m/e 445.2073, found 445.2099.

3,6-Dihydro-2*H*-6-methoxy-*N*-(3-hydroxyphenyl)-1,2-oxazine (19). To a stirred solution of **18** (314 mg, 0.7 mmol) in 2 mL of dry THF was added TBAF (0.74 mL, 0.74 mmol) as a 1 M solution in THF at 0 °C under a N_2 atmosphere. After being stirred for 5 min the brown reaction mixture was poured in saturated aqueous NH_4Cl and extracted several times with EtOAc, and the combined extracts were dried over $MgSO_4$. Concentration of the organic extracts and purification by flash column chromatography (7:3 Et_2O/hex) gave 140 mg of (95%) **22** as a colorless oil: IR ($CHCl_3$) 3350 (s), 1610 (s), 1500 (s), 1200 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.58 (s, 3 H), 3.61 (dd, 1 H, J = 12.7, 1.7 Hz), 3.89 (dd, 1 H, J = 12.7, 4.9 Hz), 5.12 (br s, 1 H), 5.51 (br s, 1 H), 5.94 (br d, 1 H, J = 10 Hz), 6.13 (ddd, 1 H, J = 10, 4.9, 1.7 Hz), 6.47 (dd, 1 H, J = 8.1, 1.5 Hz), 6.66–6.72 (m, 2 H), 7.14 (t, 1 H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 51.32, 55.75, 98.64, 103.19, 107.78, 109.72, 124.19, 127.73, 129.66, 151.52, 156.44; MS *m/z* (M^+) 207 (66), 84 (100); high-resolution MS calcd for $C_{11}H_{13}NO_3$ *m/e* 207.0895, found 207.0891.

4-Methoxy-5-(1*H*-pyrrol-1-yl)phenol (23). To a stirred solution of **19** (45 mg, 0.22 mmol) in MeOH (35 μL, 0.87 mmol) and 2 mL of dry CH_2Cl_2 was added BF_3-Et_2O (29 μL, 0.24 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for an additional hour before diluting with CH_2Cl_2 and quenching with saturated aqueous $NaHCO_3$. The resulting mixture was decanted from the insoluble black polymeric material coating the reaction vessel and extracted with 2 × 6 mL of CH_2Cl_2. The extracts were washed with 1 × 6 mL of $NaHCO_3$, dried ($MgSO_4$), and concentrated to give 20 mg of a brown oil. Purification by flash column chromatography (4:6 Et_2O/hex) gave 9 mg (20%) of **23** as a colorless foam: IR ($CHCl_3$) 3540 (m), 1520 (s), cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.92 (s, 3 H), 5.72 (s, 1 H), 6.31 (t, 2 H), 6.87 (d, 2 H), 7.00 (m, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 56.25, 107.99, 109.89, 111.10, 112.05, 119.59, 135.18, 144.66, 146.25; MS *m/z* (M^+) 189 (100), 174 (36), 146 (28); high-resolution MS calcd for $C_{11}H_{11}NO_2$ *m/e* 189.0789, found 189.0801; NOE, irradiation of the methyl ether protons at δ 3.92 gave a 9% enhancement of the downfield pyrrole protons at δ 7.00.

3,6-Dihydro-2*H*-6-methoxy-*N*-(3-carbomethoxy-5-methoxy-6-methylphenyl)-1,2-oxazine (22). To a stirred solution of amine **20** (0.55 g, 2.83 mmol) in 8 mL of CH_2Cl_2 at −23 °C (CCl_4/CO_2) was added Me_2S (212 μL, 2.88 mmol) under a N_2 atmosphere. A solution of NCS (0.39 g, 2.90 mmol) in 22 mL of CH_2Cl_2 was then added dropwise via cannula over ca. 10 min. The reaction was stirred for an additional 40 min (−23 °C) after which 11 mL of 5% NaOH was added. The organic layer was then removed, washed with 11 mL of 5% NaOH, and dried over Na_2SO_4. The crude dry filtrate was then poured into an ice-cold solution of 80–85% MCPBA (0.74, 3.5 mmol) in 15 mL of CH_2Cl_2. The resulting green solution was stirred for 30 min at 0 °C, poured into saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with Na_2CO_3, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in 15 mL of CH_2Cl_2 and cooled to 0 °C under a N_2 atmosphere. To this stirred solution was added (0.37 mL, 3.7 mmol) of diene **17**. Stirring was discontinued, and the reaction mixture was placed in the refrigerator overnight. The reaction was then concentrated in vacuo, and the residue (~1 g) was purified by flash column chromatography (25:75 Et_2O/hex) to yield 370 mg (45%) of light yellow solid: mp 103–105 °C; IR ($CHCl_3$) 1715 (s), 1585 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.27 (s, 2 H), 3.44 (s, 3 H), 3.57 (m, 2 H), 3.89 (s, 3 H), 3.92 (s, 3 H), 5.12 (br s, 1 H), 5.91 (br d, 1 H, J = 10 Hz), 6.17 (br d, 1 H, J = 110 Hz), 7.40 (br s, 1 H), 7.84 (br s, 1 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 10.54, 51.74, 52.92, 55.42, 55.62, 99.08, 108.24, 113.96, 124.93, 126.84, 127.96, 128.52, 149.47, 157.90, 166.72; MS *m/e* (M^+) 293 (10), 235 (24), 84 (100); high-resolution MS calcd for $C_{15}H_{19}NO_5$ *m/e* 293.1263, found 293.1271. Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.47; H, 6.54; N, 4.72.

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Metalation of Cyclopropane Rings: A Novel Trilithiation of a Biscyclopropyl Carbinol

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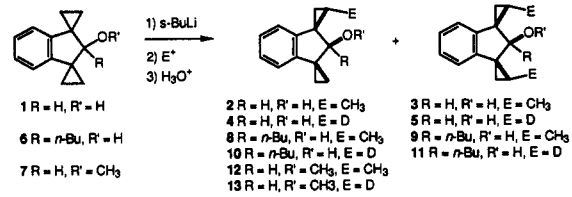
In conjunction with syntheses of systems for radical double clock experiments, we needed a number of ring-substituted biscyclopropylcarbinyl derivatives.[1] The thorough and elegant investigations by Klumpp and coworkers on directed lithiations of cyclopropylcarbinyl alcohols and ethers provides a basis for the efficient regio- and stereocontrolled syntheses of such systems.[2] Application of this approach to the substitution of dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-ol (**1**) is shown below. We expected the sequence of lithiation and methylation to provide the monomethylated product **2** but found that significant amounts of the dimethylated product **3** were also formed. We report here a brief study of this apparent polylithiation and the lithiations of the related alcohol **6** and the methyl ether **7**.



1 R = H, R' = H
6 R = *n*-Bu, R' = H
7 R = H, R' = CH_3

2 R = H, R' = H, E = CH_3
4 R = H, R' = H, E = D
8 R = *n*-Bu, R' = H, E = CH_3
10 R = *n*-Bu, R' = H, E = D
12 R = H, R' = CH_3, E = CH_3
13 R = H, R' = CH_3, E = D

3 R = H, R' = H, E = CH_3
5 R = H, R' = H, E = D
9 R = *n*-Bu, R' = H, E = CH_3
11 R = *n*-Bu, R' = H, E = D

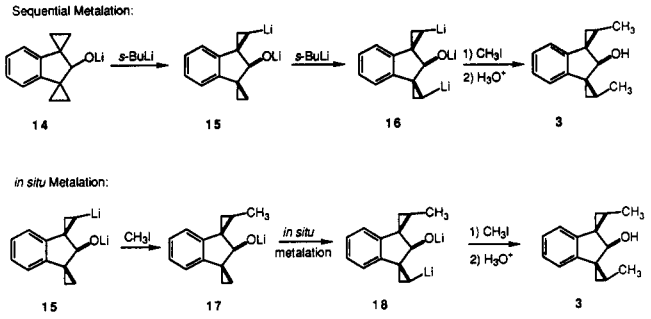
The alcohol **1** was prepared in 90% yield by lithium aluminum hydride reduction of the known ketone.[3] Treatment of **1** with potassium hydride and methyl iodide provided the methyl ether **7** in 70% yield. The *n*-butyl alcohol **6** was synthesized in 95% yield by addition of *n*-butyllithium to the ketone.

Investigation of the lithiation of **1** provided conditions under which formation of either **2** or **3** could be favored. Treatment of **1** with 3.0 equiv of *sec*-butyllithium (*s*-BuLi) in ether at room temperature for 1 h, followed by addition of excess methyl iodide, provided 59% of the monomethylated product **2** and 15% of the dimethylated product **3**. Treatment of **1** with 6 equiv of *s*-BuLi for 50 h in ether at ~30 °C gave a heterogeneous reaction mixture, which, after reaction with methyl iodide for 12 h, provided 13% **2** and 46% **3**. The products have elemental analyses and ^1H and ^{13}C NMR, IR, and mass spectrometric data consistent with the assigned structures. Determination of the structure of **3** by X-ray diffraction confirms the assignment of the stereochemistry of both methyl groups to be anti to the phenyl ring and syn to the hydroxyl group. The geometry of the products is consistent with a lithium alkoxide directed metalation and retention of cyclopropyl anion configuration as observed in related systems.[2] The formation of disubstituted products tended to be quite variable, which we attribute to the heterogeneous conditions and the relatively slow reaction of methyl iodide.

(1) Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454.
(2) Klumpp, G. W. *Recl. Trav. Chim. Pay. Bas.* **1986**, *105*, 1 and references therein. For other directed lithiations of cyclopropyl rings, see: Eaton, P. E.; Daniels, R. G.; Cassucci, D.; Cunkle, G. T.; Engel, P. *J. Org. Chem.* **1987**, *52*, 2100 and references therein. For configurational stability of cyclopropyl anions, see: Applequist, D. E.; Peterson, A. H. *J. Am. Chem. Soc.* **1961**, *83*, 862. Motes, J. M.; Walborsky, H. M. *J. Am. Chem. Soc.* **1970**, *92*, 2445.
(3) Klages, C. P.; Voss, J. *Chem. Ber.* **1980**, *113*, 2255.

0022-3263/91/1956-0853$02.50/0

Scheme I



The lithiation reactions were also quenched with methanol-*d* or acetic acid-*d* to provide the mono- and dideutero products **4** and **5**. As with methylation, conditions could be found to favor either the monosubstituted or disubstituted product. Thus, the formation of disubstituted products does not appear to be dependent on the electrophile.

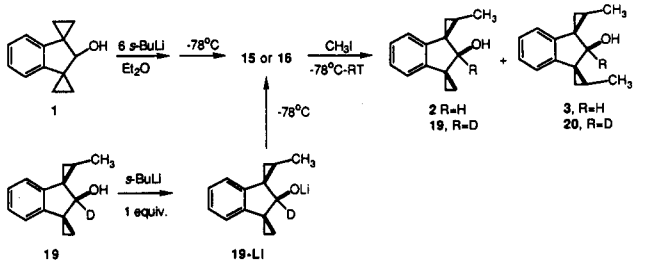
Metalation of the *n*-butyl-substituted alcohol **6** provided similar results. Treatment of **6** with *s*-BuLi in ether for 18 h produced a homogeneous reaction mixture, which after reaction with methyl iodide provided 22% of the monomethyl product **8** and 47% of the dimethyl product **9**. Similarly, quenching of the reaction mixture with methanol-*d* or acetic acid-*d* provided the deuterated products **10** and **11**. Since the product ratios obtained from these reactions are similar to those from the metalation and electrophilic substitution of **1**, it does not appear that the heterogeneity of that reaction is required for the formation of disubstituted products.

The metalation of the dispiroindanyl ether **7** was also investigated. Treatment of **7** with 5 equiv of *s*-BuLi in ether at room temperature for 20 h provided a homogeneous reaction mixture, which on reaction with methyl iodide provided only the monomethyl dispiroindanyl ether **12**. No disubstituted product could be detected. Quenching of the metalation reaction of **7** with methanol-*d* gave only the monodeuterio product **13** (75% d_1). It appears that both an alkoxide-directing group and the geometry of the dispiroindanol system are necessary for the apparent trilithiation, since treatment of dicyclopropylcarbinol under similar conditions provided only monosubstituted products.

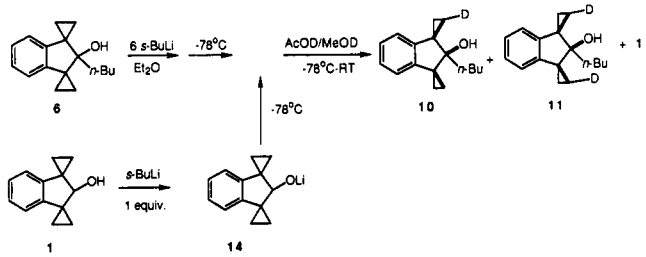
Two possible mechanisms for the formation of disubstituted products are shown in Scheme I for the metalation of **1** and reaction with methyl iodide. The most straightforward involves a sequence in which the alkoxide **14** is metalated to form the monocarbanion **15**, which then undergoes a second metalation to form the dicarbanion **16**. Reaction with methyl iodide provides the monomethyl dispiroindanol **2** from **15** and the dimethyl dispiroindanol **3** from **16**.

A second possibility, also shown in Scheme I, is that only the monocarbanion **15** is formed. On addition of methyl iodide, an in situ alkylation/metalation to form the monolithio monomethyl alkoxide **18** could occur, which could then lead to **3**. In situ trapping/metalations such as this have been reported for more-activated systems.[4]

An experiment using **1** and the monomethyl deuterium-labeled alcohol **19** was designed to distinguish between these possibilities.[5] The dispiro alcohol **1** was subjected to the standard metalation conditions (6 equiv of *s*-BuLi) and after 24 h, the reaction was cooled to −78 °C and a solution of the alkoxide **19-Li** also cooled to −78 °C was added, directly followed by methyl iodide. The reaction was then allowed to warm to room temperature overnight. These conditions normally provided a mixture of mono- and disubstituted products **2** and **3**. If the dimethyl product **3** is arising from the dicarbanion **16** and no in situ metalation is occurring, then the dimethylated product should contain no deuterium. If in situ metalation is occurring, then the presence of deuterium in **3** might be expected, since **19-Li** is the deuterated analogue of the proposed intermediate **17**. Analysis of the dimethyl product **3** isolated from the reaction indicated a deuterium incorporation of about 9%. This indicates that a small amount of in situ metalation could occur during the methylation reaction, but it does not appear to be enough to account for formation of all of **3**. It is possible that some metalation of **19-Li** occurred during the warming of the reaction prior to reaction of *s*-BuLi with methyl iodide.[6]



The mechanism of formation of the dideuterated products was also investigated by using a similar experiment. The *n*-butyl dispiroindanol **6** was subjected to the standard disubstitution conditions and then cooled to −78 °C, and a solution of the alkoxide of alcohol **1** was transferred into the reaction mixture. A mixture of acetic acid-*d* and methanol-*d* was added, and the reaction was allowed to warm slowly to room temperature. After workup and analysis by FIMS, the *n*-butyl compound was shown to be 48% d_2 and 28% d_1. The reisolated alcohol **1** had no deuterium incorporation. The fact that there is a significant amount of dideuterated **6** but no deuterium incorporation of **1** strongly suggests that disubstituted products arise from a trilithio dicarbanion.



Both the first and second directed lithiations appear to be accelerated by a favorable geometry in these biscyclopropyl carbinols.[7,8] The first metalation of **1** and **6** are complete in 20–30 min, yet the metalations of unactivated cyclopropylcarbinyl alcohols require up to 24 h and even

(4) Crowley, P. J.; Leach, M. R.; Meth-Conn, O.; Wakefield, B. J. *Tetrahedron Lett.* **1986**, 2909.

(5) The alcohol **19** was synthesized from the parent ketone by lithium aluminum deuteride reduction followed by the lithiation and methyl iodide quenching sequence.

(6) It is also possible that some metalation could occur in the mixing time of the alkoxides (~1 min) at −78 °C. We were initially misled by mixing the components at higher temperatures and finding high deuterium incorporation in **4**.

(7) The rationalization that a complexed directing group is a poorer director has been used to explain the formation of only monolithio species in the ortho lithiation of *N,N*-dialkylbenzylamines. See: Gschwend, H. W.; Rodriquez, H. R. *Org. React.* **1984**, *26*, 1 and references cited therein.

(8) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

under forcing conditions only monolithiation of dicyclopropyl carbinol is observed. The directing alkoxide functionality is also important for dilithiation since the methyl ether 7 does not undergo the second metalation. Research on the effects of the geometry and the nature of functional group on oxygen-directed metalation is currently underway.

Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were recorded at 200 or 300 MHz, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported relative to TMS for ^1H spectra and $CDCL_3$ for ^{13}C spectra. In cases where GCMS analysis was used to determine isotope ratios, the entire peak (~10–20 scans) was averaged to account for any isotopic discrimination. Preparative high performance liquid chromatography (HPLC) was performed on a Dynamax 21.4-mm preparative silica column. Medium pressure chromatography (MPLC) was performed on Merck silica gel, 32–63 mesh. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Microanalyses were obtained from the University of Illinois Microanalytical Service Laboratory.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium/benzophenone, ethyl acetate over potassium carbonate, and hexane over 3-Å molecular sieves. The solution of *sec*-butyllithium in cyclohexane (*s*-BuLi) was obtained from Lithium Corporation. Organolithium reagents were titered prior to use by the method of Suffert.[9] Dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-one was synthesized according to literature procedures.[3] All other reagents were obtained from commercial sources and used without purification unless otherwise noted. Standard workup refers to pouring the reaction mixture into a saturated NH_4Cl solution followed by separation of the layers, extraction of the aqueous layer with additional ether, drying of the combined organic layers over $MgSO_4$, filtering, and removal of solvent in vacuo.

Dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-ol (1). A solution of dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-one (9.55 g, 52 mmol) in 150 mL of dry ether was added dropwise over 0.5 h to a mechanically stirred suspension of lithium aluminum hydride (1.27 g, 31.8 mmol) in 350 mL of dry ether cooled to 0 °C. The mixture was stirred overnight at 25 °C and quenched by addition of an aqueous Na_2SO_4 slurry until the liquid phase turned clear. The mixture was filtered, and the filtrate was dried ($MgSO_4$). Removal of the solvent in vacuo afforded 8.65 g (90%) of 1 as a white solid: mp 136–137 °C; ^1H NMR ($CDCl_3$) δ 0.98–1.38 (m, 8 H), 1.54 (d, J = 7.3 Hz, OH), 3.67 (d, J = 7.1 Hz, *H*CO), 6.65–6.70 (m, 2 H), 7.09–7.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 10.5, 18.1, 32.9, 83.4, 118.3, 126.4, 145.4; MS (70 eV) m/z (rel intensity) 186 (M^+, 40), 171 (22), 168 (6), 158 (100), 155 (9), 153 (10), 143 (13), 141 (17), 129 (46), 115 (48), 102 (5), 91 (6), 89 (5), 77 (11), 63 (10). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.86; H, 7.50.

Metalation and Methyl Iodide Reaction of 1 with 3.0 equiv of *s*-BuLi. To a solution of 0.107 g of 1 in 8 mL of dry Et_2O was added 1.72 mmol of *s*-BuLi (1.23 mL, 1.4 M, 3.0 equiv). The reaction mixture was stirred at room temperature for 1 h and then quenched by addition of 0.5 mL of CH_3I and stirred at room temperature for 10 h. Standard workup gave a crude mixture of *anti*-2-methyldispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-*syn*-2′-ol (2), *anti*-2,2″-dimethyldispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-*syn*-2′-ol (3), and recovered 1 in a ratio of 4.8:1.2:1, as determined by capillary GC. Purification by preparative HPLC (15% EtOAc/hexane) afforded 0.0676 g (59%) of 2 as a white solid and 0.0192 g (16%) of 3 as a white solid. 2: mp 140–142 °C; ^1H NMR ($CDCl_3$) δ 0.83–0.86 (m, 1 H), 0.87 (dd, J = 4.1, 8.7 Hz, 1 H), 0.94 (dd, J = 4.3, 5.9 Hz, 1 H), 1.17–1.27 (m, 3 H), 1.40 (d, J = 6.3 Hz, CH_3), 1.68 (br s, OH), 1.69–1.72 (m, 1 H), 3.59 (br s, CHO-), 6.71–6.73 (m, 2 H), 7.11–7.14 (m, 2 H), irradiation of the signal at 1.69–1.72 ppm simplified the signals at 0.87 and 0.94 ppm to doublets and the signal at 1.40 ppm to a singlet; ^{13}C NMR ($CDCl_3$) δ 8.3, 16.4, 17.2, 19.0, 26.4, 34.0, 36.8, 85.4, 118.5, 126.4, 126.5, 145.1, 146.4; IR (cm^{-1}, KBr) 3312, 3061, 2994, 1607, 1483, 1084, 1044, 1038, 1020; EIMS (10 eV) m/z (rel intensity) 200 (M^+, 87), 185 (16), 182 (32), 172 (89), 169 (9), 167 (38), 158 (82), 156 (100), 153 (12), 143 (28), 141 (45), 129 (78), 115 (21), 91 (2), 55 (2). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.75; H, 8.02. 3: mp 160–162 °C; ^1H NMR ($CDCl_3$) δ 0.85 (m, 4 H, cyclopropyl), 1.38 (d, J = 7 Hz, 6 H, CH_3), 1.66 (m, 3 H, CH and OH), 3.84 (d, J = 6 Hz, HCO), 6.84 (m, 4 H, aromatic H). Shaking with D_2O caused loss of the highest central resonance of the 1.66 multiplet and collapsed the 3.84 resonance to a sharp single; ^{13}C NMR ($CDCl_3$) δ 16.0, 16.3, 25.8, 37.3, 84.6, 118.6, 126.3, 146.0; MS (70 eV) m/z (rel intensity) 214 (20, M^+), 185 (34), 181 (22), 172 (69), 170 (90), 157 (41), 157 (41), 155 (51), 143 (24), 141 (38), 129 (100), 128 (57), 115 (47). Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.46. Found: C, 83.79; H, 8.18.

Metalation and Methyl Iodide Reaction of 1 with 6 equiv of *s*-BuLi. To 0.1342 g (0.722 mmol) of dispiroindanol 1 in 10 mL of dry Et_2O cooled to 0 °C was added 4.42 mmol of *s*-BuLi (3.4 mL, 1.3 M). The reaction mixture was stirred at room temperature for 1 h and then stirred at ~30 °C for 50 h. The reaction mixture was cooled to room temperature, excess (0.9 mL) CH_3I was added, and the reaction mixture stirred for 12 h. Standard workup yielded a yellow solid, which was shown by capillary GC to contain 1:2:3 in a ratio of 1:0.82:4.9. Purification by HPLC (15% EtOAc/hexane) provided 0.0194 g of 2 (0.097 mmol, 13%) and 0.0705 g of 3 (0.329 mmol, 46%).

Representative Metalation and Acetic Acid-*d* Reaction of 1. To 0.0911 g (0.490 mmol) of 1 in 10 mL of dry Et_2O cooled to 0 °C was added 3.0 mmol of *s*-BuLi (3 mL, 1.0 M). The reaction mixture was stirred for 1 h at room temperature and then heated at 30 °C for 48 h. The reaction mixture was cooled to room temperature and quenched by addition of excess (0.5 mL) acetic acid-*d* and stirred for 8 h. The reaction mixture was poured into saturated $NaHCO_3$ solution, ether was added, and the layers were separated. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo to yield a yellow solid, which was purified by MPLC (20% EtOAc/hexane) to provide 0.0808 g (~87%) of a mixture of d_0, d_1, and d_2 material. GCMS analysis relative to an undeuterated standard showed that the material was 81% d_2, 11% d_1, and 8% d_0.

2′-Butyldispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-ol (6). To 1.075 g (5.84 mmol) of dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-one in 75 mL of dry Et_2O cooled to 0 °C was added 12.0 mmol of *n*-BuLi (10 mL, 1.2 M). The reaction mixture was stirred overnight at room temperature, then the reaction mixture was poured into 100 mL of H_2O. The layers were separated and the aqueous layer was extracted with 80 mL of Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to yield a yellow-white solid. The solid was purified by MPLC (30% EtOAc/hexane) to yield 1.343 g (5.55 mmol, 95%) of 7 as a white solid: mp 120–121 °C; ^1H NMR ($CDCl_3$) δ 0.65–0.75 (m, 2 H, cyclopropyl), 0.82 (t, J = 6.9 Hz, 3 H, CH_3), 1.05–1.39 (m, 13 H), 6.62–6.65 (m, 2 H, CH aromatic), 7.07–7.10 (m, 2 H, CH aromatic); ^{13}C NMR ($CDCl_3$) δ 12.3, 14.0, 14.8, 23.4, 25.0, 35.0, 37.9, 79.4, 117.6, 126.4, 145.9. Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.21; H, 9.09.

Dispiro[cyclopropane-1,1′-indan-3′,1″-cyclopropan]-2′-yl Methyl Ether (7). To 1.8 g of KH in 25 mL of dry THF was added 1.0 g (5.38 mmol) of dispiroindanol 1 in 50 mL of dry THF dropwise. The mixture was stirred at room temperature for 15 min, 2.8 mL of CH_3I was added, and the mixture was stirred overnight. The reaction mixture was quenched by slow addition of 10 mL of H_2O and then poured into 50 mL of saturated NH_4Cl solution, and the layers were separated. The water layer was extracted with 75 mL of Et_2O and the combined organic layers were dried ($MgSO_4$). Filtering and removal of solvent in vacuo yielded a red oil, which was purified by MPLC (7.5% EtOAc/hexane) to yield 0.750 g (3.75 mmol, 70%) of 7 as a clear liquid: ^1H NMR ($CDCl_3$) δ 0.98 (m, 2 H), 1.12 (m, 5 H), 1.41 (m, 2 H), 3.14 (s, 3 H, CH_3), 3.71 (s, 1 H, H_3COCH), 6.64 (m, 2 H), 7.08 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 11.2, 19.5, 28.7, 52.9, 90.3, 117.2, 126.11, 146.4; IR (neat, cm^{-1}) 3075, 2995, 2974, 2826, 1607, 1487, 1462, 1425, 1350, 1088; MS (70 eV) m/z (rel intensity) 200 (M^+, 39), 172 (93), 157 (48), 129 (100), 115 (45). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 84.12; H, 8.06.

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Metalation and Methyl Iodide Reaction of Dispiroindanyl Ether 7. To 0.090 g (0.448 mmol) of **7** in 6 mL of dry Et_2O cooled to 0 °C was added 1.44 mmol of *s*-BuLi (1.2 mL, 1.2 M). The reaction mixture was allowed to warm to room temperature, stirred for 24 h, and then quenched by addition of excess (0.4 mL) CH_3I. Standard workup provided a pale yellow oil, which was shown by GC to contain 90% of one new product and 10% starting material. After being passed through a short silica flash column, the product was isolated by HPLC (2% EtOAc/hexane) to provide 0.075 g (0.350 mmol, 78%) of *anti*-2-methyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-2'-yl methyl ether (**12**) as a clear oil: ^1H NMR ($CDCl_3$) δ 0.86–0.96 (m, 3 H), 1.16–1.26 (m, 2 H), 1.39 (d, J = 6.22 Hz, CH_3), overlapping with multiplet at 1.36–1.42 (total, 4 H), 1.70–1.79 (m, 1 H), 3.17 (s, 3 H, OCH_3), 3.77 (s, 1 H, OC*H*), 6.63–6.67 (m, 2 H), 7.07–7.10 (m, 2 H); ^{13}C NMR δ 9.4, 16.2, 18.8, 20.1, 27.9, 29.6, 32.2, 52.2, 91.4, 117.1, 126.1, 126.2, 146.7; IR (neat, cm^{-1}) 3067, 2930, 2824, 1607, 1485, 1462, 1196, 1086. Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.15; H, 8.42.

Representative Metalation and Methyl Iodide Reaction of 6. To 0.103 g (0.426 mmol) of **9** in 6 mL of Et_2O cooled to 0 °C was added 3.64 mmol of *s*-BuLi (2.6 mL, 1.4 M). The ice bath was removed, and the reaction mixture was stirred at room temperature for 20 h; then excess (0.5 mL) methyl iodide was added and the reaction mixture was stirred for 15 h. Standard workup yielded a yellow oil, which was purified by passage through a short silica column, followed by HPLC (5% EtOAc/hexane) to yield 0.0242 g of 2'-butyl-*anti*-2-methyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-*syn*-2'-ol (**8**) (0.0945 mmol, 22%) as a clear oil and 0.0541 g (0.200 mmol, 47%) of 2'-butyl-*anti*-2,2''-dimethyldispiro[cyclopropane-1,1'-indan-3',1''-cyclopropan]-*syn*-2'-ol (**9**) as a clear oil. **8**: ^1H NMR ($CDCl_3$) δ 0.70–0.79 (m, 1 H), 0.846 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.47 (d, J = 6.3 Hz, 3 H, $CHCH_3$) overlapping with multiplet at 1.0–1.6 (total = 16 H), 6.56–6.63 (m, 2 H, aromatic H), 7.07–7.10 (m, 2 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.0, 15.9, 22.3, 23.4, 25.2, 26.9, 36.1, 37.4, 39.4, 82.2, 117.3, 117.6, 126.1, 126.4, 145.5, 147.3. Anal. Calcd for $C_{18}H_{24}O$: C, 84.33; H, 9.44. Found: C, 84.17; H, 9.49. **9**: ^1H NMR ($CDCl_3$) δ 0.841 (t, J = 6.7 Hz, 3 H, CH_2CH_3), 1.08–1.30 (m, 11 H), 1.44 (d, J = 6.3 Hz, 6 H, $CHCH_3$), 1.55–1.60 (m, 2 H), 6.40–6.52 (m, 2 H), 7.02–7.05 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.3, 23.4, 23.8, 25.5, 27.4, 37.8, 40.7, 85.8, 117.3, 126.1, 146.7. Anal. Calcd for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.36; H, 9.65.

Lithiation of 1 and Addition of 19-Li Followed by Reaction with Methyl Iodide. To 0.0467 g (0.251 mmol) of **1** in 2 mL of dry Et_2O cooled to 0 °C was added 1.56 mmol of *s*-BuLi (1.2 mL, 1.3 M, 6 equiv.). The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h, and then cooled to −78 °C.

To 0.0308 g (0.153 mmol) of **19** in 2 mL of dry Et_2O cooled to 0 °C was added 0.156 mmol of *s*-BuLi (0.12 mL, 1.3 M, 1.0 equiv). The ice bath was removed, and the solution was stirred for 30 min and then cooled to −78 °C. This solution was transferred by cannula to the lithiation reaction above. After ~1 min, 0.5 mL of CH_3I was added, and the reaction mixture was slowly allowed to warm to room temperature and stirred for 15 h. Standard workup provided a yellow solid, which contained **1**:**2**:**3** in a ratio of 2.5:6.9:1 as shown by capillary GC. FIMS analysis relative to an undeuterated standard showed that the dimethyl product **3** had a deuterium incorporation of 9%.

Lithiation of 6 and Addition of 1-Li Followed by Reaction with Methyl Iodide. To 0.0681 g (0.281 mmol) of **6** in 4 mL of dry Et_2O cooled to 0 °C was added 1.70 mmol of *s*-BuLi (1.3 mL, 1.3 M, 6 equiv). The ice bath was removed, and the reaction mixture was stirred at room temperature for 24 h and then cooled to −78 °C.

To 0.0308 g (0.153 mmol) of **1** in 2 mL of dry Et_2O cooled to 0 °C was added 0.182 mmol of *s*-BuLi (0.14 mL, 1.3 M, 1.1 equiv). The ice bath was removed, and the solution was stirred for 30 min and then cooled to −78 °C. This solution was transferred by cannula to the lithiation reaction above. After ~30–45 s, 1 mL of a mixture of acetic acid-*d* and methanol-*d* (50% v/v) was added, and the reaction mixture was slowly allowed to warm to room temperature and stirred for 5 h. Standard workup provided a yellow solid. FIMS analysis relative to undeuterated standards showed that there was no deuterium (<3%) incorporation in **1**, while the *n*-butyl compound **6** was shown to be 48% d_2 and 28% d_1.

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Supplementary Material Available: ORTEP plots of **3** with selected distances, angles, and thermal parameters and experimental procedures for the synthesis of **19** and the lithiation and methanol-*d* trapping of **7** (12 pages). Ordering information is given on any current masthead page.

Assignment of the Configuration of Disubstituted 1,3-Dienes by Nuclear Overhauser Effect Measurements

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As a rule, the geometry of simple substituted olefins can be safely predicted from the coupling constants and chemical shifts of their ^1H and ^{13}C NMR spectra.[1,2] However, when several substituents are present, prediction becomes uncertain since the chemical shift differences are usually smaller and the number of informative couplings is reduced.[3] Conjugated dienes are subject to the same limitations, although chemical evidence, such as Diels–Alder additions and experiments involving 1,5-hydride shifts, should permit their structures to be deduced.[4,5] However, these methods, where feasible,[2b] need to be carried out on both the *E* and *Z* isomers in order to minimize ambiguity. We now describe how nuclear Overhauser effect (NOE) difference spectroscopy[6] can be used in a

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