Synthesis of 2′-Alkylspiro[2-X-cyclohexan-1,3′-3′*H*-indole] (X = H; X = CH_3) by an Unexpected Reaction between an Organomagnesium Halide and 2′-Methylspiro[2-X-cyclohexan-1,3′-3′*H*-indole]. X-ray Structure of a Fluorescent Dimeric Compound

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The reaction of 2′-methylspiro[cyclohexan-1,3′-3′*H*-indole] (**1a**) with methylmagnesium iodide gives 2′-ethyl-, 2′-isopropyl-, and 2′-*tert*-butylspiro[cyclohexan-1,3′-3′*H*-indole] as the unexpected 2′-methyl insertion products; their presence and ratio are dependent upon the reaction conditions. Influence of a methyl substituent in 2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (**1b**) on the reaction with methylmagnesium iodide has been analyzed; the 2′-ethyl (**2b**) and 2′-isopropyl (**3b**) derivatives were obtained as the insertion products together with a luminescent compound that was identified by X-ray diffraction analysis as *meso*-(1*R*,2*S*),(1*S*,2*R*)-α,*β*-di{(2′-(spiro[2-methylcyclohexan-1,3′-3′*H*-indolyl]}ethene (**10**). The reaction of **1a** or **1b** with some active organomagnesium halides (allyl or benzyl) afforded the 2′-methyl-2′-alkyl-3′*H*-indole derivative (allyl, **5a** or **5b**; benzyl, **6a**) as an apparent addition product. The reaction possibly occurs through a mechanism of radical intermediates.

Introduction

A family of the spiranic indole derivatives at position 3 with different substituents and variable steric size at position 2 has been synthesized, following the molecular modeling of some relevant natural alkaloids by their pharmacological properties. Some of these having the C-3 spiroindole structure have been isolated from plants such as gelsemine (from Gelsemium alkaloids) or aristoserratenine and tasmanine (from Aristotelia alkaloids),[1] or those with the C-2 spiroindole structure such as in aristotelone, a Φ-indoxyl derivative isomeric with tasmanine.[2] Moreover, some spirocarbolines such as (−)-roemeridine and its isomer roemerine have recently been isolated.[3]

The spiro-3*H*-indoles are of interest because of their unusual geometry and the inherent strain due to the spirocyclohexyl substituent on the reactivity of the C═N bond for the preparation of the corresponding indolines by addition of organometallic reagents.[4a,b]

The spiro tricyclic systems reported here were synthesized by the requirement of steric hindrance close to C-3 or C-2 in the indole ring as a partial structural construction which confers important dopaminergic or serotoninergic properties in the central nervous system.[5]

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(1) Rodríguez, J. G.; Urrutia, A.; Martín-Villamil, R. *Trends Heterocycl. Chem.* **1993**, *3*, 397 and references therein.
(2) (a) Manske, R. H. F. *The Alkaloids Chemistry and Physiology*; Academic Press: 1960; Vol. VII, p 153. (b) Brossi, A. *The Alkaloids*; Academic Press: 1985; Vol. XXIV, pp 113−151.
(3) Saxton, J. E. *Nat. Prod. Rep.* **1990**, 199.
(4) (a) Rodríguez, J. G.; Benito, Y.; Temprano, F. *Chem. Lett.* **1985**, 487. (b) Rodríguez, J. G.; Urrutia, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 665.
(5) Rodríguez, J. G.; et al. To be published.

Table 1. Influence of the Solvent in the Reaction of 1a with MeMgI

solvent	IMgMe (equiv)	**2a** (%)	**3a** (%)
diethyl ether	5	47	14
diethyl ether/THF (1:1)	5	52	
diethyl ether/THF (1:2)	5	60	
diethyl ether/THF (1:3)	10	68	
diethyl ether/THF (1:5)	10	79	
diethyl ether/toluene (1:1)	15		45
diethyl ether/toluene (2:1)	15		47
THF/toluene (3:1)	15	26	11

Results and Discussion

Synthesis of 2′-methylspiro[cyclohexan-1,3′-3′*H*-indole] **1a** was carried out by the Fischer reaction of the phenylhydrazone of cyclohexyl methyl ketone in acetic acid in good yield.

The reaction of the C═N bond in compound **1a** with different organometallic reagents was analyzed by using the reactive behavior of the C═N bond in spiro[cycloalkan-1,3′-3′*H*-indole] [4a] and in 4a-methyl-1,2,3,4-tetrahydro-4a*H*-carbazole[4b] as a reference.

In this way, the reaction of compound **1a** with organolithium reagents (*n*-butyl-, methyl-, phenyl-, or *tert*-butyllithium) in toluene afforded to the corresponding addition product in very low yield (about 5% by ^{1}H NMR). Moreover, the reaction of **1a** with the methylmagnesium iodide/cuprous chloride system in toluene [4a,b] gives some addition products in very low yield.

In contrast, compound **1a** and an excess of methylmagnesium iodide (5 equiv) in diethyl ether transform to a mixture of the unexpected 2′-ethyl **2a** and 2′-isopropyl **3a** derivatives by insertion of the Me group of the Grignard reagent into the 2′-methyl substituent (Table 1, Scheme 1).

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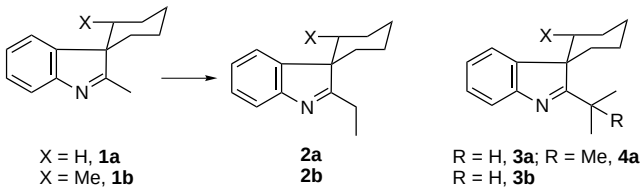
Scheme 1



An apparent insertion reaction was found in the reaction of 2,3,3-trimethyl-3*H*-indole with an excess of methylmagnesium iodide to give the 2-acetyl-3,3-dimethyl-3*H*-indole as the main product (22%) together with traces of 2-ethyl-3,3-dimethyl-3*H*-indole.[6]

The optimization of the yield for each of the products **2a** and **3a** in the reaction of **1a** with methylmagnesium iodide in different solvents has been analyzed. Thus, the reaction of **1a** with an excess of methylmagnesium iodide (10 equiv) in a mixture of 1:5 diethyl ether/THF gives only the 2'-ethyl derivative **2a** in good yield, while **1a** with an excess of methylmagnesium iodide (15 equiv) in a mixture of 2:1 diethyl ether/toluene gives the 2′-isopropyl derivative **3a** as the unique product in moderate yield (Table 1).

An important influence of the solvent in the reaction was observed. From Table 1, it can be seen that when the reaction was carried out in diethyl ether/THF, only the 2'-ethyl derivative **2a** was obtained. Moreover, the yield increases with increasing amounts of THF until a limit in the mixture of solvents is reached; for 1:5 diethyl ether/THF, the reaction reaches the maximum yield (79% after column chromatography). However, the same reaction does not take place when THF is used as the solvent. Moreover, in this reaction the use of toluene instead of THF in the mixture of solvents affords only the isopropyl derivative **3a** in moderate yield (45%) for 1:1 diethyl ether/toluene. The yield was practically unmodified by an increase in the diethyl ether amount (2:1) or reaction time, although after 72 h of reaction, the presence of another insertion product was observed and identified as the 2′-*tert*-butylspiro[cyclohexan-1,3′-3′*H*-indole] (**4a**, 5%). The reaction does not take place in pure toluene. However, methylmagnesium iodide transforms **1a** into a low-yield mixture of **2a** and **3a** in THF/toluene, Table 1.

The 2′-alkyl substituent in **3a** and **4a** shows a strong steric hindrance with the spirocyclohexyl group; by ^{1}H NMR the isopropyl (**3a**) and *tert*-butyl (**4a**) derivatives exhibit well-defined signals for the methyl groups which revealed a restricted rotation of these alkyl groups around C2′.

Unfortunately, the insertion reaction of the Grignard reagent was not of a general type for other organomagnesium reagents, because the same reaction of **1a** with ethyl-, propyl-, or *n*-butylmagnesium halides (having β-hydrogen atoms) in diethyl ether/THF fails and neither insertion or addition products were detected.

On the other hand, the reaction of **1a** with some more active organomagnesium reagents with an alkyl group without β-hydrogen atoms was analyzed. Thus, allylmagnesium bromide (5 equiv) in diethyl ether/toluene (1:1) gives only the addition product 2′-allyl-2′-methylspiro[cyclohexan-1,3'-3'*H*-indole] **5a** in excellent yield (91%) (Scheme 2).

(6) Jackson, A. H.; Smith, P. *J. Chem. Soc. C* **1968**, 1667.

Scheme 2

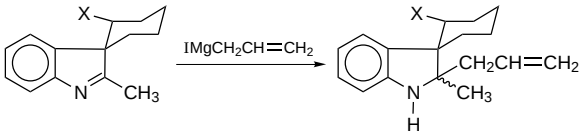
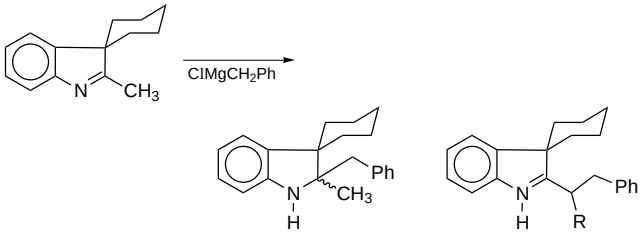


Table 2. Influence of the Solvent in the Reaction of 1a with $PhCH_2MgCl$



	yield (%)		
solvent	**6a**	**7a**	**8a**
diethyl ether	39		
THF		17	
diethyl ether/THF (1:1)	32	43	10
diethyl ether/toluene (1:1)	50		
diethyl ether/toluene (1:3)	62		
toluene	75		

In a comparative analysis, the reaction of **1a** with benzylmagnesium chloride gives a mixture of the addition (**6a**) and the insertion (**7a**) products in a variable ratio which was dependent upon the solvent, Table 2. Thus, in diethyl ether or toluene or their mixtures, only **6a** was isolated, while in THF or mixtures with diethyl ether, only **7a** was observed. Moreover, the double insertion product 2′-(dibenzylmethyl)spiro[cyclohexan-1,3′-3′*H*-indole] **8a** has occasionally been observed.

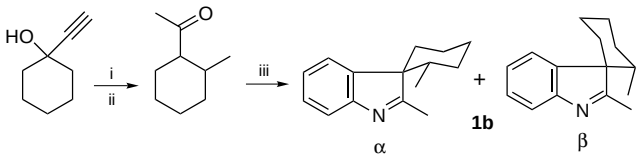
Afterward, the same reaction analysis with the Grignard reagents was carried out for the 2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] **1b** to verify the influence of the steric volume of the methyl substituent in the cyclohexane ring on the reactivity of the C=N double bond.

2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (1b). 2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] **1b** was synthesized starting from *trans*-1-acetyl-2-methylcyclohexane, which was prepared from the reaction of 1-ethynylcyclohexanol with aqueous formic acid, followed by treatment of the resulting 1-acetylcyclohexene[7] with lithium dimethylcuprate in diethyl ether, Scheme 3.

The *trans*-1-acetyl-2-methylcyclohexane was transformed into 2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] **1b** in good yield by treatment with phenylhydrazine hydrochloride in acetic acid (96%). The 3*H*-indole **1b** was characterized as a mixture of two isomers which was isolated by silica gel column chromatography. On the basis of the ^{1}H NMR signal of the 2-methyl substituent, these isomers were assigned as the racemates 1*R**,2*S** (α) and 1*R**,2*R** (β) in a 2:1 ratio, respectively, Scheme 3.

(7) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.

Scheme 3[a]



[a] i, HCO_2H (85%); ii, $(CH_3)_2CuLi$/diethyl ether; iii, $PhNHNH_2$·HCl/AcOH.

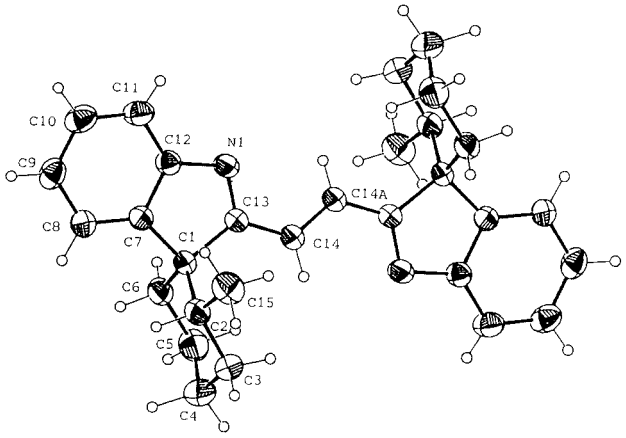


Figure 1. ORTEP view of the molecule. Thermal ellipsoids are shown at the 30% probability level.

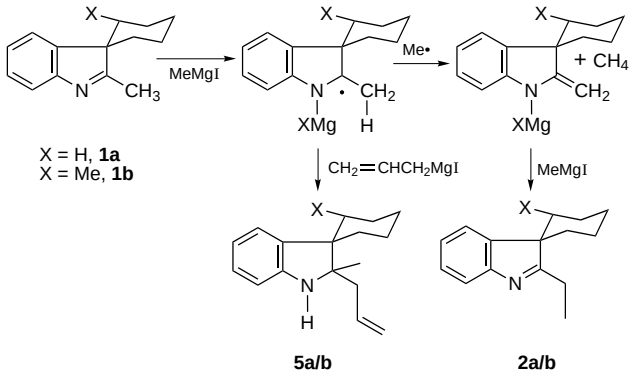
The stereochemistry of compound **1b** is related to the 2-methylcyclohexane ring configuration, a chair conformation, and to the relative position of the methyl group in an equatorial position. Thus, two chairs are possible: (i) that in the α-isomer, which is the more stable for the 2-methylcyclohexyl derivative in the *meso* structure of the dimer **10** (Figure 1), and (ii) that in the *β*-isomer, which is the more stable one in the absence of the 2-methyl substituent in the chromo tricarbonyl complex of **1a**,[8] Scheme 3.

The chair of the α-isomer of compound **10**, by ^{1}H NMR shows the equatorial 2-methyl group at 0.42 ppm as a doublet with a coupling constant of 6.6 Hz. The chair of the *β*-isomer shows the equatorial 2-methyl substituent at 0.27 ppm as a doublet with a coupling constant of 6.6 Hz. In both cases the equatorial methyl group suffers a strong shielding that is due to the anisotropic effect of the C=N group, because by saturation of this bond with lithium aluminum hydride,[5] the effect disappears (see also the frequency of the methyl group in **5b** isomers).

A comparative reaction of the 2′-methylspiro derivative **1b** with Grignard reagents was carried out to analyze the steric influence of a methyl substituent in position 2 of the cyclohexane ring on the C=N group. Thus, the 2′-ethylspiro derivative **2b** (1*R**,2*S** and 1*R**,2*R**, 2:1) was isolated in moderate yield (40%), by treatment of the diastereomeric mixture of **1b** with methylmagnesium iodide (10 equiv), in 1:5 diethyl ether/THF, after 24 h at room temperature; the reaction was incomplete and the starting product **1b** was also recovered (50%, as the diastereomeric mixture, 2:1). Moreover, in this reaction was also isolated luminescent product **10** in low yield (5%) as a crystalline yellow solid.

The 2′-isopropyl derivative **3b** (as the diastereomeric mixture of 1*R**,2*S** and 1*R**,2*R**, 2:1) was obtained by

Scheme 4



treatment of the diastereomeric mixture of **1b** with a solution of methylmagnesium iodide (10 equiv) in diethyl ether/toluene (1:1) in low yield (15%), after 5 days at room temperature. Moreover, in the same reaction, **2b** (1*R**,2*S** and 1*R**,2*R**, 2:1) was isolated in low yield (5%) while the starting compound **1b** was also recovered (70% as the diastereomeric mixture, 2:1).

In contrast, the reaction of the main isomer (1*R**,2*S**) of **1b** with allylmagnesium chloride (10 equiv) in diethyl ether/THF (1:1) gives only the addition product as a mixture of the diastereoisomers (1*R**,2*S**,2′*R**/1*R**,2*S**,2′*S**, 4:1) of 2′-allyl-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (**5b**, 54%), Scheme 2, X = Me. The stereochemistry of the two diastereomeric products of **5b** was determined by ^{1}H NMR; two signals for the 2- and 2′-methyl groups were observed at 0.89 and 0.71 as doublets and 1.43 and 1.25 ppm as singlets, respectively.

The reaction of methylmagnesium iodide to the 2′-methyl substituent has been analyzed by EPR spectroscopy. A solution of **1a** and methylmagnesium iodide, reproducing the experimental reaction parameters, was prepared in the resonance tube and introduced in the cavity at room temperature. The EPR spectrum exhibits a not well defined broad triplet (aN = 0.98 mT, g = 2.0244), which by comparison with structurally related radical spectra, agrees well with the radical on the 2′-carbon atom in compound **1a**.[9]

Then, the unexpected insertion reaction would occur through a radical intermediate on C-2′, initiated from the C−Mg radical cleavage of an organomagnesium salt on the nitrogen atom, which stabilizes the exocyclic double bond, by a *β* C−H cleavage. Thus, the insertion reaction would be the result of the attack of a new molecule of methylmagnesium iodide to the exocyclic double bond with elimination of the MgX radical and regeneration of the N=C double bond of the 3*H*-indole, Scheme 4. However, the same reaction with allylmagnesium chloride would give a *stable* allylic radical which couples with the radical on C-2′, giving the addition product **5a** (or **5b**) instead of the *β* C−H cleavage; alternative ionic mechanisms can be also considered.

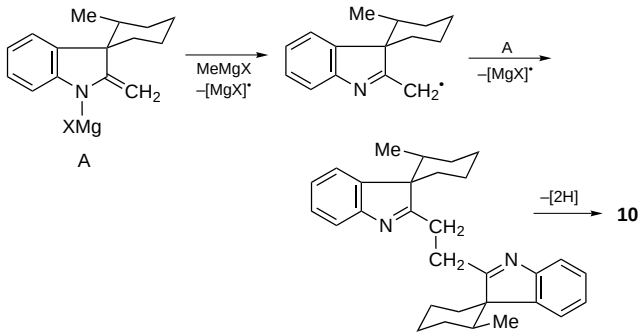
Compound **10** obtained from **1b** exhibits an efficient fluorescence radiation when compared to other conjugated indole derivatives.[10] By ^{1}H and ^{13}C NMR data, the compound shows an olefinic (129.8 ppm) spiroindole structure, and by IR, the compound exhibits a weak vibration tension band of the C=N group and the CH

(8) Rodríguez, J. G.; Urrutia, A.; Fonseca, I.; Sanz, J. *J. Organomet. Chem*. **1996**, *522*, 231.

(9) Rodríguez, J. G.; et al. To be published.

(10) Mateo, C. A.; Urrutia, A.; Rodríguez, J. G.; Fonseca, I.; Cano, F. H. *J. Org. Chem*. **1996**, *61*, 810.

Scheme 5



aromatic ortho-disubstitution band similar to that in compound **1b**. The mass spectrum shows a molecular peak at *m*/*z* 422, practically with twice the molecular mass of the 2′-methylspiro derivative **1b**.

Prismatic yellow crystals of compound **10** were obtained from a solution of dichloromethane, and thus, their structure was unambiguously determined by monocrystal X-ray diffraction analysis.

Molecular Structure of 10. The molecular structure of dimer **10** is shown in Figure 1 together with its numbering scheme. The molecular structure consists of two 1,3′-cyclohexane spiro-3′*H*-indole moieties internally related by a center of symmetry located on the double bond (C14−C14A). The configurations of the chiral centers C1 and C2 were established as *S* and *R* while C1A and C2A were *R* and *S*, respectively, with the centrosymmetric dimer being in the *meso* form.

In connection with Scheme 4, the conjugate dimeric structure of compound **10** (Figure 1) would probably be formed by addition of the methylene radical at the 2′ position to the intermediate salt A with elimination of the MgX radical and regeneration of the N═C bond of the 3*H*-indole (see Scheme 4) and successive hydrogen elimination, Scheme 5.

In general, the reaction of compound **1b** with methylmagnesium iodide gives the insertion products in lower yield than that with **1a**, and thus, the volume of the methyl substituent at the 2′ position of the spirocyclohexane ring decreases the kinetic energy and yield in the ethyl and the isopropyl products while it permits the formation of the dimer **10**.

Experimental Section

General Methods. Melting points were determined in open capillary tubes or on a hot stage microscope and are uncorrected. Nuclear magnetic resonance spectra were recorded at 200 MHz. Mass spectra were recorded using an electronic impact technique at 70 eV. X-ray data were recorded on an automatic four-circle diffractometer. All experiments were carried out in previously flame-dried round-bottom flasks or Schlenk tubes under an argon atmosphere and, in some cases, covered from the sunlight; solvents and chemicals were reagent grade.

2′-Methylspiro[cyclohexan-1,3′-3′*H*-indole] (1a). (a) Phenylhydrazone of the Cyclohexyl Methyl Ketone. In a round-bottom flask equipped with a Dean−Stark system were placed a solution of phenylhydrazine (2.73 mL, 27.74 mmol) and cyclohexyl methyl ketone (3.8 mL, 27.74 mmol) in toluene (55 mL). The mixture was heated at the reflux temperature to remove the water of the reaction azeotropically (above 5 h). Then, the solvent was removed and the phenylhydrazone of cyclohexyl methyl ketone was isolated as a yellow oil, 5.7 g, 95% yield.

(b) 2′-Methylspiro[cyclohexan-1,3′-3′*H*-indole]. A solution of the phenylhydrazone of cyclohexyl methyl ketone (5.7 g, 25.3 mmol) in acetic acid (96%, 50 mL) was heated at the reflux temperature for 3 h. The mixture was neutralized with sodium hydroxide (20%) (75 mL), extracted with dichloromethane (50 mL), and dried with magnesium sulfate. After filtration the solvent was removed and the residual brown oil was purified by silica gel column chromatography under pressure, using 1:1 hexane/ethyl acetate to give **1a** as a yellow-orange solid, mp 43−4 °C, 4.53 g, 82% yield. IR (film): 1590, 1580, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.72 (dd, 1H, J = 7.3 and 0.8 Hz), 7.57 (d, 1H, J = 7.5 Hz), 7.33 (td, 1H, J = 7.5 and 1.4 Hz), 7.17 (td, 1H, J = 7.4 and 1.3 Hz), 2.29 (s, 3H), 1.7−2.0 (m, 8H), 1.2−1.6 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 187.1, 153.8, 144.1, 127.0, 123.7, 119.6, 57.3, 30.6, 25.1, 21.1, 15.6. Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.07; H, 8.48; N, 6.65.

2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (1b). (a) 1-Acetylcyclohexene was prepared from 1-ethynyl-1-cyclohexanol by following a previously described method.[7]

(b) 1-Acetyl-2-methylcyclohexane. To a solution of Me_2-CuLi, prepared with methyllithium, 81.9 mL (1.6 M in diethyl ether, 131 mmol), and copper(I) iodide 90 mL (0.87 M in dry diethyl ether, 78.6 mmol), was added at −78 °C a solution of 1-acetylcyclohexene (6.5 g, 52.4 mmol) in dry diethyl ether (10 mL). The mixture was stirred between −5 and 10 °C for 10 min and then was hydrolyzed with a saturated aqueous solution of ammonium chloride (100 mL) at room temperature for 1 h, extracted with diethyl ether (100 mL), and dried with magnesium sulfate. After filtration, solvent was evaporated and the residual oil was purified by silica gel column chromatography using 1:6 ethyl acetate/hexane as the eluent. The *trans*-1-acetyl-2-methylcyclohexane was isolated as a yellow oil, bp 64−65 °C,[11] 6.09 g, 83% of yield.

***trans*-1-Acetyl-2-methylcyclohexane.** IR (KBr): 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.46 (m, 1H), 2.25 (m, 1H), 2.04 (s, 3H), 1.0−1.9 (br m, 8H), 0.81 (d, 3H, J = 7.1 Hz).

(c) 2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (1b). A solution of *trans*-1-acetyl-2-methylcyclohexane (0.12 g, 0.86 mmol) and phenylhydrazine hydrochloride (0.12 g, 0.86 mmol) in acetic acid (96%, 6 mL) was warmed at 110 °C for 3 h and at room temperature for 12 h. The mixture was neutralized with sodium hydroxide (20%, 10 mL) and then extracted with dichloromethane (10 mL) and dried with anhydrous magnesium sulfate. After filtration the solvent was evaporated under reduced pressure to give a brown oil which was purified by silica gel column chromatography using 1:4 ethyl acetate/hexane as the eluent. A fraction was obtained as a brown oil, 0.14 g, 78% yield, as a racemic mixture of (1*R**,2*S**)- and (1*R**,2*R**)-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole], in 2:1 ratio (by ^1H NMR).

The diastereomeric mixture was isolated by silica gel column chromatography using 1:5 hexane:diethyl ether as the eluent. The main product (enantiomeric mixture 1*R**,2*S**) was an orange solid, mp 50−52 °C, while the 1*R**,2*R** product was isolated as a red oil.

(1*R,2*S**)-2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole].** IR (film): 1700, 1560, 750, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.50 (d, 1H, J = 7.5 Hz), 7.1−7.3 (m, 3H), 2.49 (s, 3H), 1.4−2.1 (m, 9H), 0.38 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 185.7, 152.9, 145.7, 127.1, 125.0, 120.4, 118.9, 61.4, 37.4, 33.1, 30.0, 25.5, 23.0, 21.8, 15.9. MS (70 eV): *m*/*z* 213 (M^+, 100); 198 (95); 184 (40); 170 (43); 156 (19); 144 (72); 130 (22); 115 (35). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.22; H, 8.75; N, 6.40.

(1*R,2*R**)-2′-Methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole].** IR (film): 1700, 1580, 780, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.62 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.8 Hz), 7.54 (d, 1H, J = 7.4 Hz), 7.34 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 7.5 Hz, J_3 = 1.3 Hz), 7.17 (ddd, 1H, J_1 = 7.7 Hz, J_2 = 7.5 Hz, J_3 = 1.2 Hz), 2.24 (s, 3H), 1.3−2.0 (m, 7H), 1.25 (m, 2H), 0.27 (d, 3H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 187.1, 154.4, 141.1, 127.2, 124.4,

(11) Turner, R. B. *J. Am. Chem. Soc.* **1950**, *72*, 878.

123.9, 119.6, 62.4, 35.3, 32.2, 29.7, 25.6, 23.0, 21.0, 15.3. MS (70 eV): *m*/*z* 213 (M^+, 100); 198 (95); 184 (40); 170 (43); 156 (19); 144 (72); 130 (22); 115 (35). Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.12; H, 8.56; N, 6.25.

Reaction of 2′-Methylspiro[cyclohexan-1,3′-3′*H*-indole] (1a) with methylmagnesium iodide (2a, 3a, 4a). (a) 2′-Ethylspiro[cyclohexan-1,3′-3′*H*-indole], 2a. To a solution of methylmagnesium iodide (25 mmol) in anhydrous diethyl ether (7 mL) was added dropwise at 0 °C a solution of **1a** (500 mg, 2.5 mmol) in THF (35 mL). The flask was covered from the sunlight, and the mixture was stirred at 0 °C for 4 h and then hydrolyzed with a saturated aqueous solution of ammonium chloride (30 mL), extracted with dichloromethane (50 mL), and dried with Na_2SO_4. The solvent was removed, and the residual brown oil was purified by silica gel column chromatography using 1:5 ethyl acetate/hexane as the eluent. The title compound **2a** was isolated as a yellow solid, mp 105−7 °C, 420 mg, 79% yield. IR (film): 2920, 2860, 1670, 1570, 1450, 1350, 750 cm^{-1}. ^1H NMR: δ 7.62 (d, 1H, J = 6.5 Hz), 7.35 (t, 1H, J = 6.5 Hz), 7.32 (d, 1H, J = 8.2 Hz), 7.18 (t, 1H, J = 8.1 Hz), 2.60 (q, 2H, J = 7.3 Hz), 1.5−2.2 (m, 8H), 1.35 (t, 3H, J = 7.3 Hz), 1.25 (m, 2H). ^{13}C NMR: δ 191.3, 154.2, 144.4, 127.2, 124.0, 123.9, 120.0, 57.8, 30.9, 25.1, 21.4, 22.0, 10.8. Anal. Calcd for $C_{15}H_{14}N$: C, 86.50; H, 6.78; N, 6.72. Found: C, 86.24; H, 6.48; N, 6.35.

(b) 2′-Isopropylspiro[cyclohexan-1,3′-3′*H*-indole] (3a) and 2′-*tert*-butylspiro[cyclohexan-1,3′-3′*H*-indole] (4a). To a solution of methylmagnesium iodide (37.7 mmol) in anhydrous diethyl ether (40 mL) was added dropwise at 0 °C a solution of **1a** (500 mg, 2.5 mmol) in anhydrous toluene (20 mL). The flask was covered from the sunlight, and the mixture was stirred at room temperature for 60 h and then hydrolyzed with a saturated aqueous ammonium chloride solution (30 mL), extracted with dichloromethane (50 mL), and dried with Na_2SO_4. The solvent was removed, and the residual brown oil was purified by column chromatography using 1:3 ethyl acetate/hexane as the eluent. The title compound **3a** was obtained as an orange solid, mp 75−77 °C, 270 mg, 47% of yield. The 2′-*tert*-butyl derivative **4a** was also isolated as a yellow oil, 30.8 mg (5%).

Compound 3a. ^1H NMR: δ 7.71 (d, 1H, J = 7.5 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.33 (td, 1H, J_1 = 7.4, J_2 = 1.1 Hz), 7.15 (td, 1H, J_1 = 7.4, J_2 = 1.1 Hz), 2.97 (sept, 1H, J = 6.8 Hz), 2.1−1.8 (m, 10H), 1.30 (d, 6H, J = 6.8 Hz). ^{13}C NMR: δ 195.6, 154.5, 143.8, 127.3, 124.1, 124.0, 120.1, 58.4, 29.9, 27.5, 25.2, 22.1, 22.0. IR (film): 2920, 1630, 1590, 740 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N$: C, 84.52; H, 9.31; N, 6.16. Found: C, 84.25; H, 8.96; N, 6.35.

Compound 4a. ^1H NMR: δ 7.72 (d, 1H, J = 7.5 Hz), 7.58 (d, 1H, J = 7.6 Hz), 7.32 (td, 1H, J_1 = 7.6, J_2 = 0.8 Hz), 7.14 (td, 1H, J_1 = 7.5, J_2 = 0.8 Hz), 2.41 (td, 2H, J_1 = 12.98, J_2 = 4.7 Hz), 1.48 (s, 9H), 2.1−1.2 (m, 8H). MS (70 eV): *m*/*z* 241 (M^+, 11), 226 (12), 184 (100), 156 (46), 143 (13), 130 (16), 57 (6). Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.37; H, 9.26; N, 5.55.

2′-Ethylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (2b). In a round-bottom flask previously flamed, in argon atmosphere, and covered from the sunlight was prepared a solution of methylmagnesium iodide (6.04 mmol) in dry THF (60 mL). To this solution was slowly added **1b** (as the diastereomeric pair 1*R**,2*S** and 1*R**,2*R**) (0.13 g, 0.6 mmol) in diethyl ether (12 mL). The mixture was stirred at room temperature overnight and then was hydrolyzed with a saturated aqueous ammonium chloride solution (100 mL), extracted with dichloromethane (50 mL), and dried on anhydrous magnesium sulfate. After filtration the solvent was removed at reduced pressure, giving a residual oil which was purified by silica gel column chromatography using 1:4 ethyl acetate/hexane as the eluent. Compound **2b** was obtained as a red oil, 0.053 g, 40% yield, as a 2:1 diastereomeric mixture. Moreover, luminescent product **10** was isolated as a yellow solid, mp 99−102 °C, 13 mg (5%), which was identified unambiguously as the *meso*-α,β-di{(1*R*,2*S*),(1*S*,2*R*)-2′-(spiro[2-methylcyclohexan-1,3′-3′*H*-indolyl]}ethene. Starting product **1b** was also recovered, 0.065 g (50%, 1*R**,2*S** and 1*R**,2*R**, in 2/1 ratio).

(1*R,2*S**)-2′-Ethylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (2b).** IR (film): 1690, 1570, 785, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.52 (d, 1H, J = 7.1 Hz), 7.3−7.1 (m, 3H), 2.74 (q, 1H, J = 7.0 Hz), 2.70 (q, 1H, J = 7.5 Hz), 2.1−1.4 (m, 9H), 1.38 (dd, 3H, J_1 = 7.5 Hz, J_2 = 7.0 Hz), 0.35 (d, 3H, J = 6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 189.9, 153.5, 147.5, 127.1, 124.9, 121.4, 120.5, 61.6, 37.7, 33.2, 30.3, 25.6, 22.1, 21.4, 16.1, 10.8. MS (70 eV): *m*/*z* 227 (M^+, 45), 212 (34), 198 (100), 184 (43), 170 (45), 156 (44), 144 (25), 130 (58), 115 (29). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.23; H, 9.44; N, 5.85.

(1*R,2*R**)-2′-Ethylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (2b).** IR (film): 1680, 1570, 780, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.61 (d, 1H, J = 7.4 Hz), 7.60 (d, 1H, J = 7.5 Hz), 7.33 (ddd, 1H, J_1 = 7.6 Hz, J_2 = 7.4 Hz, J_3 = 1.4 Hz), 7.17 (ddd, 1H, J_1 = 7.5 Hz, J_2 = 7.4 Hz, J_3 = 1.3 Hz), 2.54 (q, 1H, J = 7.4 Hz), 2.51 (q, 1H, J = 7.3 Hz), 2.1−1.4 (m, 5H), 1.37 (t, 3H, J = 7.3 Hz), 1.25 (m, 2H), 0.93 (m, 2H), 0.26 (d, 3H, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$): δ 192.8, 148.2, 142.7, 127.3, 124.6, 121.0, 120.1, 63.6, 35.5, 32.4, 30.1, 25.9, 21.8, 21.3, 16.3, 10.6. MS (70 eV): *m*/*z* 227 (M^+, 45), 212 (34), 198 (100), 184 (43), 170 (45), 156 (44), 144 (25), 130 (58), 115 (29). Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.21; H, 9.47; N, 5.87.

***Meso*-α,β-di{(1*R*,2*S*),(1*S*,2*R*)}-2′-(spiro[2-methylcyclohexan-1,3′-3′*H*-indolyl]ethene) (10).** IR (KBr): 1690, 1600, 770, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.85 (s, 2H), 7.65 (d, 2H, J = 7.0 Hz), 7.4−7.2 (m, 6H), 2.1−1.5 (m, 18H), 0.42 (d, 6H, J = 6.6 Hz).^{13}C NMR ($CDCl_3$): δ 181.6, 154.3, 146.8, 129.8, 127.6, 126.1, 120.9, 120.8, 61.5, 38.3, 34.0, 31.1, 26.0, 22.9, 16.3. MS (70 eV): *m*/*z* 422 (M^+, 100), 407 (33), 393 (6), 379 (38), 365 (28), 351 (11), 339 (45), 211 (17), 180 (13), 168 (15), 154 (13), 141 (31). Anal. Calcd for $C_{30}H_{34}N_2$: C, 85.26; H, 8.11; N, 6.63. Found: C, 84.92; H, 8.34; N, 6.55.

2′-Isopropylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (3b). In a round-bottom flask previously flamed and in argon atmosphere was prepared a solution of methylmagnesium iodide (14.8 mmol) in diethyl ether (30 mL). On this solution was slowly added a solution of **1b** (211 mg, 0.99 mmol) in dry toluene (30 mL). The mixture was vigorously stirred at room temperature for 5 days and then was hydrolyzed with a saturated aqueous solution of ammonium chloride (15 mL), extracted with dichloromethane (20 mL), and dried on anhydrous magnesium sulfate.

After filtration the solvent was removed at reduced pressure, giving a residual oil, which was purified by silica gel column chromatography using 1:4 ethyl acetate/hexane as the eluent. The title compound **3b** was obtained as a red oil, 34.5 mg (15%), as a diastereomeric mixture (1*R**,2*S** and 1*R**,2*R**, in 2:1 ratio) which was isolated by silica gel column chromatography using 1:5 hexane/diethyl ether as the eluent. The 2′-methylspiro derivative **2b** was also isolated, 10.83 mg (5%).

(1*R,2*S**)-2′-Isopropylspiro[2-methylcyclohexan-1,3′-3′*H*-indole], 3b.** IR (film): 1680, 1600, 775, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.58 (m, 1H), 7.4−7.1 (m, 3H), 3.25 (sept, 1H, J = 7.0 Hz), 2.1−1.4 (m, 9H), 1.39 (d, 3H, J = 6.5 Hz), 1.29 (d, 3H, J = 6.5 Hz), 0.39 (d, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$): δ 194.9, 153.9, 145.4, 127.0, 125.0, 124.0, 119.4, 62.1, 38.7, 33.4, 30.3, 29.6, 25.9, 22.8, 21.4, 16.9. MS (70 eV): *m*/*z* 241 (M^+, 41), 226 (28), 212 (7), 198 (100), 184 (27), 170 (38), 156 (20), 144 (13), 130 (25), 115 (17). Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.27; H, 9.38; N, 5.66.

(1*R,2*R**)-2′-Isopropylspiro[2-methylcyclohexan-1,3′-3′*H*-indole], 3b.** IR (film): 1680, 1600, 775, 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.58 (m, 1H), 7.4−7.1 (m, 3H), 2.93 (sept, 1H, J = 6.5 Hz), 2.1−1.4 (m, 9H), 1.38 (d, 3H, J = 6.5 Hz), 1.24 (d, 3H, J = 6.5 Hz), 0.28 (d, 3H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$): δ 192.3 (C-2′), 155.5, 141.0, 127.3, 124.4, 122.1, 120.5, 64.6, 34.2, 32.5, 30.2, 29.0, 25.8, 22.4, 20.8, 16.5. MS (70 eV): *m*/*z* 241 (M^+, 41), 226 (28), 212 (7), 198 (100), 184 (27), 170 (38), 156 (20), 144 (13), 130 (25), 115 (17). Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.25; H, 9.35; N, 5.45.

2′-Allyl-2′-methylspiro[cyclohexan-1,3′-3′*H*-indole], 5a. To a solution of allylmagnesium chloride (6.04 mmol) in

anhydrous diethyl ether (10 mL) was added dropwise a solution of **1a** (1 g, 5 mmol) in anhydrous toluene (30 mL). The reaction mixture was stirred at room temperature for 5 h and then hydrolyzed with a saturated aqueous ammonium chloride solution (60 mL) and extracted with dichloromethane (70 mL). The solvent was removed, and the residual brown oil was purified by silica gel column chromatography using toluene as the eluent. The title compound **5a** was obtained as a transparent oil, 732 mg, 91% yield (hydrochloride, mp 202−4 °C). IR (film): 3360, 1605, 745, 750, 710 cm^{-1}. ^1H NMR: δ 7.45 (dd, 1H, J = 7.4 and 1.2 Hz), 7.3 (m, 4H), 7.05 (m, 2H), 6.73 (td, 1H, J = 7.5 and 1.1 Hz), 6.59 (d, 1H, J = 7.7 Hz), 3.65 (s br, 1H), 2.7 (AB system, 2H), 2.0−1.2 (m, 10H), 1.05 (s, 3H). ^{13}C NMR: δ 148.7, 138.3, 137.2, 130.6, 128.1, 127.0, 126.2, 126.0, 117.7, 109.2, 68.9, 50.0, 40.1, 31.8, 29.7, 26.1, 23.0, 22.4, 19.2. Anal. Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.25; H, 9.35; N, 5.45.

2′-Allyl-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole], 5b. In a round-bottom flask previously flamed under an argon atmosphere was prepared a solution of allylmagnesium iodide (6.04 mmol) in dry diethyl ether (3 mL). On this solution was slowly added a solution of (1*R**,2*S**)-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole] (**1b**) (0.69 mmol) in dry toluene (3 mL), and the mixture was vigorously stirred at room temperature for 5 h. Then, the solution was hydrolyzed with an aqueous saturated ammonium chloride solution (10 mL), extracted with dichloromethane (10 mL), and dried with anhydrous magnesium sulfate. After filtration the solvent was removed at reduced pressure, giving a residual oil, which was purified by silica gel column chromatography using 1:4 ethyl acetate/hexane as the eluent. Compound **5b** was obtained as a 4:1 diastereomeric mixture, as yellow solids, mp 44−47 and 55−58 °C, 0.14 g, 54% yield. The starting product was recovered in 7% yield.

(1*R,2*S**,2′*R**)/(1*R**,2*S**,2′*S**)-2′-Allyl-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole].** IR (film): 3350, 1630, 1600, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (d, 1H, J = 7.0 Hz), 6.99 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.0 Hz), 6.71 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz), 6.51 (d, 1H, J = 7.0 Hz), 5.84 (m, 1H), 5.16 (dd, 1H, J_1 = 10.2 Hz, J_2 = 2.3 Hz), 4.96 (dd, 1H, J_1 = 16.4 Hz, J_2 = 1.6 Hz), 3.92 (s, 1H), 2.2−1.1 (m, 11H), 1.43 (s, 3H), 0.89 (d, 3H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 149.1, 137.5, 134.4, 127.0, 123.1, 119.6, 118.1, 108.6, 67.8, 52.6, 43.7, 41.8, 31.5, 30.9, 26.0, 22.9, 22.4, 17.6. MS (70 eV): m/z 255 (M^+, 2), 240 (2), 214 (100), 198 (14), 184 (10), 170 (13), 156 (8), 144 (92), 130 (10), 115 (9). Anal. Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.33; H, 9.54; N, 5.28.

(1*R,2*R**,2′*R**)/(1*R**,2*R**,2′*S**)-2′-Allyl-2′-methylspiro[2-methylcyclohexan-1,3′-3′*H*-indole].** IR (film): 3350, 1630, 1600, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (d, 1H, J = 7.0 Hz), 6.99 (dd, 1H, J_1 = 7.8 Hz, J_2 = 7.0 Hz), 6.71 (ddd, 1H, J_1 = 7.8 Hz, J_2 = 7.0 Hz, J_3 = 1.6 Hz), 6.51 (d, 1H, J = 7.0 Hz), 5.84 (m, 1H), 5.04 (m, 1H), 4.89 (m, 1H), 3.92 (s, 1H), 2.1−1.2 (m, 11H), 1.25 (s, 3H), 0.71 (d, 3H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$): δ 149.1, 138.2, 134.7, 126.3, 123.1, 119.6, 117.5, 109.0, 69.0, 52.1, 43.7, 40.6, 31.2, 30.6, 29.6, 23.6, 22.9, 18.1. MS (70 eV): m/z 255 (M^+, 2), 240 (2), 214 (100), 198 (14), 184 (10), 170 (13), 156 (8), 144 (92), 130 (10), 115 (9). Anal. Calcd for $C_{18}H_{25}N$: C, 84.65; H, 9.87; N, 5.48. Found: C, 84.60; H, 9.59; N, 5.32.

2′-Benzyl-2′-methylspiro[cyclohexan-1,3′-3′*H*-indole], 6a. (a) In Diethyl Ether/Toluene. To a solution of benzylmagnesium chloride (25.1 mmol) in anhydrous diethyl ether (10 mL) was added dropwise a solution of **1a** (1 g, 5 mmol) in anhydrous toluene (30 mL). The mixture was stirred at room temperature for 5 h and then hydrolyzed with a saturated aqueous ammonium chloride solution (60 mL) and extracted with dichloromethane (70 mL). The solvent was removed, and the residual brown oil was purified by silica gel column chromatography using toluene as the eluent. Compound **6a** was obtained as a transparent oil (hydrochloride, mp 202−4 °C), 0.951 g, 65% of yield. IR (film): 3360, 1605, 750, 745, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.45 (dd, 1H, J = 7.4 and 1.2 Hz), 7.30 (m, 4H), 7.05 (m, 2H), 6.73 (td, 1H, J = 7.5; 1,1 Hz), 6.59 (d, 1H, J = 7.7 Hz), 3.65 (s br, 1H), 2.70 (AB system, 2H), 2.0−1.2 (m, 10H), 1.05 (s, 3H). ^{13}C NMR: δ 148.7, 138.30, 137.2, 130.6, 128.1, 127.0, 126.2, 126.0, 117.7, 109.2, 68.9, 50.0, 40.1, 31.8, 29.7, 26.1, 23.0, 22.4, 19.2. Anal. Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.29; H, 8.35; N, 4.78.

(b) In Diethyl Ether/THF. To a solution of benzylmagnesium chloride (6.3 mmol) in anhydrous diethyl ether (6 mL) was added dropwise a solution of 2′-methylspiro[cyclohexan-1,3′-3′*H*-indole] (250 mg, 1.26 mmol) in anhydrous tetrahydrofuran (6 mL). The mixture was stirred at room temperature for 24 h and then hydrolyzed with an aqueous saturated ammonium chloride solution (20 mL), extracted with dichloromethane (20 mL), and dried on sodium sulfate. The solvent was removed, and the residual brown oil (420 mg) was purified by silica gel column chromatography using 5:1 hexane/ethyl acetate as the eluent. Three reaction products were isolated and identified: compound **6a** as a transparent oil (hydrochloride, mp 202−4 °C), 120 mg, 32%; the 2′-phenethyl derivative **7a** as a transparent oil (hydrochloride, mp 228−230 °C dec**,** 158 mg, 43%; and the 2′-(dibenzylmethyl) derivative **8a** as a colorless oil, 49 mg, 10%.

2′-Phenethylspiro[cyclohexan-1,3′-3′*H*-indole], 7a. ^1H NMR ($CDCl_3$): 7.70 (m, 2H), 7,5−7,2 (m, 7H), 3.20 (t, 2H, J = 8,2 Hz), 2.82 (t, 2H, J = 8,2 Hz), 2.0−1.2 (m, 10H). Anal. Calcd for $C_{21}H_{23}N$: C, 87.15; H, 8.01; N, 4.84. Found: C, 86.89; H, 8.15; N, 4.65.

2′-(Dibenzylmethyl)spiro[cyclohexan-1,3′-3′*H*-indole], 8a. ^1H NMR ($CDCl_3$): δ 7.8−7.6 (m, 4H), 7.5−7.1 (m, 10H), 4.05 (quintuplet, 1H, J = 7.3 Hz), 3.2−2.8 (m, 4H), 2.0−1.0 (m, 10H). Anal. Calcd for $C_{28}H_{29}N$: C, 88.61; H, 7.70; N, 3.69. Found: C, 88.34; H, 7.75; N, 3.35.

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Supporting Information Available: Experimental and X-ray crystal analysis details of **10** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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