemental analyses or HRMS (for **8e** and **10**), and their structures were unambiguously elucidated on the basis of ^{1}H/^{1}H COSY, ^{1}H/^{13}C gHSQC, ^{1}H/^{13}C gHMBC, and ^{1}H/^{1}H NOESY NMR correlation techniques and confirmed by X-ray diffraction analysis in the cases of **6a**, **6g**, **7b**, and **9b**.

DFT Study of the Dimerization of the Enone 5g. To explain the formation of spirocompounds of structures **6**/**7** and **8**/**9**, the mechanism of the dimerization reaction of 2-(*E*)-benzylidene-1-indanone (**5g**) was studied theoretically using DFT methods at the B3LYP/6-31G* level.[6] The reaction of the enone **5g** to give the dimer **7g** is a process that comprises the following steps: (i) C3−H proton abstraction from **5g** to give the carbanion **11**, (ii) Michael addition of **11** to the conjugate *β*-position of a second molecule of **5g** to give the anionic intermediate **12**, (iii) intramolecular Michael addition in this intermediate to give anion **13**, containing the new five-membered ring present in **7g**, and finally, (iv) protonation of **13** with formation of the cis-fused dimer **7g**. The transition-state structures (**TS5g** → **12** and **TS12** → **13**) and intermediates (**12** and **13**) associated with the formation of the five-membered ring along this process, steps ii and iii, have been located and characterized. Steps i and iv are proton-transfer reactions with a thermodynamic control. The different stationary points characterized along this process are presented in Scheme 2, while the energetic results are summarized in Table 3.

This process is initiated by a C3−H proton abstraction by the ethoxide anion to give the enolate **11**. In THF, this process is exothermic both in the gas phase (34.0 kcal/mol) and in THF (12.4 kcal/mol). In the second step, a nucleophilic attack of the C3 position of **11** to the conjugate *β*-position of the enone **5g** gives the anionic intermediate **12**. In the gas phase, the TS associated to this nucleophilic attack, **TS5g** → **12**, is located 1.8 kcal/mol below reactants **5g** + **11**, while in THF it is located 6.4 kcal/mol above them. These results are a consequence of a solvation of enolate **11** larger than that of **TS5g** → **12** by THF. Formation of the intermediate **12** is exothermic both in the gas phase (11.3 kcal/mol) and in THF (4.4 kcal/mol) relative to **5g** + **11**. The intramolecular nucleophilic attack of the carbanionic center to the conjugate *β*-position of intermediate **12** accounts for the formation, via **TS12** → **13**, of the central five-membered ring present in dimer **7g**. Formation of this new C−C bond presents an activation barrier of 16.6 kcal/mol in the gas phase (12.8 kcal/mol in THF). In THF, the intramolecular Michael addition has a larger barrier than the intermolecular one. This fact is a consequence of the large stabilization of the intermediate

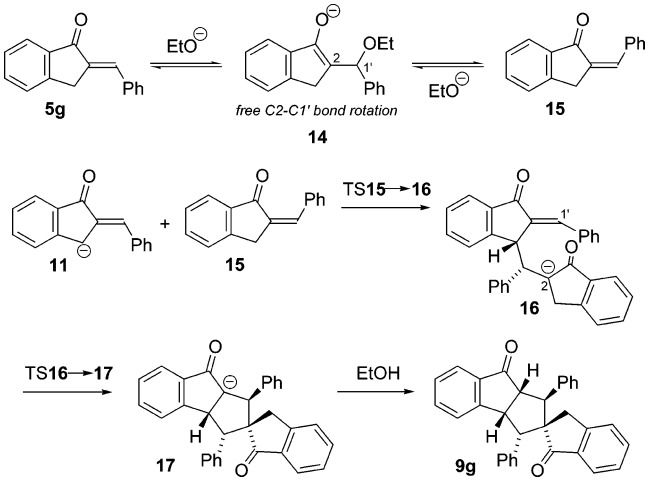
(6) For details and references about calculations, see the Supporting Information.

TABLE 3. B3LYP/6-31G* Total Energies[a] (*E*, au) and Relative Energies (Δ*E*, kcal/mol) of the Stationary Points for the Dimerization Reaction of 5g, in Vacuo, and in THF

	E	Δ*E*	E_{THF}	ΔE_{THF}
5g	−692.156020		−692.167942	
15	−692.151558	2.8[b]	−692.161921	3.8[b]
11	−691.573939		−691.638557	
TS5g → 12	−1383.732882	−1.8[c]	−1383.796345	6.4[c]
12	−1383.747928	−11.3[c]	−1383.813536	−4.4[c]
TS12 → 13	−1383.721516	5.3[c]	−1383.793166	8.4[c]
13	−1383.737813	−4.9[c]	−1383.813908	−4.6[c]
7g	−1384.330392	−11.5[d]	−1384.350496	−9.2[d]
trans-**7g**	−1384.302673	5.9[d]	−1384.322258	8.5[d]
TS15 → 16	−1383.724186	0.8[e]	−1383.786916	8.5[e]
16	−1383.745922	−12.8[e]	−1383.810309	−6.2[e]
TS16 → 17	−1383.715894	6.0[e]	−1383.786222	8.9[e]
17	−1383.732353	−4.3[e]	−1383.806637	−3.9[e]
9g	−1384.319810	−4.9[d]	−1384.339851	−2.5[d]

[a] The total energies of EtOH and EtO^- in the gas phase are −155.033801 and −154.397514 au, respectively (−155.040853 and −154.491731 au, respectively, in THF). [b] Relative to **5g**. [c] Relative to **5g** + **11**. [d] Relative to **5g** + **5g**. [e] Relative to **15** + **11**.

SCHEME 3. Mechanism of Formation of Spirocompound 9g from 5g



12. Note that, in THF, **TS5g → 12** and **TS12 → 13** present closer relative energies, 6.4 and 8.4 kcal/mol, relative to that of **5g** + **11**, respectively. Formation of the anionic pentacyclic intermediate **13** is exothermic both in the gas phase (4.9 kcal/mol) and in THF (4.6 kcal/mol) relative to that of **5g** + **11**. Finally, protonation of the anion **13** affords the pentacyclic derivative **7g**. This process is endothermic both in the gas phase (27.4 kcal/mol) and in THF (7.9 kcal/mol). The overall transformation **5g** + **5g** → **7g** is exothermic both in the gas phase (11.5 kcal/mol) and in THF (9.2 kcal/mol).

The minor epimer **9g** formed in this reaction has a trans relationship of the two aryl substituents, with an inverted configuration at position 3 relative to **7g**. Since dimer **9g** can be formed by a process similar to that shown for **7g**, it requires the nucleophilic attack of the carbanion **11** to the *Z* isomer of **5g** (**15**) (Scheme 3). At the ground state, the *E* → *Z* isomerization of **5g** has a large TS energy (ca. 64 kcal/mol). However, the reversible conjugate addition of ethoxide ion to **5g** can give the intermediate **14**, which can easily rotate around the C2−C1′ bond (Scheme 3). An energy analysis for the C2−C1′ bond rotation in **14** shows that the different rotamers are within a narrow range of energy (5.5 kcal/mol in the gas phase). Enone **15** is less stable than **5g** both in the gas phase (by 2.8 kcal/mol) and in THF (by 3.8 kcal/mol). These energetic results are in reasonable agreement with the lower yield of epimer **9g**.

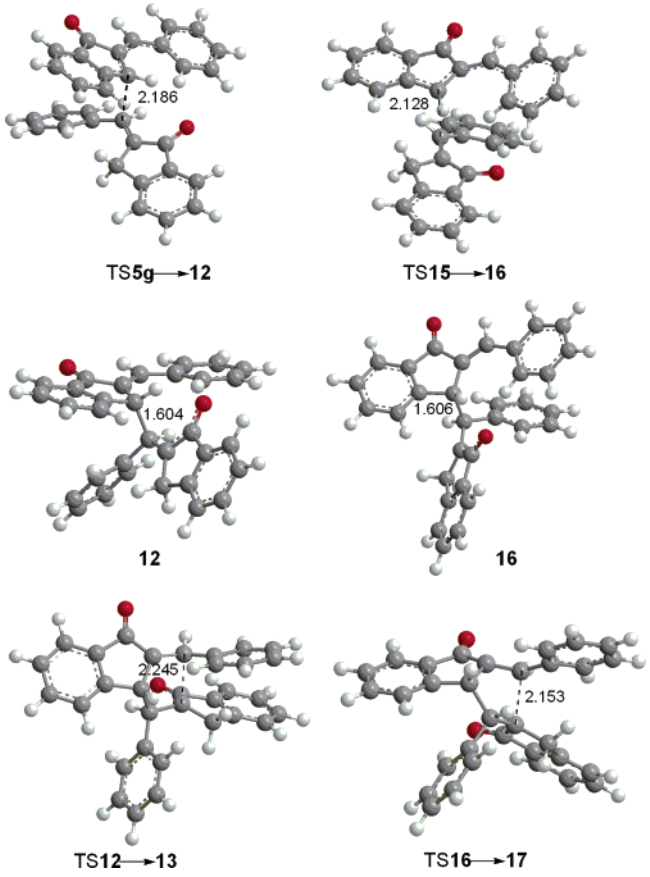


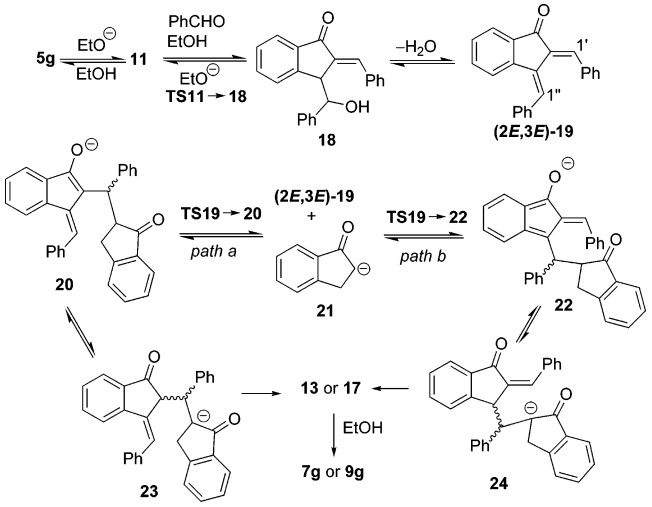
FIGURE 1. B3LYP/6-31G* geometries of the transition structures and intermediates involved in the dimerization reactions of enone **5g**. The bond lengths between the atoms directly involved in the reaction are given in Å.

Formation of **9g** takes place through a process similar to that for the formation of **7g**, involving two consecutive Michael additions, an inter and an intramolecular addition (Scheme 3). The energetic results associated with this process are summarized in Table 3. The relative energies for this process are similar to those for the reaction of **5g** + **11**. The overall transformation **5g** + **5g** → **9g** is less exothermic both in the gas phase (4.9 kcal/mol) and in THF (2.5 kcal/mol) than the transformation **5g** + **5g** → **7g**.

The geometries of the TSs and intermediates involved in the two consecutive Michael additions are given in Figure 1. In the TSs associated with the intermolecular Michael addition of **11** to **5g** and **15**, the length of the C3−C1′ forming bonds are 2.186 Å for **TS5g → 12** and 2.128 Å for **TS15 → 16**, while for the intermediates **12** and **16** the bond lengths are 1.604 and 1.606 Å, respectively, indicating that the C3−C1′ bonds are formed. In the TSs associated with the intramolecular Michael addition, the length of the C2−C1′ forming bonds are 2.245 Å for **TS12 → 13** and 2.153 Å for **TS16 → 17**. Therefore, the TS and intermediates associated with these processes show similar geometrical parameters.

In the anions **13** and **17**, the arrangement of the carbon atoms bonded to the carbanionic center (C8a) points out an sp^3 hybridization for this carbon atom. An sp^3 lobe is filled by the negative charge transferred in the intramolecular Michael addition. This lobe that presents a cis relationship relative to

SCHEME 4. Possible Alternative Mechanism of Formation of Spirocompounds 7g and 9g from 5g



the bridgehead vicinal C3a−H bond accounts for the cis C8a−H/C3a−H relationship in the dimers **7g** and **9g** (Schemes 2 and 3). Further protonation of **13** and **17** on this lobe gives the cis-fused derivatives **7g** and **9g**. Geometrical optimization of the C8a epimer of **7g** gives an isomeric structure, *trans*-**7g**, that is less stable than **7g** both in the gas phase (by 11.8 kcal/mol) and in THF (by 17.7 kcal/mol). Thus, formation of *trans*-**7g** is thermodynamically disfavored, in clear agreement with the sole formation of the cis isomer **7g**.

The electronic structures of the TSs and intermediates involved in these processes were analyzed by using the Wiberg bond order (BO) indexes.[7] For **TS5g → 12** and **TS15 → 16**, the BO values between C3 and C1′ carbon atoms were 0.39 and 0.47, respectively, while for the intermediates **12** and **16** the C3−C1′ BO values were 0.90 and 0.91, respectively. The O−C1 and C1−C2 BOs for these intermediates, ca. 1.5 and 1.3, respectively, point to an oxyallylic arrangement for the O−C1−C2 framework that possesses the negative charge. Finally, for **TS12 → 13** and **TS16 → 17** the BO values between the C2 and the C1′ carbon atoms were 0.40 and 0.43, respectively.

The analysis of the atomic motion at the unique imaginary frequency of **TS5g → 12** (251.55i cm^{-1}) and **TS15 → 16** (258.83i cm^{-1}) indicates that these TSs are associated with the movement of C3 and C1′ carbon atoms along the C3−C1′ bond. This analysis accounts for a two-center addition associated with an intermolecular Michael addition. For **TS12 → 13** and **TS16 → 17**, the analysis of the atomic motion at the unique imaginary frequency, 252.88i cm^{-1} and 291.63i cm^{-1}, respectively, indicates that these TSs are associated with the movement of the C2 and C1′ atoms along the C2−C1′ bond. This analysis accounts also for a two-center addition associated with an intramolecular Michael addition.

As suggested by a reviewer, by taking into account the isolation of byproduct **10**, an alternative mechanism could be imagined for the formation of the spirocyclic compounds **7g** and/or **9g** (Scheme 4). Condensation of enone **5g** with benzaldehyde could give aldol **18**, which on dehydration via an E1cb mechanism could give compound **19**, probably as a mixture of (*E*,*E*)-, (*Z*,*Z*)-, (*Z*,*E*)-, and (*E*,*Z*)-diastereomers. Isomerization of the double bonds in **19** could take place as described before in Scheme 3 for the isomerization of **5g** to **15**. Michael addition of the anion **21**, derived from indanone **2**, to **19** could take place at position 1′ to give intermediate **20** (path a in Scheme 4), which can be converted into enolate **23**. Intramolecular Michael addition in **23** would give the enolates **13** or **17**. Alternatively, Michael addition of the anion **21** could take place at position 1″ to give enolate **22** (path b in Scheme 4). Equilibration with enolate **24**, structurally equivalent to **16** (Scheme 3), followed by intramolecular Michael addition would give enolates **13** or **17**. Finally, protonation of these enolates would give the spirocyclic compounds **7g** or **9g**, respectively, as previously shown in Schemes 2 and 3.

A full computational study of these alternative processes is out of the scope of this work and would be very complex due to: (i) the presence of four stereoisomers of compound **19** and (ii) the possible formation of enolates **20**, **22**, **23**, and **24** as stereoisomeric mixtures. B3LYP/6-31G* relative energy for the transition state of the condensation of anion **11** and benzaldehyde (TS**11 → 18**) was calculated to be 6.0 kcal/mol in vacuo and 5.2 kcal/mol in THF. The relative energies of the diastereoisomers of **19** differ by only about 1 kcal/mol both in vacuo and in THF. The transition states for the condensation of (2*E*,3*E*)-**19** with anion **21** to give enolates **20** and **22** (TS**19 → 20** and TS**19 → 22**) were calculated to be −10.0 and −11.2 kcal/mol in vacuo and 5.6 and 8.8 kcal/mol in THF, respectively. In THF, the relative energies of the different TSs are comparable to the transition states **TS5g → 12** (6.4 kcal/mol, Scheme 2) and **TS15 → 16** (8.5 kcal/mol, Scheme 3). Thus, calculations suggest that the mechanism shown in Scheme 4 could also be operative in providing the spirocyclic compounds **6**/**7** or **8**/**9**.

Experimentally, on only one occasion and in very low yield (7%), we had isolated a compound, **10**, which might be a possible intermediate in the formation of the spirocyclic compounds **6d** and **8d**, according to the mechanism shown in Scheme 4. To prove this hypothesis, we reacted indanone **1** with an excess of aldehyde **3d** (2 equiv) under conditions A with the aim of obtaining compound **10** as the main product. However, to our surprise, only enone **4d** was obtained from this reaction. When a solution of enone **4d** and aldehyde **3d**, in a ratio about 1:1, in THF was heated under reflux for 3 and 16 h in the presence of sodium ethoxide (0.85 equiv), neither compound **10** nor compound **6d** was formed, and enone **4d** was completely recovered. The fact that compound **6d** was not formed under these conditions seems to be due to the presence of the excess of **3d**, which could consume the base if it is previously oxidized to the corresponding carboxylic acid, since reaction of enone **4d** under conditions C gives a mixture of compounds **6d** and **8d** in good overall yield (59 and 19% isolated yields, respectively). We also performed the reaction of indanone **1** and **3d** under conditions B and observed that the yield of the spirocyclic compounds **6d** and **8d** was higher when the reaction was carried out in an argon atmosphere instead of in an open vessel.

Consequently, although calculations for the reaction of indanone **2** and benzaldehyde suggest that the mechanism shown in Scheme 4 could energetically compete with those shown in Schemes 2 and 3 for the formation of spirocyclic compounds **6**/**7** or **8**/**9**, at least in the reaction of indanone **1** with aldehyde **3d** there is no experimental evidence in favor of this mechanism, as there is in favor of the dimerization of the intermediate enones **4**/**5**.

(7) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.

Conclusions

Reaction of 1-indanones with aromatic aldehydes under NaOEt base catalysis in THF affords spiro{cyclopenta[*a*]indene-2,2′-indene}diones. The main diastereomer in this reaction arises from two molecules of each starting compound with formation of four new carbon−carbon bonds, leading to the construction of a new five-membered ring that bears five contiguous stereogenic centers with a well-defined relative configuration. Different amounts of a minor epimer thereof and/or the intermediate enones are also isolated from these reactions.

Although other mechanisms might be imagined, the reaction leading to the spirocompounds from indanones **1**/**2** and aldehydes **3** seems to proceed through dimerization of the initially formed 2-alkylidene-1-indanones **4**/**5**, arising from the aldol condensation reaction. The dimerization takes place through a process involving an intermolecular Michael addition of the carbanion obtained by C3−H deprotonation of the enone to a second molecule of enone, followed by an intramolecular Michael addition in the corresponding intermediate, and final protonation of the resulting pyramidalized carbanion, which accounts for the formation of the cis-fused pentacyclic system.

The experimental results can be explained on the basis of the C3−H acidity in the intermediate enones: the more acidic enones (i.e., those lacking the methoxy substituents on the indanone ring and bearing a phenyl or 2-, 3-, or 4-pyridyl substituent) give dimers under less drastic conditions. Enones derived from pivalaldehyde failed to give dimers, probably for steric reasons.

Experimental Section

General Procedures for the Reaction of Indanones 1 or 2 with Aldehydes 3. A mixture of 5,6-dimethoxy-1-indanone (**1**, 1 mmol) or 1-indanone (**2**, 1 mmol), the aldehyde **3** (1.2 mmol), and NaOEt (0.86 mmol) in THF (2.4 mL/mmol of **1** or 1.7 mL/mmol of **2**) was thoroughly stirred at room temperature (Method A) or under reflux (Method B) for 16 h. Unless otherwise stated, the resulting suspension was filtered in vacuo at room temperature, the filtrate was concentrated under reduced pressure, and the resulting residue was submitted to column chromatography through silica gel to give the aldol condensation products **4** or **5** and/or the dimerization products thereof **6**/**8** or **7**/**9**.

General Procedure for the Dimerization of Enones 4 or 5 (Method C). A mixture of the enone **4** or **5** (1 mmol) and NaOEt (0.86 mmol) in THF (4.7 mL) was heated under reflux for 16 h. The resulting suspension was cooled to room temperature and filtered in vacuo. Unless otherwise stated, the filtrate was concentrated under reduced pressure, and the resulting residue was submitted to column chromatography through silica gel to give products **6**/**8** or **7**/**9**.

Reaction of Indanone 2 with Aldehyde 3d. Method A: *E*-2-[(2-Furyl)methylene]indan-1-one (5d), (1*RS*,2*RS*,3*SR*,3a*SR*,8a*SR*)-1,3-Di(2-furyl)-3a,8a-dihydrospiro{cyclopenta[*a*]-indene-2,2′(1*H*,3′*H*)-indene}-1′,8(3*H*)-dione (7d) and (1*RS*,2*RS*,3*RS*,3a*SR*,8a*SR*)-1,3-Di(2-furyl)-3a,8a-dihydrospiro-{cyclopenta[*a*]indene-2,2′(1*H*,3′*H*)-indene}-1′,8(3*H*)-dione (9d). This reaction was carried out from a mixture of indanone **2** (800 mg, 6.06 mmol), aldehyde **3d** (0.60 mL, 696 mg, 7.25 mmol), and NaOEt (374 mg, 5.22 mmol) in THF (10 mL). The resulting yellow oily residue (1.67 g) was submitted to column chromatography (35−70 μm of silica gel (167 g), hexane/AcOEt mixtures, gradient elution). On elution with hexane/AcOEt 95:5, enone **5d** (274 mg, 22% yield) was isolated as a light yellow solid. On elution with hexane/AcOEt 90:10, **7d** (612 mg, 48% yield) was isolated as a light yellow solid. On elution with hexane/AcOEt 90:10 to 80:20, **9d** (271 mg, 21% yield) was separated as a light yellow solid.

5d: mp 118−119 °C (MeOH) (described 113 °C).[4] R_f 0.38 (SiO_2, hexane/AcOEt 4:1).

7d: mp 196−197 °C (MeOH). R_f 0.25 (SiO_2, hexane/AcOEt 4:1). IR (KBr): ν 3117, 3075, 3042, 2924, 2856, 1705 (C=O st), 1605 and 1590 (Ar−C−C st), 1466, 1285, 1013, 766, 747 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.03 (d, J = 17.5 Hz, 1H, 3′-H_a), 3.13 (d, J = 17.5 Hz, 1H, 3′-H_b), 3.71 (d, J = 10.5 Hz, 1H, 3-H), 3.74 (dd, J = 11.0 Hz, J' = 8.5 Hz, 1H, 8a-H), 3.90 (d, J = 11.0 Hz, 1H, 1-H), 4.43 (dd, J = 10.5 Hz, J' = 8.5 Hz, 1H, 3a-H), 6.15 [ddd, J = 3.0 Hz, J' = J'' = 1.0 Hz, 1H, 3-H 3-(2-furyl)], 6.16 [dd, J = 3.5 Hz, J' = 2.0 Hz, 1H, 4-H 1-(2-furyl)], 6.19 [dd, J = 3.0 Hz, J' = 2.0 Hz, 1H, 4-H 3-(2-furyl)], 6.26 [ddd, J = 3.5 Hz, J' = J'' = 1.0 Hz, 1H, 3-H 1-(2-furyl)], 7.05 [dd, J = 2.0 Hz, J'=1.0 Hz, 1H, 5-H 1-(2-furyl)], 7.17 [dd, J = 2.0 Hz, J' = 1.0 Hz, 1H, 5-H 3-(2-furyl)], 7.18 (ddd, J = 7.5 Hz, J' = J'' = 1.0 Hz, 1H, 4′-H), superimposes in part 7.258 (broad d, J = 7.5 Hz, 1H, 4-H), superimposes in part 7.260 (broad dd, J = J' = 7.5 Hz, 1H, 6′-H), 7.42 (ddd, J = J' = 7.5 Hz, J'' = 1.0 Hz, 1H, 5′-H), 7.44 (broad dd, J = J' = 7.5 Hz, 1H, 6-H), 7.55 (ddd, J = J' = 7.5 Hz, J'' = 1.5 Hz, 1H, 5-H), 7.71 (broad d, J = 7.5 Hz, 1H, 7′-H), 7.78 (broad d, J = 7.5 Hz, 1H, 7-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 31.1 (CH_2, C3′), 46.3 (CH, C3a), 47.8 (CH, C1), 52.6 (CH, C3), 53.1 (CH, C8a), 68.2 (C, C2), 107.9 [CH, C3 3-(2-furyl)], 108.1 [CH, C3 1-(2-furyl)], 110.0 [CH, C4 1-(2-furyl)], 110.1 [CH, C4 3-(2-furyl)], 123.8 (CH, C7′), 124.5 (CH, C7), 125.5 (CH, C4), 125.9 (CH, C4′), 127. 1 (CH, C6′), 128.5 (CH, C6), 134.6 (CH, C5′), 135.4 (CH, C5), 135.6 (C, C7a), 136.5 (C, C7a′), 141.9 [CH, C5 1-(2-furyl)], 142.2 [CH, C5 3-(2-furyl)], 151.7 [C, C2 3-(2-furyl)], 151.8 [C, C2 1-(2-furyl)], 152.7 (C, C3a′), 155.0 (C, C3b), 204.7 (C, C8), 205.9 (C, C1′). Elemental analysis calcd (%) for $C_{28}H_{20}O_4$ (420.46): C, 79.98; H, 4.79. Found: C, 79.93; H, 4.78.

9d: mp 185−186 °C (MeOH). R_f 0.19 (SiO_2, hexane/AcOEt 4:1). IR (KBr): ν 3147, 3103, 3070, 3028, 2939, 1704 (C=O st), 1606 and 1588 (Ar−C−C st), 1505, 1464, 1286, 1150, 1014, 734 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.94 (d, J = 17.5 Hz, 1H, 3′-H_b), 3.06 (d, J = 17.5 Hz, 1H, 3′-H_a), 3.66 (dd, J = 9.0 Hz, J' = 5.0 Hz, 1H, 8a-H), 4.15 (d, J = 9.0 Hz, 1H, 3-H), 4.22 (d, J = 5.0 Hz, 1H, 1-H), 4.52 (dd, J = J' = 9.0 Hz, 1H, 3a-H), 5.63 [dd, J = 3.0 Hz, J' = 1.0 Hz, 1H, 3-H 3-(2-furyl)], 6.01 [dd, J = 3.0 Hz, J' = 2.0 Hz, 1H, 4-H 3-(2-furyl)], 6.25 [ddd, J = 3.0 Hz, J' = J'' = 1.0 Hz, 1H, 3-H 1-(2-furyl)], 6.31 [dd, J = 3.0 Hz, J' = 2.0 Hz, 1H, 4-H 1-(2-furyl)], 6.75−6.80 (m, 1H, 4-H), 7.04 [dd, J = 2.0 Hz, J' = 1.0 Hz, 1H, 5-H 3-(2-furyl)], 7.261 (ddm, J = J' = 7.5 Hz, 1H, 6′-H), 7.262 (dm, J = 7.5 Hz, 1H, 4′-H), 7.33 [dd, J = 2.0 Hz, J' = 1.0 Hz, 1H, 5-H 1-(2-furyl)], 7.34−7.38 (complex signal, 2H, 5-H and 6-H), 7.47 (ddd, J = J' = 7.5 Hz, J'' = 1.0 Hz, 1H, 5′-H), 7.57 (dm, J = 7.5 Hz, 1H, 7′-H), 7.81−7.85 (m, 1H, 7-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 37.1 (CH_2, C3′), 45.4 (CH, C1), 47.6 (CH, C3a), 51.2 (CH, C3), 56.2 (CH, C8a), 65.7 (C, C2), 107.8 [CH, C3 1-(2-furyl)], 109.3 [CH, C3 3-(2-furyl)], 109.7 [CH, C4 3-(2-furyl)], 110.3 [CH, C4 1-(2-furyl)], 123.4 (CH, C7), 124.2 (CH, C7′), 125.9 (CH, C4′), 126.8 (CH, C4), 127. 4 (CH, C6′), 127.7 (CH, C6), 133.6 (CH, C5), 134.6 (CH, C5′), 136.1 (C, C7a′), 138.4 (C, C7a), 141.6 [CH, C5 3-(2-furyl)], 141.9 [CH, C5 1-(2-furyl)], 150.9 [C, C2 3-(2-furyl)], 151.4 (C, C3a′), 153.0 (C, C3b), 154.9 [C, C2 1-(2-furyl)], 205.0 (C, C1′), 205.6 (C, C8). Elemental analysis calcd (%) for $C_{28}H_{20}O_4$ (420.46): C, 79.98; H, 4.79. Found: C, 79.86; H, 4.82.

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Supporting Information Available: Experimental procedures, spectral and analytical characterization data of all of the new compounds (except for **7d** and **9d**, herein described), computational details, and X-ray crystal structure data and ORTEP of spirocompounds **6a**, **6g**, **7b**, and **9b**. ^{1}H, ^{13}C, $^{1}H/^{1}H$ COSY, $^{1}H/^{13}C$ HSQC, $^{1}H/^{13}C$ HMBC, and $^{1}H/^{1}H$ NOESY NMR spectra of all the new compounds and crystallographic information files (CIF) of spirocompounds **6a**, **6g**, **7b**, and **9b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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