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General Synthesis of 8-Aryl-2-tetralones

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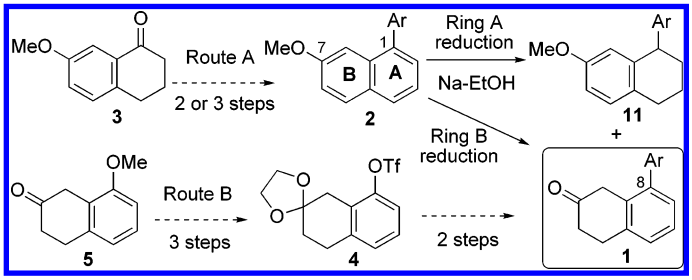

Two alternative routes are described for the synthesis of 8-aryl-2-tetralones (**1**). Route A starts from α-tetralone **3** and involves 3 or 4 steps, with the selective Na−EtOH reduction of 1-aryl-7-methoxy-naphthalenes **2** being the key step. The exclusive reduction of the A ring of naphthalenes **2** occurs when the aryl group at C-1 has no substituent at the ortho positions, affording tetrahydronaphthalenes **11**. Reduction of the B ring of **2** becomes the major process when the aryl fragment has two substituents at the ortho positions, affording 8-aryl-2-tetralones **1** as the major component. Route B involves 5 steps starting from 2-tetralone **5**, with the key step being the Suzuki coupling with triflate **4**. This approach allows the synthesis of 8-aryl-2-tetralones **1** with no substituent at the ortho positions of the aryl fragment and with naphthalene and anthracene rings at C-8.

Introduction

Substituted 2-tetralones have played an important role in organic synthesis as a result of their high reactivity and suitability as starting materials for a wide range of synthetic heterocyclic compounds,[1] pharmaceuticals[2] with biological activities, and other useful properties, as well as precursors of several natural products and their derivatives.[3]

However, unlike their congeners, the 1-tetralones, which are inexpensive, easy to prepare, and commercially available substances, 2-tetralones are often very expensive and much more difficult to synthesize. In addition, preparation of 2-tetralones has long been hampered either by poor yields or by difficulty in finding accessible starting materials.

The most frequently employed methods for the preparation of 2-tetralones[4] involve 1,2-transposition of the carbonyl group of 1-tetralones,[5] reduction of substituted 2-methoxy-naphthalenes, followed by hydrolysis of the resulting enol ethers,[6] cyclization of the diazoketones,[7] and the Friedel−Crafts reaction of the aromatic acyl chlorides with olefins.[2c−d,3c,8]

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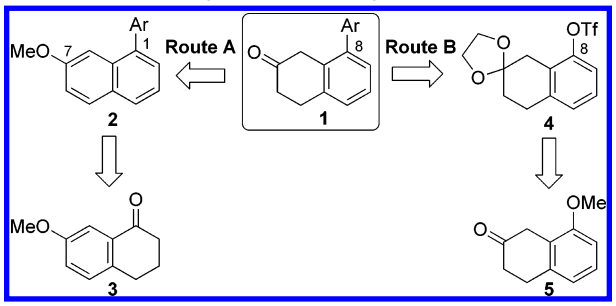
SCHEME 1. Retrosynthesis of 8-Aryl-2-tetralones



In connection with a program devoted to the synthesis of polyaromatic compounds such as helicenes,[9] we needed to prepare several 8-aryl-2-tetralones (**1** in Scheme 1) bearing different substituents at the aryl moiety. On revising the literature, we found that the synthesis of 8-aryl-2-tetralones had been only addressed using the carbanion-induced condensation of differently substituted 2*H*-pyran-2-ones with a 1,4-cyclohexanedione monoketal.[10] Although different substituents were admitted in the 2*H*-pyran-2-ones, the necessary starting materials were not easily accessible.

We thus decided to explore the reduction of 7-methoxy-1-arylnaphthalenes **2** as a route to the required 8-aryl-2-tetralones **1**, after hydrolysis of the resulting enol ether. The presence of different aromatic rings at the C-1 position of the starting naphthalenes **2**, required to know the ring selectivity of the process (Scheme 1). The study of the Na/EtOH reduction of compounds **2** bearing differently substituted phenyl groups at C-1 allowed us to synthesize a few 8-aryl-2-tetralones with one or two susbtituents at the ortho position of the 8-aryl group with yields ranging from 29 to 60%.[11] Looking for an improved and more general access to these targets, we thought of a different strategy starting from 2-tetralones bearing at the C-8 position a substituent that enabled the introduction of the 8-aryl moiety at the final steps. We now report a full account of our results, which allowed the synthesis of **1** using both alternative strategies.

Results and Discussion

Two retrosynthetic routes were envisaged for the desired 8-aryl-2-tetralones **1** (Scheme 1). The first one (route A) involved the Na/EtOH reduction of the corresponding 7-methoxy-1-arylnaphthalenes **2**, which, in turn, could be formed from the commercially available α-tetralone **3** by introduction of the aryl substituent at the required position and aromatization. Two alternative ways could be used to place the 8-aryl group from **3**: addition of an aryl Grignard, followed by dehydration of the resulting carbinol or metal-catalyzed cross-coupling reaction between an aryl organometallic species and the enol triflate derived from ketone **3**.

In the second approach (route B), we considered a Pd-catalyzed cross-coupling reaction of the triflate **4** as the key step to introduce the desired aryl substitution at the C-8 of the protected tetralone. Compound **4** could be easily accessible from commercially available 2-tetralone **5**, by carbonyl protection, ether cleavage, and formation of the triflate.

We first investigated the Na/EtOH reduction of 2-methoxynaphthalenes (route A),[12] initially described by Cornforth et al.,[13] because this strategy had been successfully applied by us for the selective synthesis of differently substituted 8-alkyl-2-tetralones from the corresponding 8-alkyl-2-methoxynaphthalenes.[9a,14] It is well-known that metal-mediated reductions[15] of naphthalenes bearing electron-releasing substituents at C-1 occur at the unsubstituted aromatic ring, whereas electron-withdrawing groups at C-1 direct the reduction to the same ring.[16] Before our study, the ring selectivity of the reduction of 1-aryl-substituted naphthalenes had been only reported for 1-phenylnaphthalene itself, which, upon treatment with Na and ammonia, afforded exclusively the products resulting from the reaction of the naphthalene ring bearing the phenyl substituent.[17] The effect of the presence of alkyl or alkoxy substituents on the aryl ring at C-1 of 1-aryl-7-methoxynaphthalenes **2** on the selectivity of the reduction remained unknown.

Synthesis of 8-Aryl-2-tetralones (Route A). The retrosynthetic route A depicted in Scheme 1, first required the introduction of the aromatic substituent at C-1 of the commercially available 7-methoxy-1-tetralone (**3**). From the two possible alternatives, we initially chose the route based on the addition of differently substituted aryl Grignard reagents **6** to α-tetralone **3** (Scheme 2).[18]

Thus, the reaction between **3** and *p*-tolylmagnesium bromide **6a** took place in ethyl ether at room temperature to give an

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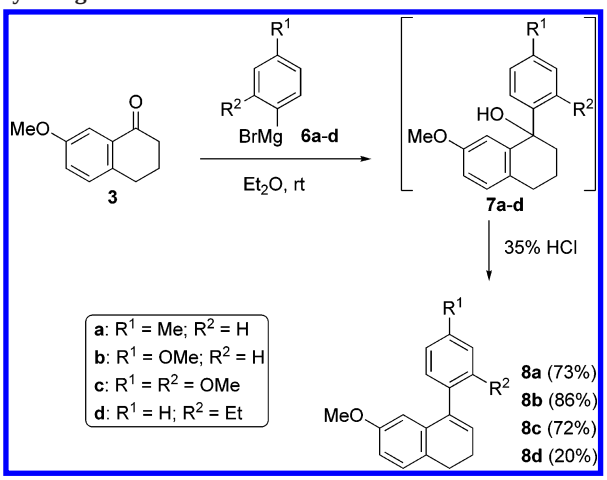
SCHEME 2. Synthesis of Dihydronaphthalenes 8a−d from Aryl Grignard Additions on α-Tetralone 3

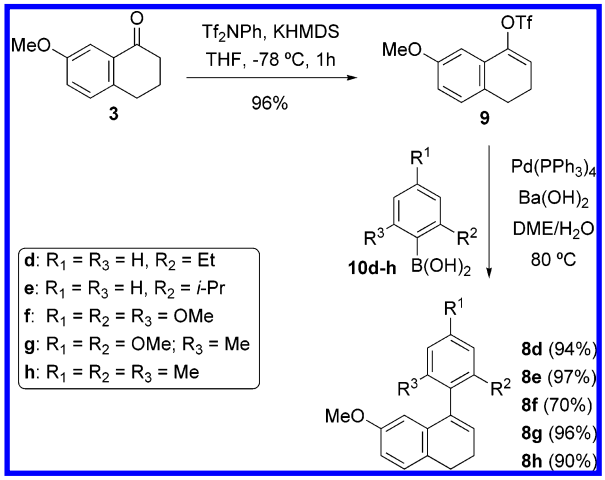


intermediate carbinol **7a**, which was directly transformed into 4-(*p*-tolyl)-6-methoxy-1,2-dihydronaphthalene (**8a**) by treatment with 35% HCl (73% yield for the two steps, Scheme 2). Dihydronaphthalenes **8b** and **8c** were similarly obtained by reaction of **3** with 4-methoxyphenylmagnesium bromide (**6b**) or the 2,4-dimethoxyphenyl derivative **6c**, in 86 and 72% overall yields, respectively. Nevertheless, when the reaction of **3** was carried out with the Grignard reagent **6d**, bearing a bulky ethyl substituent at the ortho position, compound **8d** was formed in a poor 20% yield. Moreover, when the reagent of choice was 2,4,6-trimethylphenylmagnesium bromide, no reaction was observed, even at higher temperatures (refluxing Et_2O) or in the presence of several Lewis acids such as $BF_3{\cdot}OEt_2$ or $Yb(OTf)_3$.[19]

With these results in hand, we decided to evaluate the synthetic alternative pathway to dihydronaphthalenes **8**, on the basis of the metal-catalyzed cross-coupling reaction between the enoltriflate derived from **3** and an aryl organometallic species. Among the different organometallic reagents available in the synthetic arsenal, we decided to use boronic acids[20] as a result of their accessibility and the excellent results achieved in their cross-coupling reactions even with sterically hindered derivatives.[21]

The synthesis of 6-methoxy-4-[(trifluoromethanesulfonyl)-oxy]-1,2-dihydronaphthalene **9**[22] was carried out from the reaction of α-tetralone **3** with *N*-phenyl-bis(trifluoromethanesulfonamine) (Tf_2NPh) at −78 °C in the presence of a 0.5 M solution of potassium hexamethyldisilazane (KHMDS) in THF, in 96% yield (Scheme 3). All cross-coupling reactions were performed under the experimental conditions reported by Suzuki et al. [$Pd(PPh_3)_4$, $Ba(OH)_2{\cdot}8H_2O$, DME/H_2O, 80 °C][21] using commercially available boronic acids **10d−h**, except in the case of **10g**, which was prepared as previously described.[23]

SCHEME 3. Synthesis of Dihydronaphthalenes 8d−h from Suzuki Coupling between Boronic Acids 10d−h and Enol Triflate 9



Thus, the reaction between enol triflate **9** and 2-ethylphenyl boronic acid (**10d**), under the above-mentioned conditions, furnished in only 40 min dihydronaphthalene **8d** with an excellent 94% yield (Scheme 3), enhancing the poor 20% yield obtained using the Grignard reagent addition to **3**, as indicated in Scheme 2. Under the same experimental conditions, the cross-coupling reactions of compound **9** with differently substituted aryl boronic acids **10e−h**, bearing one or two substituents at the ortho positions of the aryl moiety, took place in short reaction times (15−120 min), affording the corresponding dihydronaphthalenes **8e−h** with yields ranging from 70 to 97% (Scheme 3). It is worth mentioning the excellent 90% yield achieved in the preparation of compound **8h**, which could not be synthesized using the Grignard addition strategy.

Once the dihydronaphthalenes **8a−h** were prepared, the synthetic sequence toward the desired 8-aryl-2-tetralones (Scheme 1) required the full aromatization of the dihydroaromatic ring of **8a−h** to the corresponding 1-aryl-7-methoxynaphthalenes **2a−h**. This was easily achieved using 2,3-dichloro-5,6-dicyanoquinone (DDQ) as the oxidant agent.

Thus, the reaction of dihydronaphthalene **8a** with 1.2 equiv of DDQ in CH_2Cl_2 afforded, after 15 min at room temperature, 1-(4-methylphenyl)-7-methoxynaphthalene (**2a**) in 71% yield (Scheme 4). Under the same experimental conditions, 1-aryl-7-methoxynaphthalenes **2b−g**, bearing different substituents at the aryl moiety (Scheme 4), were obtained from the corresponding dihydronaphthalenes **8b−g** in good to excellent yields (80−97%).

With 1-arylnaphthalenes **2a−g** in hand, we undertook the study of the selectivity of their reductions with Na−EtOH. All reactions were performed by adding an excess of sodium (6 or 7 pieces of ca. 0.5 cm) to a solution of the corresponding 1-aryl-7-methoxynaphthalene **2** in refluxing EtOH until the disappearance of all starting material (followed by TLC). Heating the external bath to 100 °C was essential to attain good results. After consumption of the excess of sodium, the resulting mixture was treated with 35% HCl and investigated by ^1H NMR.

The reduction of 1-(*p*-tolyl)-7-methoxynaphthalene (**2a**), under the above conditions, gave rise exclusively to 1-(*p*-tolyl)-

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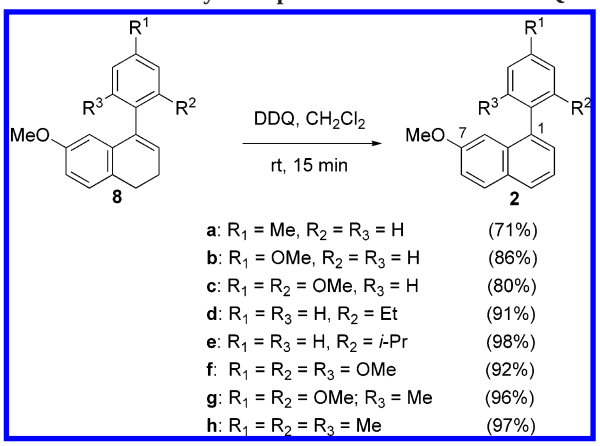
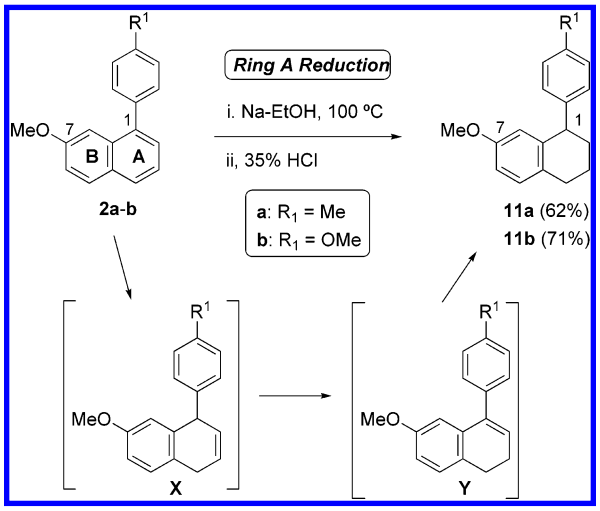
SCHEME 4. Synthesis of Naphthalenes 2a−h by Aromatization of Dihydronaphthalenes 8a−h with DDQ



SCHEME 5. Exclusive Na−EtOH Reduction of the A Ring of Naphthalenes 2a,b

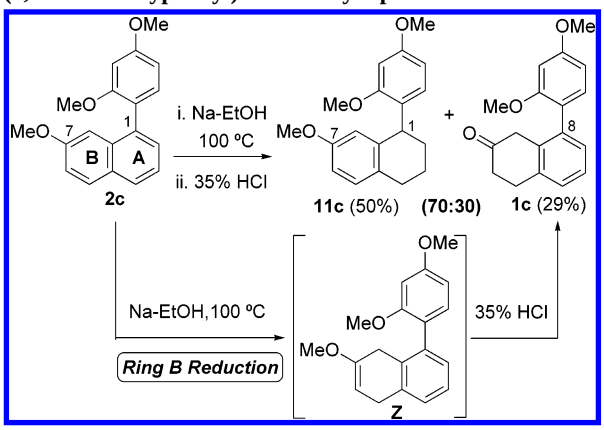


7-methoxy-1,2,3,4-tetrahydronaphthalene (**11a**) in 62% yield (Scheme 5). Compound **11a** was probably formed from the initial reduction of the A ring of **2a**, bearing the *p*-tolyl substituent, to the corresponding 1,4-dihydroaromatic intermediate **X** (Scheme 5), isomerization of the double bond to derivative **Y**, and over-reduction of the conjugate double bond formed. The intermediate formation of 1,2-dihydrotetralins had been already recognized in Birch reductions.[24] The ring selectivity observed by us was not unexpected because Rabideau et al.[16a] had shown that the Na−NH_3 reduction of 1-phenylnaphthalene afforded exclusively the product resulting from the reduction of the naphthalene ring bearing the phenyl substituent.

When 7-methoxynaphthalene **2b**, bearing a *p*-methoxyphenyl substituent at C-1, was submitted to the typical reduction conditions, we obtained 1-(*p*-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**11b**), also proceeding from the over-reduction of the A ring of **2b**, as the exclusive product, which was isolated in 71% yield (Scheme 5). This result indicated that the presence of a more electron-donating substituent had no influence on the ring selectivity of the process.

Nevertheless, reduction of compound **2c**, possessing two methoxy groups at the ortho and para positions of the phenyl group at C-1 (Scheme 6) gave a 70:30 mixture of two products

SCHEME 6. Ring Selectivity in the Na−EtOH Reduction of 1-(2,4-Dimethoxyphenyl)-7-methoxynaphthalene 2c



identified as 1-(2,4-dimethoxyphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene **11c**, proceeding from the over-reduction of the A ring of **2c**, and 8-(2,4-dimethoxyphenyl)-3,4-dihydro-2(*1H*)-naphthalenone (**1c**), which was formed after the reduction of the B ring of **2c**, followed by acidic hydrolysis of the initially formed vinyl ether intermediate **Z**. Compounds **11c** and **1c** could be isolated pure in 50 and 29% yields, respectively, after chromatographic separation.

To evaluate if the variation observed in the selectivity of the process was due to the presence of two electron-donating groups or to the existence of a OMe substituent at the ortho position of the 1-aryl group in **2c**, we performed the reduction of 1-(2-ethylphenyl)-7-methoxynaphthalene (**2d**). In this case, the phenyl substituent at C-1 possesses a bulkier ethyl group at the ortho position, but the electronic density of the aryl ring in **2d** is smaller if compared with the 2,4-dimethoxy-substituted phenyl ring in **2c**. Under the typical reduction conditions (Table 1, entry 4), naphthalene **2d** gave rise to a 50:50 mixture of tetrahydronaphthalene **11d** and *β*-tetralone **1d**, both being isolated pure in 36% yield. This result seemed to indicate that the presence of a bulky substituent at the ortho position of the aryl ring at C-1 could favor the ring B reduction of the naphthalene derivative, enhancing the ratio of the desired 2-tetralone in the final mixture.

This assumption was confirmed after reduction of compound **2e**, bearing an isopropyl group at the ortho position of the 1-aryl substituent, which afforded a 40:60 mixture of compounds **11e** and **1e**, isolated in 20 and 45% yields, respectively (Table 1, entry 5). In this case, the reduction of the B ring of naphthalene **2e** was favored, thus confirming that the steric hindrance at the ortho positions of the aryl group at C-1 was playing an essential role in defining the ring selectivity of the process. An identical result was observed when 7-methoxy-1-(2,4,6-trimethoxyphenyl)naphthalene (**2f**), with two methoxy groups at the ortho positions of the phenyl moiety at C-1, was submitted to the reduction conditions. In this case (Table 1, entry 6), a 28% yield of 1-(2,4,6-trimethoxyphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**11f**) and a 32% yield of the corresponding 2-tetralone **1f** were obtained after chromatographic separation of the initially formed 40:60 mixture of compounds.

With the aim of further increasing the ratio of the B ring reduction of 1-aryl-7-methoxynaphthalenes **2** and, as a consequence, the yield of the 8-aryl-2-tetralones **1**, we performed the reduction of 7-methoxy-1-(2,4-dimethoxy-6-methylphenyl)naphthalene **2g**, bearing a methoxy and a methyl group at the ortho positions of the aryl substituent at C-1 (Table 1, entry 7). In

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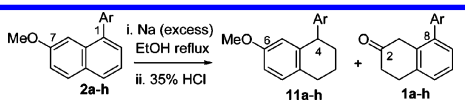
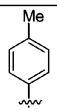
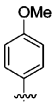
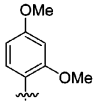
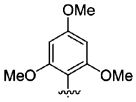
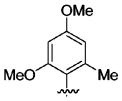
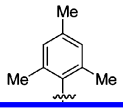
TABLE 1. Ring Selectivity in the Na−EtOH Reductions of 1-Aryl-7-methoxynaphthalenes 2a−h



Entry	Substrate	Ar	t (min)	Relative ratio 11a-h:1a-h	Yield (%) 11a-h	Yield (%) 1a-h
1	**2a**		105	**100:0**	65	0
2	**2b**		75	**100:0**	71	0
3	**2c**		90	**70:30**	50	29
4	**2d**		60	**50:50**	36	36
5	**2e**		90	**40:60**	20	45
6	**2f**		80	**40:60**	28	32
7	**2g**		50	**25:75**	22	60
8	**2h**		60	**15:85**	8	54

this case, a 25:75 mixture of tetrahydronaphthalene **11g** (22% isolated yield) and β-tetralone **1g** (60% yield) was formed.

Finally, the best result, referred to the B ring selective Na−EtOH reduction of compounds **2**, was achieved from derivative **2h**, bearing two methyl groups at the ortho positions of the aryl moiety at C-1 (Table 1, entry 8). In this case, a 15:85 mixture of 1-(2,4,6-trimethylphenyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (**11h**) and 8-(2,4,6-trimethylphenyl)-2-tetralone (**1h**) was formed from which both compounds could be isolated in 8 and 54% yields, respectively.

It is worth mentioning that in the ^{1}H NMR spectrum ($CDCl_3$) of tetrahydronaphthalene **11g**, bearing an aryl substituent at C-1 with a methoxy and a methyl group at the ortho positions, several broad nonwell-resolved signals appeared (Figure 1). This could probably be due to the presence of atropisomers **A** and **B**, caused by a restricted rotation around the $C_{1'}(sp^2)$ aryl−C_4-(sp^3) single bond.[25] When a solution of **11g** in $C_2D_2Cl_4$ was heated at 390 °K, the broad signals observed for H_1 (δ = 4.90 and 4.20 ppm), OMe (o) (δ = 3.80 and 3.40 ppm), and Me (δ = 2.18 and 1.98 ppm), at room temperature, coalesced to a multiplet at 4.50 ppm, a singlet at 3.58 ppm, and a singlet at 2.08 ppm, respectively (Figure 1).

(25) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. In *Basic Organic Stereochemistry*; Wiley: New York, 2001; p 629.

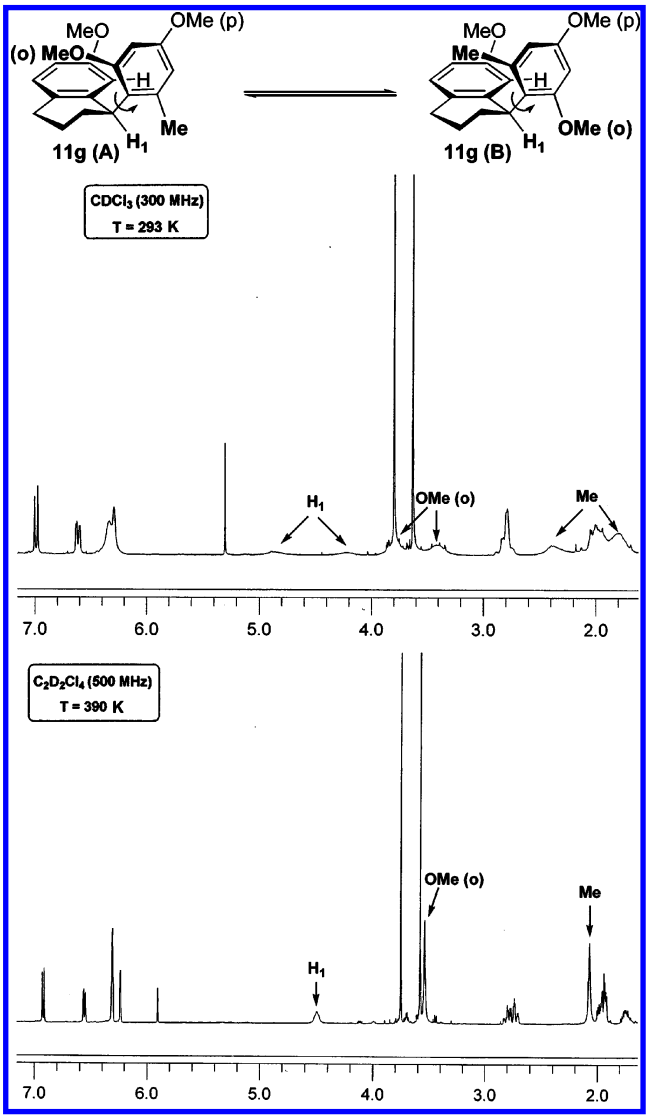


FIGURE 1. ^{1}H NMR spectra of tetrahydronaphthalene **11g** at different temperatures.

This type of restricted rotation about a C(sp^3)−C(sp^2) bond had also been observed for similar conveniently functionalized systems such as 9-arylfluorenes,[26] 9-aryltriptycenes,[27] 9-arylxanthenes,[28] and 9-aryl-9,10-dihydroanthracenes.[29]

The comparison of the ^{1}H NMR data of the three tetrahydronaphthalenes **11f**−**h**, possessing an aryl group at C-1 with two substituents at the ortho positions, suggested three different situations. Compound **11f**, bearing two methoxy groups, must have a free rotation around the C(sp^3)−C(sp^2) bond at room temperature, because both OMe groups are equivalent and appear at the same chemical shift (3.65 ppm; Figure 2). In the ^{1}H NMR spectrum of **11h**, with two bulkier ortho methyl groups at the aryl substituent at C-1, two different signals for the two nonequivalent methyl groups could be observed at 2.26 and 1.79 ppm, respectively (Figure 2). This could be due to a restricted

(26) Ford, W. T.; Thompson, T. B.; Snoble, K. A. J.; Timko, J. M. *J. Am. Chem. Soc.* **1975**, *97*, 95−100.
(27) Nakamura, M.; Oki, M. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2106−2111.
(28) Nakamura, M.; Oki, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2977−2980.
(29) Rabideau, P. W.; Govindarajan, U. *J. Org. Chem.* **1989**, *54*, 988−990.

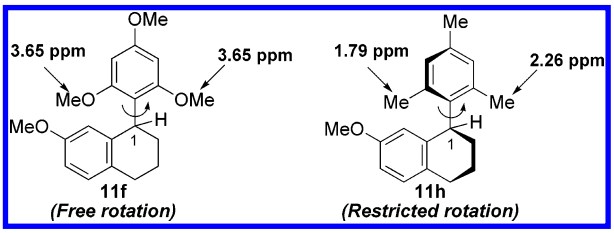
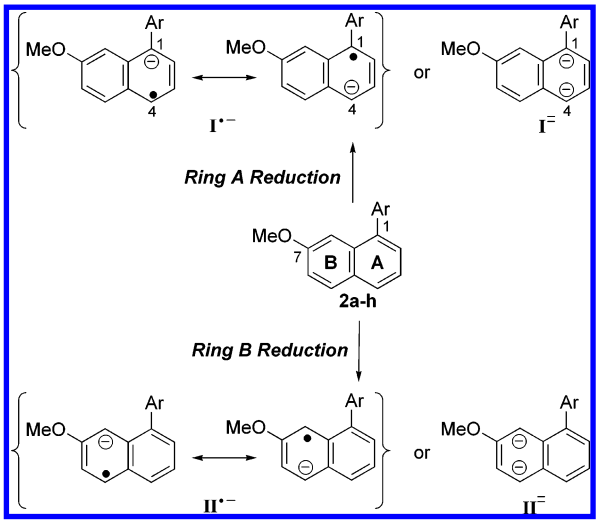


FIGURE 2. ^{1}H NMR data of tetrahydronaphthalenes **11f** and **11h**, suggesting free or restricted rotation of the aryl ring at C-1.

SCHEME 7. Mechanistic Proposal for the Na−EtOH Reduction of 1-Aryl-7-methoxynaphthalenes 2a−h



rotation about the C(sp^3)−C(sp^2) bond at room temperature. Finally, as indicated above, in the case of derivative **11g**, with a methyl and a methoxy ortho groups, a partially restricted rotation around the C(sp^3)−C(sp^2) must occur at room temperature, because a broadening of several signals in the ^{1}H NMR spectrum is observed as a consequence of the presence of two atropisomeric species **A** and **B** (Figure 1).

Mechanistic Proposal. The mechanism of the Birch and related metal−alcohol processes has been extensively studied both from the experimental and from the theoretical points of view.[30] The reduction of the aromatic ring is thought to begin by the formation of a radical anion by electron transfer from the metal. After protonation by the alcohol, the resulting radical is further reduced to a carbanion by a second electron transfer from the metal. Finally, a second proton is transferred from the alcohol to this anion. In the case of polynuclear arenes, a second electron addition to the initially formed radical anion may take place to produce a dianion.[16c,31] In both cases, the first protonation is the rate-determining step. The structure of the final metal-mediated reduction product will be defined by the site of protonation of the radical anion or the dianion, which, in turn, will be the position of the highest electron density.[16a]

In the case of the reduction of naphthalenes **2a**,**b**, the selective formation of tetrahydronaphthalenes **11a**,**b**, resulting from the exclusive reduction of the A ring, must be a consequence of the intermediate formation of the radical anion **I**$^{\bullet-}$ or dianion **I**$^{2-}$, which must be favored over the analogues **II**$^{\bullet-}$ and **II**$^{2-}$.

(30) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 4th ed.; Kluwer: Norwell, MA, 2000.

(31) Rabideau, P. W.; Burkholder, E. G. *J. Org. Chem.* **1978**, *43*, 4283−4288.

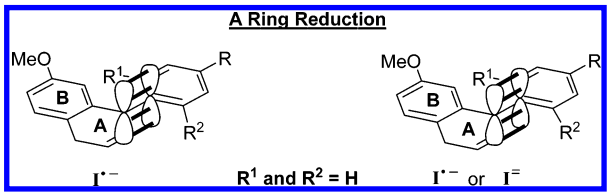


FIGURE 3. Extended conjugation of intermediates **I** ($R^1 = R^2 = H$) favoring exclusive reduction of the A ring of 1-arylnaphthalenes **2a**,**b**.

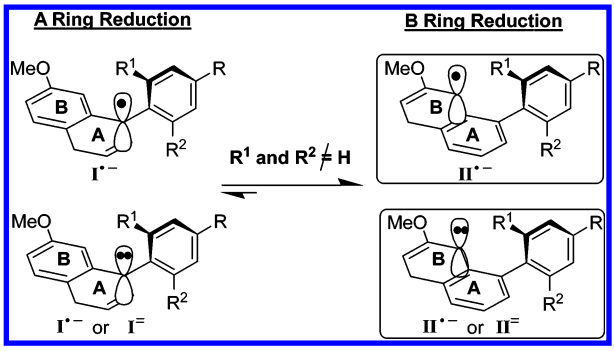


FIGURE 4. Steric inhibition of the resonance in intermediates **I** ($R^1 = R^2 \neq H$) favoring reduction of the B ring of 1-arylnaphthalenes **2f**−**h** through intermediates **II**.

The stabilization of the negative charge or the electron situated at C-1 in species **I**$^{\bullet-}$ or **I**$^{2-}$ is possible if the aryl group is situated in the same plane with respect to the dihydronaphthalene moiety to allow delocalization (Scheme 7 and Figure 3).

This situation is optimal in the intermediates of type **I** bearing a *p*-methyl (resulting from **2a**) or a *p*-methoxy substitution (from **2b**) at the aryl group at C-1, without substituents at the ortho positions, which allows the extended conjugation (Figure 3). Further protonation of such species, followed by evolution through the intermediates shown in Scheme 5, accounts for the exclusive formation of tetrahydronaphthalenes **11a**,**b**.

When a small substituent such as an OMe group is introduced at the ortho position of the C-1 aryl group (compound **2c**), a nonnegligible 30% of evolution through the B ring reduction is also observed (Scheme 6). If the ortho substituent is an ethyl group (compound **2d**), there is no selectivity in the reduction of the A or B rings (50:50 mixture of **11d** and **1d**, Table 1, entry 4). These results could be a consequence of the higher volume of the ortho ethyl substituent, which could force the C-1 aryl fragment out of the plane, thus inhibiting the resonance stabilization of intermediates **I**. In such a situation, the B ring reduction through evolution of intermediates **II** becomes competitive. The bulkier isopropyl substituent present in the aryl group at C-1 of **2e** could be in the origin of the slight but significant inversion of the ring selectivity reduction observed in favor of the B ring (40:60 mixture of **11e** and **1e**, Table 1, entry 5). Going down in the results shown in Table 1, the preference for the A ring reduction in compounds **2f**−**h** decreased significantly when increasing the number or the size of the ortho substituents in the aryl group at C-1. These observations are in agreement with the increasing steric inhibition of the resonance due to the presence of two ortho substituents in the aryl fragment at C-1 of naphthalenes **2**, which force the disposition of this group out of the plane, destabilizing intermediates **I** and favoring the B ring reduction of naphthalenes **2f**−**h** to give compounds **1** as majors (Figure 4).

Moreover, when the radical or the negative charge is located at C-1 of the A ring (intermediates **I** in Figure 4), the steric

hindrance due to the presence of ortho substituents R^1 and R^2 in the orthogonal aryl fragment at C-1, could also inhibit or cause their protonation to be more difficult, which also would favor the B ring reduction process.

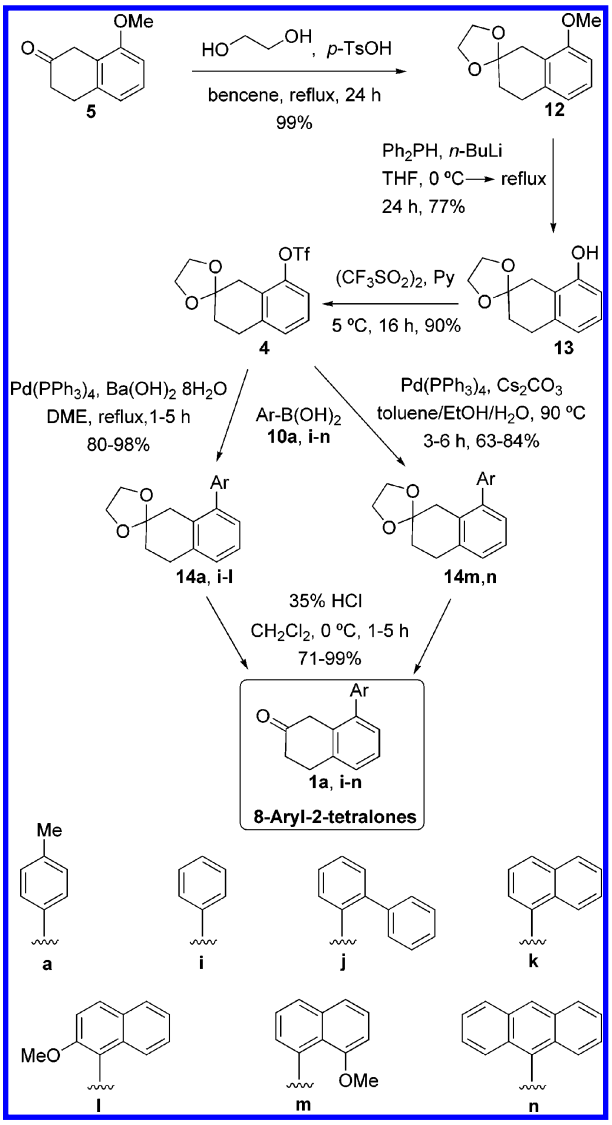
Synthesis of 8-Aryl-2-tetralones (Route B). Although the above synthetic strategy allowed us to show that the ring selectivity of the Na−EtOH reduction of 1-aryl-7-methoxynaphthalenes **2** could be modulated by the substitution pattern at the 1-aryl fragment, from the synthetic point of view, the preparation of 8-aryl-2-tetralones **1** by this route presented serious drawbacks. First, although β-tetralones **1c**−**h** could be isolated pure, they were always obtained as mixtures with the corresponding 4-aryl-6-methoxy-1,2,3,4-tetrahydronaphthalenes **11c**−**h**. Moreover, this method did not allow the synthesis of the simplest 8-aryl-2-tetralones **1a**,**b** without substituents at the ortho positions of the 8-aryl moiety. On the other hand, the synthesis of 8-naphthyl-substituted 2-tetralones **1** by this strategy appeared complicated by the competitive reduction of both naphthalene fragments under the Na−EtOH reductive conditions employed.

Therefore, with the aim of describing a more general method to access to 8-aryl-2-tetralones **1**, we turned our attention to the synthetic alternative pathway proposed in Scheme 1 as Route B. The starting material in this approach could be a preformed 2-tetralone, such as **5**, bearing at C-8 a methoxy group, which could be easily transformed into the aryl moiety present in derivatives **1**.

Thus, the initial protection of commercially available 8-methoxy-2-tetralone (**5**) as dioxolane, afforded compound **12**[32] in nearly quantitative yield (Scheme 8). Demethylation of **12** proved to be very difficult under various aryl methyl ether cleavage protocols[33] as a result of the presence of the sensitive acetal moiety. After considerable experimentation, success was achieved using lithium diphenylphosphide,[34] prepared in situ from diphenylphosphine and *n*-butyllithium, in refluxing THF for 24 h. Under these conditions, compound **12** furnished phenol **13** in 77% yield. The corresponding triflate **4**, necessary for the introduction of the aryl groups by Suzuki coupling, was prepared from **13** by a reaction with trifluoromethanesulfonic anhydride in the presence of pyridine in 90% yield (Scheme 8).

With triflate **4** in hand, we performed the introduction of the aryl groups at the desired position by Suzuki coupling using differently substituted aryl boronic acids **10** (Scheme 8). For these reactions, we used two phenyl boronic acids with no substituents at the ortho positions, **10a** and **10i**, one derivative with a phenyl group at the ortho position, **10j**, three naphthyl boronic acids with different substitutions at the naphthalene ring, **10k**−**m**, and, finally, one derivative bearing an anthracenyl moiety, **10n**. All cross-coupling reactions were performed under

SCHEME 8. Synthesis of 8-Aryl-2-tetralones 1a,i−n from 2-Tetralone 5



the experimental conditions described by Suzuki et al.[21] [Pd(PPh$_3$)$_4$, Ba(OH)$_2$·8H$_2$O, DME, reflux], slightly modified, using commercially available arylboronic acids **10a**,**i**−**k**, or previously described derivatives **10l**,[35] **10m**,[36] and **10n**.[37] Under these conditions, biaryls **14a**,**i**−**l** were obtained in excellent yields (80−98%), after flash chromatography. Nevertheless, when more hindered arylboronic acids such as **10m** and **10n** were used, low yields of the corresponding biaryls were obtained using the above-mentioned procedure. In these cases, the application of the experimental conditions reported by Tanaka et al.[38] [Pd(PPh$_3$)$_4$, Cs$_2$CO$_3$, toluene/EtOH/H$_2$O, 90 °C] for the Suzuki coupling with triflate **4**, furnished biaryls **14m** and **14n** in 63 and 84% yields, respectively (Scheme 8).

Finally, the treatment of derivatives **14a**,**i**−**n** with 35% HCl at 0 °C (Scheme 8) afforded 8-aryl-2-tetralones **1a**,**i**−**n** with

(32) (a) Cordi, A. A.; Lacoste, J.-M.; Descombes, J.-J.; Courchay, Ch.; Vanhoutte, P. M.; Laubie, M.; Verbeuren, T. J. *J. Med. Chem.* **1995**, *38*, 4056−4069. (b) Lee, S.; Frescas, S. P.; Nichols, D. E. *Synth. Commun.* **1995**, *25*, 2775−2780. (c) Turner, R. B.; Miller, R. B.; Lin, J.-L. *J. Am. Chem. Soc.* **1968**, *90*, 6124−6130.

(33) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

(34) (a) Ireland, R. E.; Walba, D. M. *Organic Syntheses*; Wiley & Sons: New York, 1988; Collect. Vol. No. VI, pp 567−570. For more recent references, see: (b) Wipf, P.; Jung, J.-K. *J. Org. Chem.* **2000**, *65*, 6319−6337. (c) Ohira, S.; Kuboki, A.; Hasegawa, T.; Kikuchi, T.; Kutsukake, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 4641−4644. (d) Zheng, S.-L.; Yu, W.-Y.; Xu, M.-X.; Che, Ch.-M. *Tetrahedron Lett.* **2003**, *44*, 1445−1447. (e) Moriarty, R. M. *J. Org. Chem.* **2004**, *69*, 1890−1902.

(35) Castanet, A.-S.; Colobert, F.; Broutin, P.-E.; Obringer, M. *Tetrahedron: Asymmetry* **2002**, *13*, 659−665.

(36) Ford, A.; Sinn, E.; Woodward, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 927−934.

(37) (a) Suzuki, K.; Seno, A.; Tanabe, H.; Ueno, K. *Synth. Met.* **2004**, *143*, 89−96. (b) Li, Z. H.; Wong, M. S.; Tao, Y.; D'Iorio, M. *J. Org. Chem.* **2004**, *69*, 921−92.

(38) Yoshikawa, S.; Odaira, J.; Kitamura, Y.; Bedekar, A. V.; Furuta, T.; Tanaka, K. *Tetrahedron* **2004**, 60, 2225−2234.

good to excellent yields (71−99%), demonstrating the generality of this synthetic methodology for the efficient preparation of 8-aryl-*β*-tetralones bearing different substitution at the aryl moiety at C-8.

Conclusions

We have reported two complementary strategies to synthesize 8-aryl-substituted 2-tetralones. When the 8-aryl groups bear a bulky ortho substituent or two ortho substitutents, the method of choice was based on the use of 1-aryl-7-methoxy naphthalenes **2** as precursors. Their selective Na−EtOH reductions occurred preferentially at the methoxy-substituted B ring to give a 1,4-dihydro-2-methoxy-8-arylnaphthalene derivative, which, after in situ acidic hydrolysis, gave rise to the corresponding 8-aryl-2-tetralones. The study of the Na−EtOH reduction of several 1-aryl-7-methoxynaphthalenes **2** has shown the influence of the different substitutions at the 1-aryl moiety on the ring selectivity of the process. The other route to 8-aryl-2-tetralones used a Suzuki coupling between triflate **4** and differently substituted aryl boronic acids as the key step to the targets. This strategy allowed us to prepare derivatives with phenyl rings at C-8 with no substituent at the ortho positions, as well as 2-tetralones bearing aryl groups at C-8 with more than one ring (naphthalene or anthracene moieties).

Experimental Section

General Procedure for the Addition of Aryl Grignard Reagents. Synthesis of 4-Aryl-6-methoxy-1,2-dihydronaphthalenes 8a−c. Method A. A solution of the corresponding commercially available aryl bromide (11.2 mmol, 2.6 equiv) in dry ethyl ether (9 mL) was added to magnesium turnings (177 mg, 7.3 mmol, 1.8 equiv) at 60 °C under argon. After the disappearance of all magnesium (ca. 3−7 h), the reaction was cooled to room temperature, and a solution of commercially available 7-methoxy-2-tetralone (**3**; 752 mg, 4.3 mmol) in dry ethyl ether (20 mL) was added. The reaction mixture was stirred for the time indicated in each case, quenched with NH_4Cl, and extracted with Et_2O. After workup, the residue was dissolved in 10 mL of CH_2Cl_2, and 35% HCl was slowly added at 0 °C until acidity was reached. The mixture was stirred for 30 min, extracted with CH_2Cl_2, and washed with sodium bicarbonate. After workup and flash chromatography, the corresponding pure 4-aryl-6-methoxy-1,2-dihydronaphthalene **8a−c** was obtained.

6-Methoxy-4-trifluoromethanesulfonyloxy-1,2-dihydronaphthalene (9). To a solution of commercially available 7-methoxy-1-tetralone (**3**; 1.50 g, 8.51 mmol) and *N*-phenyl-bis(trifluoromethanesulfonimide) (3.33 g, 9.36 mmol) in dry THF (80 mL) was slowly added a solution of 0.5 M KHMDS in THF (18.7 mL, 9.36 mmol) at −78 °C under argon. The mixture was stirred for 1.5 h and quenched with H_2O at −78 °C. After warming to room temperature, workup, and flash chromatography (eluent CH_2Cl_2/hexane 1:4), compound **9**[22] was obtained as a colorless oil, in 96% yield: ^{1}H NMR δ 2.48 (m, 2H), 2.80 (t, J = 8.1 Hz, 2H), 3.80 (s, 3H), 6.03 (t, J = 4.3 Hz, 1H), 6.80 (dd, J = 2.7 and 8.7 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 7.09 (d, J = 8.6 Hz, 1H); ^{13}C NMR δ 22.6, 25.8, 55.2, 107.1, 114.3, 118.3, 118.1 (q, J = 319 Hz), 128.1, 128.6, 129.5, 146.2, 158.6; MS (EI) *m*/*z* (%) 115 (29), 147 (81), 173 (22), 175 (66), 308 (M^+, 100); HRMS (EI) calcd for $C_{12}H_{11}O_4F_3S$ (M^+), 308.0330; found, 308.0323.

General Procedure for the Suzuki Coupling Reaction. Synthesis of 4-Aryl-6-methoxy-1,2-dihydronaphthalenes 8d−h. Method B. To a mixture of the corresponding arylboronic acid **10d−g** (3.5 mmol, 1.1 equiv), $Pd(PPh_3)_4$ (74 mg, 2% mol), and $Ba(OH)_2{\cdot}8H_2O$ (1.5 g, 4.8 mmol, 1.5 equiv) was added a solution of 6-methoxy-4-trifluoromethanesulfonyloxy-1,2-dihydronaphthalene (**9**; 1.0 g, 3.2 mmol) in DME (20 mL) and H_2O (4 mL). The reaction mixture was heated at 80 °C with vigorous stirring for the time indicated in each case, cooled to room temperature, and filtered over Celite. After extraction with CH_2Cl_2, workup, and flash chromatography, the corresponding pure 4-aryl-6-methoxy-1,2-dihydronaphthalene **8d−h** was obtained.

General Procedure for the Aromatization of Dihydronaphthalenes. Synthesis of 1-Aryl-7-methoxynaphthalenes 2a−h. Method C. To a solution of the corresponding 6-methoxy-4-aryl-1,2-dihydronaphthalene **8a−h** (2.6 mmol) in CH_2Cl_2 (50 mL) at room temperature was added DDQ (711 mg, 3.1 mmol, 1.2 equiv). The reaction mixture was stirred for 15 min and washed with a saturated aqueous solution of sodium bicarbonate. After workup and flash chromatography, pure 1-aryl-7-methoxynaphthalenes **2a−h** were obtained.

General Procedure for the Na−EtOH Reductions. Synthesis of 1-Aryl-7-methoxy-1,2,3,4-tetrahydronaphthalenes, 11a−h, and 8-Aryl-2-tetralones, 1c−h. Method D. To a solution of the corresponding 1-aryl-7-methoxynaphthalene **2a−h** (0.7 mmol) in EtOH (35 mL) heated at 100 °C, under argon, was added 6 or 7 pieces of Na of about 0.5 cm in length, and during the reaction time, the same amount of Na was maintained in the reaction media. The mixture was vigorously stirred at 100 °C for the time indicated in each case, quenched with EtOH, and cooled to room temperature. When the Na had completely disappeared, H_2O was slowly added, the mixture was cooled to 0 °C, and 35% HCl was added dropwise until acidity was reached. After extraction with CH_2Cl_2, washing with sodium bicarbonate, and workup, the corresponding mixture of 1-aryl-7-methoxy-1,2,3,4-tetrahydronaphthalenes, **11a−h**, and 8-aryl-2-tetralones, **1c−h**, were obtained, which were separated by flash chromatography.

8-Methoxy-2-[spiro-(1,3-dioxolyl)]tetralin (12)[32] In a two-necked round-bottom flask equipped with a stirring bar and a Dean−Stark trap, commercially available 8-methoxy-2-tetralone (**5**; 1.1 g, 6.3 mmol) and *p*-toluenesulfonic acid (1.8 mg) were added, and the mixture was purged with N_2. Then benzene (14 mL) and ethylene glycol (0.70 mL, 12.6 mmol) were added, and the mixture was refluxed for 4 h. The solution was cooled, poured into a solution of saturated aqueous sodium carbonate, and extracted with ether. After workup, the crude was filtered over silica gel to obtain compound **12** as a white solid in 99% yield: mp 96−96 °C (lit[32a] 124−125 °C, lit[32c] 51.5−52 °C); ^{1}H NMR δ 1.93 (t, J = 6.8 Hz, 2H), 2.87 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 3.8 (s, 3H), 4.03 (m, 4H), 6.65 (d, J = 8.1 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 7.10 (m, 1H); ^{13}C NMR δ 28.1, 31.5, 33.5, 55.2, 64.5, 107.0, 108.4, 120.7, 123.3, 126.4, 136.5, 157.3.

8-Hydroxy-2-[spiro-2-(1,3-dioxolyl)]tetralin (13). To a solution of diphenylphosphine (1.0 mL, 6 mmol) in THF (5.2 mL) was added a solution of 2.5 M *n*-butyllithium in hexane (2.3 mL, 5.8 mmol). The resulting red anion was stirred for 30 min, and a solution of compound **12** (870 mg, 3.9 mmol) in THF (10.3 mL) was added. The reaction mixture was refluxed for 24 h, cooled in an ice bath, and quenched with a saturated aqueous ammomium chloride solution. Ether was added and, after workup and flash chromatography (eluent AcOEt/hexane 1:5), compound **13** was obtained as a colorless oil in 77% yield: ^{1}H NMR δ 1.93 (t, J = 6.5 Hz, 2H), 2.87 (s, 2H), 2.98 (t, J = 6.5 Hz, 2H), 4.04 (m, 4H), 4.65 (s, 1H), 6.57 (d, J = 8.1 Hz, 1H), 6.72 (d, J = 8.1 Hz, 1H), 6.99 (t, J = 8.1 Hz, 1H); ^{13}C NMR δ 28.1, 31.6, 33.3, 64.5, 108.4, 112.0, 120.8, 121.4, 126.5, 137.0, 153.5; MS (EI) *m*/*z* (%) 91 (45), 105 (21), 120 (36), 134 (55), 162 (50), 206 (M^+, 100); HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+), 206.0943; found, 206.0943.

8-(Trifluoromethanesulfonyl)oxy-2-[spiro-2-(1,3-dioxolyl)]tetralin (4). To a solution of compound **13** (499 mg, 2.4 mmol) in CH_2Cl_2 (4 mL) and pyridine (2 mL) at 0 °C was added trifluoromethanesulfonic anhydride (884 mg, 0.52 mL, 3.1 mmol). The reaction mixture was stirred at 5 °C overnight and quenched by pouring into a cold saturated aqueous sodium carbonate solution. After workup and flash chromatography (eluent AcOEt/hexane 1:5),

compound **4** was obtained as a colorless oil in 90% yield: ^{1}H NMR δ 1.96 (t, J = 6.8 Hz, 2H), 2.99 (s, 2H), 3.05 (t, J = 6.8 Hz, 2H), 4.04 (m, 2H), 7.08−7.22 (m, 3H); ^{13}C NMR δ 29.1, 32.3, 34.7, 65.6, 108.3, 119.4, 119.6 (q, J = 319 Hz), 128.1, 129.0, 129.4, 140.0, 149.3; MS (EI) *m*/*z* (%) 91 (20), 105 (12), 119 (11), 133 (16), 161 (23), 205 (100), 338 (M^+, 27); HRMS (EI) calcd for $C_{12}H_{13}O_5SF_3$ (M^+), 338.0436; found, 338.0446.

General Procedure for the Suzuki Coupling Reactions. Synthesis of 8-Aryl-2-[spiro-2-(1,3-dioxolyl)]tetralins 14a and 14i−l. Method E. To a mixture of the corresponding arylboronic acid **10a** or **10i−l** (0.21 mmol, 2.4 equiv), $Pd(PPh_3)_4$ (10.4 mg, 10 mol %), and $Ba(OH)_2 \cdot 8H_2O$ (see each individual case) was added a solution of compound **4** (30 mg, 0.09 mmol, 1 equiv) in DME (1.5 mL). The reaction mixture was heated at 80 °C with vigorous stirring for the time indicated in each case, cooled to room temperature, and filtered over Celite. After extraction with CH_2Cl_2, workup, and flash chromatography, the corresponding pure compounds **14a** or **14i−l** were obtained.

General Procedure for the Deprotection of the Ketal Moiety. Synthesis of 8-Aryl-2-tetralones 1a and 1i−n. Method F. To a solution of the corresponding 8-aryl-2-[spiro-2-(1,3-dioxolyl)]-tetralin **14a** or **14i−n** (0.07 mmol, 1 equiv) in CH_2Cl_2 (1 mL) at 0 °C was added 35% HCl until pH = 1. The resulting mixture was stirred at room temperature for the time indicated in each case, and more CH_2Cl_2 was added. After workup and filtration over silica gel, the corresponding pure 8-aryl-2-tetralones **1a** or **1i−n** were obtained.

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Supporting Information Available: General experimental paragraph, experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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