Unusual α-Methylation of Alkoxyaryl Ketones with Higher Order Methyl Cuprate and Lithium Bromide

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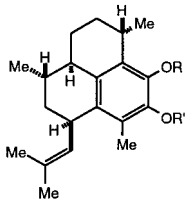
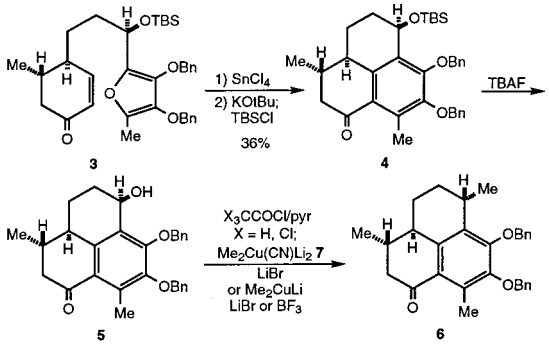
Pseudopterosins A and E, **1** and **2**, are members of a group of strongly antiinflammatory and analgesic agents that are marine metabolites from Caribbean sea whips of the genus *Pseudopterogorgia*.[2] These two compounds

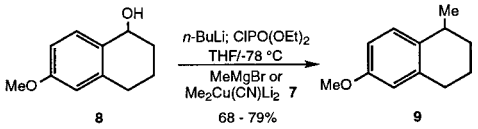


1 R = β-D-xylose R' = H
2 R = H R' = α-L-fucose

have shown the most promise as therapeutic agents for inflammation, each exceeding the potency of the drug industry standard indomethacin.[2a,d,e] Several groups have worked on the synthesis with two different total syntheses of pseudopterosin A,[3,4] and several other approaches having been published.[5] We have recently reported on our synthetic route to compounds such as **1** and **2**, which involves a novel Michael-aldol process for constructing the key hexasubstituted aromatic ring, namely, the two-step conversion of **3** into **4**.[6] To transform this phenalene system **4** into **6** and then into **1** and **2**, we decided to investigate the substitution of the acetate (or trichloroacetate) of the corresponding alcohol **5** with the higher order dimethylcyanocuprate[7] **7** in the presence of lithium bromide (LiBr) or with simple lithium dimethylcuprate in the presence of LiBr or BF_3 etherate. We describe herein the unusual course of this reaction and that of other analogues of (alkoxyaryl)ketones, namely, an α-methylation of the ketone.



We first tested the methylation reaction in a model system, namely, 6-methoxytetrahydro-1-naphthol **8**[8] (prepared in 99% yield by reduction of 6-methoxy-1-tetralone with $LiAH_4$). The acetate[9] and trichloroacetate of **8** could be easily formed but gave mainly the product of E1 elimination, namely, the dihydronaphthalene,[10] on treatment with methyllithium (or methylcuprate) and Lewis acids. We next investigated phosphate as a leaving group. Addition of *n*-butyllithium to the alcohol **8** at −78 °C in THF followed by addition of 1 equiv of diethyl chlorophosphate with stirring for 10 min presumably afforded the corresponding phosphate. This very labile benzylic phosphate was not isolated but rather treated directly with excess methylmagnesium bromide. Under these conditions, again only a small amount of coupling was observed. However, when the *n*-butyllithium was added to a mixture of **8**, diethyl chlorophosphate, and excess methyl Grignard reagent, we isolated a 68% yield of the desired methylated product **9**.[11] We found that the use



of 5 equiv of the higher order cuprate **7** in place of the Grignard reagent gave a higher overall yield (79%) of **9** with some of the dihydronaphthalene also being formed. Other leaving groups were also tested in this process without great success. The corresponding triflates or mesylates were too unstable and gave mainly the E1 elimination product under all conditions tried.

Having demonstrated that the conversion of a benzylic alcohol into a benzylic methyl group was possible under these conditions, we turned our attention directly to the key pseudopterosin substrate. Treatment of the alcohol **5** with acetyl chloride or trichloroacetyl chloride gave the

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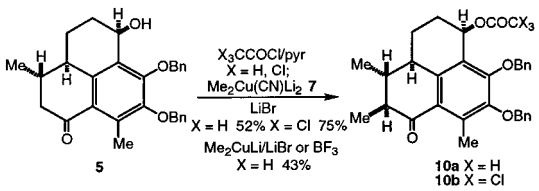
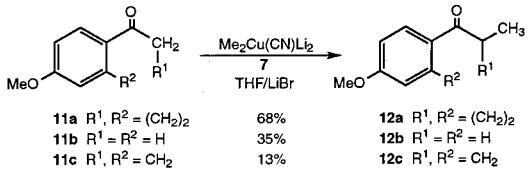
corresponding acetate and trichloroacetate in good yield. Reaction of these esters with excess (5 equiv) of the higher order cuprate **7** (prepared from low halide MeLi) and 2 equiv of LiBr with stirring at −78 °C for 5 h slowly afforded a new compound in each case. After the reaction was allowed to warm gradually to 25 °C and was stirred overnight at 25 °C, workup furnished the unexpected product of α-methylation of the ketone, namely, **10ab**.



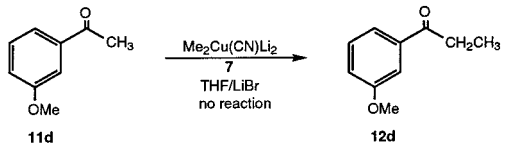
Under the best conditions, the isolated yield of this unusual product was 75% (**10a**, X = H, 52%; **10b**, X = Cl 75%). This product of α-methylation, **10a**, was also obtained in 43% yield when lithium dimethylcuprate was used in the presence of LiBr or BF_3 etherate with the acetate.

Since this is an abnormal mode of reaction for ketones with higher order cuprates, we decided to examine somewhat the scope of the process. Simple alkyl ketones, e.g., 4-*tert*-butylcyclohexanone, do not give any α-methylation, and simple alkyl aryl ketones, e.g., α-tetralone, 1-indanone, and acetophenone, give no more than trace amounts of α-methylation. In these cases, in addition to mostly recovered starting material, some tertiary alcohol (from 1,2-addition of methyl to the ketone) is also isolated, especially when BF_3 etherate is used as the Lewis acid. The reaction seems to require the presence of an alkoxy group on the aromatic ring *para* to the carbonyl group. Thus 6-methoxy-1-tetralone **11a** gave the α-methylated ketone **12a**[12] in 68% yield, 4′-methoxyacetophenone **11b** afforded **12b** in 35% yield, and 5-methoxy-1-indanone **11c** gave **12c**[13] in 13% yield (no attempts have been made to optimize these yields). However, a



meta alkoxy group did not promote the reaction, e.g., 3′-methoxyacetophenone **11d** did not give the α-methylated product **12d**. If the lithium bromide is omitted from the reaction mixture, no α-methylation is observed, even with the alkoxyaryl ketones. Other lithium salts, e.g., lithium perchlorate, did not give any alkylation. Other Lewis acidic additives (e.g., BF_3OEt_2) have given some α-methylation but the results have not been reproducible, except for LiBr.

We do not have a good hypothesis as to the mechanism for this methylation. Presumably the alkoxy group increases the basicity of the carbonyl so that it can form a more stable complex with the lithium cation, which might lead more readily to an enol (or enolate) than in



the simple aryl ketones. However, it is unclear how an enol (or enolate) and a higher order cuprate (both electron-rich species) could combine to produce an α-methyl ketone. The most likely hypothesis still seems somewhat unlikely. Oxidation of the bromide ion to bromine followed by bromination of the enol (or enolate) would give the α-bromo ketone, which might well produce the α-methyl ketone on reaction with either the lower or higher order cuprate. This would explain the lack of reaction with lithium perchlorate, since there is no source of positive halogen to generate the required α-halo ketone. When the reaction is run, a small amount of black solid metal can be seen in the flask and a large amount of brownish-red (copper-colored) metallic material coats the flask's walls, implying a reduction of the cuprate species. However, even given all of this circumstantial evidence, there is no obvious source of oxidant in this reaction (more than a catalytic amount is needed since the yields of α-methylation can be quite high and the reaction is run under an argon atmosphere), so this hypothesis is not yet assured. Further mechanistic speculation awaits more experimental work.

In summary, we have observed a novel α-methylation of alkoxyaryl ketones with higher order cuprates in the presence of lithium bromide. Since there are many excellent methods for α-methylation of ketones in high yield, this process is not useful synthetically but is of interest mechanistically.

Experimental Section

General. All temperatures and boiling points (bp) are uncorrected, and reactions were carried out under argon with the exclusion of moisture. Dichloromethane and pyridine were distilled from CaH_2. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl radical. Boron trifluoride-etherate ($BF_3{\cdot}Et_2O$) was stirred over CaH_2, distilled (67 °C at 43 mmHg) with an excess of diethyl ether (Et_2O), and stored at −23 °C under N_2. Chromatography was conducted on 230−400 mesh silica gel.

^1H and ^{13}C NMR were recorded on a Bruker AM200 or ARX500 spectrometer with tetramethylsilane as external standard. IR spectra were recorded on a Nicolet 510 FT-IR, Nicolet 205 FT-IR, or a Perkin-Elmer series 1600 spectrometer. Mass spectra were obtained on a VG Autospec and are given for the molecular ion unless otherwise stated.

General Procedure for Higher Order Cuprate Preparation.[7] In a dry one neck flask was placed highly dried CuCN (under high vacuum for 10 h at 100 °C). The vessel was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (1 mL/mmol CuCN) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the organolithium species (2 equiv relative to CuCN) dropwise. The heterogeneous mixture was allowed to warm gradually until complete dissolution resulted (may require 0 °C) and was then cooled to −78 °C (may get turbid at high concentration). The substrate was then introduced either as a solution in THF or as a net liquid, and the mixture was stirred at the appropriate temperature until starting material was consumed. Reactions were routinely followed by TLC. Following completion, the reaction was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 2−3 h.

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Standard extractive workup followed by chromatographic purification afforded the results.

6-Methoxytetrahydro-1-naphthol (8). To a solution of $LiAlH_4$ (95%, 2.6 g, 0.1 mol) in THF (200 mL) was added gradually with stirring 6-methoxy-1-tetralone (17.6 g, 0.1 mol) at 25 °C. The mixture was stirred for 18 h at reflux, then cooled to 0 °C, and quenched with cold water. After stirring for 6 h, the mixture was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the known[8] 6-methoxytetrahydro-1-naphthol **8** (17.6 g, 0.099 mol, 99%) as a reddish oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.72−2.01 (4H, m), 2.7−2.86 (2H, m), 3.79 (3H, s), 4.76 (1H, bm), 6.62 (1H, d, J = 2.6 Hz), 6.74 (1H, dd, J = 8.6, 2.7 Hz), 7.36 (1H, d, J = 8.6 Hz).

Tetrahydro-6-methoxy-1-naphthyl Acetate. To a solution of tetrahydro-6-methoxy-1-naphthol **8** (2.1 g, 11.8 mmol) in chloroform (10 mL) cooled to −78 °C was added dropwise pyridine (0.93 g, 0.95 mL, 11.8 mmol) and then acetyl chloride (4.2 g, 2.6 mL, 23.6 mmol); stirring was continued for 30 min. The excess acetyl chloride was quenched by the addition of water, and the mixture was washed with aqueous saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (10% ether in petroleum ether) gave the known[9] tetrahydro-6-methoxy-1-naphthyl acetate (0.44 g, 2 mmol, 17%) along with the known[10] eliminated product 3,4-dihydro-6-methoxynaphthalene (0.7 g, 4.4 mmol, 37%). Tetrahydro-6-methoxy-1-naphthyl acetate: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74−2.0 (4H, m), 2.07 (3H, s), 2.68−2.89 (2H, m), 3.79 (3H, s), 5.96 (1H, bm), 6.6−6.78 (2H, m), 7.19 (1H, d, J = 8.5 Hz). 3,4-Dihydro-6-methoxynaphthalene: δ 2.24−2.35 (2H, m), 2.74 (2H, t, J = 8.3 Hz), 3.8 (3H, s), 5.85−5.94 (1H, bm), 6.4 (1H, m), 6.69 (2H, m), 6.94 (1H, d, J = 9 Hz).

Tetrahydro-6-methoxy-1-methylnaphthalene (9) (with MeMgBr). To a solution of diethyl chlorophosphate (450 mg, 2.6 mmol) in THF (5 mL) was added dropwise the solution of lithium 6-methoxytetrahydro-1-naphthoxide [prepared from 6-methoxytetrahydro-1-naphthol **8** (47 mg, 0.26 mmol) upon treatment with 2.5 M *n*-BuLi (0.1 mL) followed dropping MeMgBr (5 equiv) at −78 °C]. The reaction mixture was allowed to warm gradually to room temperature and stirred for overnight. The reaction mixture was quenched by the addition of cold water, extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (33% ether in petroleum ether) gave the known[11] tetrahydro-6-methoxy-1-methyl-naphthalene **9** (31.4 mg, 0.178 mmol, 68%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (3H, d, J = 6.9 Hz), 1.45−1.96 (4H, m), 2.72 (3H, m), 3.78 (3H, s), 6.9 (1H, d, J = 2.6 Hz), 6.72 (1H, dd, J = 8.5, 2.8 Hz), 7.13 (1H, d, J = 8.5 Hz).

Tetrahydro-6-methoxy-1-methylnaphthalene (9) (with $Me_2Cu(CN)Li_2$). In a dry one neck flask was placed highly dried CuCN (under high vacuum for 10 h at 100 °C). The vessel was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (1 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium (2 mmol) dropwise. The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution the lithiated alcohol [prepared from 6-methoxytetrahydro-1-naphthol **8** (36.5 mg, 0.2 mmol) with *n*-BuLi (1 equiv)] was introduced and then diethyl chlorophosphate (3 mmol) was added dropwise. After stirring for 1.5 h, the reaction was quenched with 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. The mixture was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (33% ether in petroleum ether) gave the known[11] tetrahydro-6-methoxy-1-methylnaphthalene **9** (28 mg, 0.16 mmol, 79%).

(3α,3aα,6α)-6-Acetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one. To a solution of the alcohol **5**[6] (40 mg, 0.09 mmol) in methylene chloride (10 mL) was added pyridine (21 mg, 0.27 mmol) and acetyl chloride (35 mg, 0.45 mmol). After stirring for 1 h at 25 °C, the reaction mixture was quenched by the addition of cold water in an ice bath and extracted with methylene chloride. The organic layer washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave (3α,3aα,6α)-6-acetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis(phenyl-methoxy)-1*H*-phenalen-1-one (27 mg, 0.056 mmol, 60.3%) along with a small amount of recovered starting material (3α,3aα,6α)-2,3,3a,4,5,6-hexahydro-6-hydroxy-3,9-dimethyl-7,8-bis(phenyl-methoxy)-1*H*-phenalen-1-one **5**. (3α,3aα,6α)-6-Acetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 11.3), 1.56 (1H, m), 1.69 (1H, btt), 1.9 (3H, s), 1.95−2.05 (1H, m), 2.1 (1H, dm, J = 12 Hz), 2.18−2.38 (3H, m), 2.6 (3H, s), 2.74 (1 H, dd, J = 17.9, 4.3 Hz), 4.87 (2H, d, J = 2.8 Hz), 5.01 (1H, d, J = 11.1 Hz), 5.3 (1H, d, J = 11.1 Hz), 6.17 (1H, bs), 7.34−7.36 (10H, m). (3α,3aα,6α)-2,3,3a,4,5,6-Hexahydro-6-hydroxy-3,9-dimethyl-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one **5**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.4 Hz), 1.58 (1H, m), 1.68 (1H, btt), 1.92 (1H, m), 2.03 (1H, dm, J = 12.6 Hz), 2.15 (1H, dm, J = 13.9 Hz), 2.25 (1H, ddd, J = 11.5, 11.5, 4.7 Hz), 2.29 (1H, dd, J = 17.9, 13.0 Hz), 2.47 (1H, bs, OH), 2.60 (3H, s), 2.74 (1H, dd, J = 17.9, 4.5 Hz), 4.83 (1H, d, J = 10.7 Hz), 4.92 (1H, m), 5.01 (1H, d, J = 10.7 Hz), 5.14 (1H, d, J = 11.0 Hz), 5.36 (1H, d, J = 11.0 Hz), 7.34−7.47 (10H, m); ^{13}C NMR (200 MHz, $CDCl_3$) δ 199.6, 154.0, 148.9, 141.5, 136.9, 136.7, 135.9, 129.8, 129.0, 128.6, 128.4, 128.3, 128.2, 128.1, 75.5, 74.9, 62.4, 49.3, 35.1, 29.8, 21.6, 19.0, 14.4.

(3α,3aα,6α)-6-Trichloroacetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one. To a solution of the alcohol **5** (16 mg, 0.036 mmol) in methylene chloride (4 mL) was added pyridine (56 mg, 0.072 mmol) and trichloroacetyl chloride (32.8 mg, 0.18 mmol) at 0 °C. After stirring for 5 min, the reaction mixture was quenched by the addition of cold water in an ice bath and then extracted with methylene chloride. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave (3α,3aα,6α)-6-trichloroacetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis-(phenylmethoxy)-1*H*-phenalen-1-one (15 mg, 72%) along with a small amount of recovered starting material **5**. (3α,3aα,6α)-6-Trichloroacetyloxy-2,3,3a,4,5,6-hexahydro-3,9-dimethyl-7,8-bis-(phenylmethoxy)-1*H*-phenalen-1-one: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (3H, d, J = 6.3 Hz), 1.57 (1H, m), 1.68 (1H, btt), 1.75 (1H, bt), 1.9−2.38 (5H, m), 2.59 (3H, s), 2.74 (1 H, dd, J = 17.9, 4.4 Hz), 4.78 (2H, q, J = 13.3, 10.7 Hz), 5.13 (2H, q, J = 11.1, 8.5 Hz), 6.2 (1H, bs), 7.32−7.35 (10H, m).

(3α,3aα,6α)-6-Acetyloxy-2,3,9-trimethyl-2,3,3a,4,5,6-hexahydro-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one (10a) (X = H). In a dry one neck flask was placed highly dried CuCN (45 mg, 0.5 mmol). The flask was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (1 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added dropwise the methyllithium lithium bromide complex (1.5 M MeLi·LiBr, 0.7 mL, 1 mmol). The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced dropwise the acetate of 5 (20 mg, 0.041 mmol) as a solution in THF (1 mL). The reaction mixture was allowed to warm to 0 °C and then was stirred for 5 h. The reaction was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the (3α,3aα,6α)-6-acetoxy-2,3,3a,4,5,6-hexahydro-2,3,9-trimethyl-7,8-bis(phenyl-methoxy)-1*H*-phenalen-1-one 10a (X = H) (5.2 mg, 52%) along with a small amount of recovered alcohol 5: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (3H, d, J = 6.47 Hz), 1.26 (3H, d, J = 4.98 Hz), 1.67 (1H, btt), 1.75 (1H, bt), 1.91 (3H, s), 2.02−2.42 (5H, m), 2.52 (3H, s), 4.87 (2H, m), 4.97 (1H, d, J = 11 Hz), 5.26 (1H, d, J = 11 Hz), 6.15 (1H, bs), 7.34−7.37 (10H, m); HRMS (*m*/*z*) 498.2429, calcd for $C_{32}H_{34}O_5$ 498.2406.

(3α,3aα,6α)-6-Trichloroacetyloxy-2,3,3a,4,5,6-hexahydro-2,3,9-trimethyl-7,8-bis(phenylmethoxy)-1*H*-phenalen-1-one (10b) (X = Cl). In a dry one neck flask was placed highly dried CuCN (45 mg, 0.5 mmol). The flask was flushed with argon

and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (2 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium lithium bromide complex (1.5 M MeLi·LiBr, 0.7 mL, 1 mmol) dropwise. The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced dropwise the trichloroacetate (15 mg, 0.0255 mmol) as a solution in THF (1 mL). The reaction mixture was stirred for 1 h at −50 °C, and then $BF_3{\cdot}Et_2O$ (0.2 mL) was added. After stirring for 1 h at −50 °C, the reaction mixture was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the (3α,3aα,6α)-6-trichloroacetyloxy-2,3,9-trimethyl-2,3,3a,4,5,6-hexahydro-7,8-bis-(phenylmethoxy)-1*H*-phenalen-1-one **10b** (X = Cl) (11.5 mg, 0.019 mmol, 75%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.13 (3H, d, J = 6.43 Hz), 1.26 (3H, d, J = 7 Hz), 1.67 (1H, btt), 1.75 (1H, bt), 1.91 (3H, s), 2.05−2.45 (5H, m), 2.53 (3H, s), 4.8−4.97 (2H, ABq, J = 10.7 Hz), 5.08−5.28 (2H, ABq J = 11.2 Hz), 6.18 (1H, bs), 7.31−7.37 (10H, m); HRMS (*m*/*z*) 600.1261, calcd for $C_{32}H_{31}Cl_3O_5$ 600.1237.

3,4-Dihydro-6-methoxy-2-methyl-1(2*H*)-naphthalenone (12a). In a dry one neck flask was placed highly dried CuCN (450 mg, 5 mmol). The flask was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (5 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium lithium bromide complex (1.5 M MeLi·LiBr, 6.7 mL, 10 mmol) dropwise. The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced 6-methoxy-1-tetralone **11a** (88 mg, 0.5 mmol). The reaction mixture was stirred for 2 h at −78 °C, allowed to warm to 25 °C gradually, and then stirred for 2 days. The reaction was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the known[12] 6-methoxy-2-methyl-1-tetralone **12a** (64.7 mg, 0.34 mmol, 68%) along with the known[14] tetrahydro-6-methoxy-1-methyl-1-naphthol (29.6 mg, 0.155 mmol, 31%). 6-Methoxy-2-methyl-1-tetralone **12a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.25 (3H, d, J = 6.8 Hz), 1.8−1.95 (1H, m), 2.11−2.22 (1H, m), 2.49−2.60 (1H, m), 2.92−3.07 (2H, m), 3.75 (3H, s) 6.7 (1H, d, J = 2.4 Hz), 6.79 (1H, dd, J = 8.6, 2.5 Hz), 8.01 (1H, d, J = 8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 163.3, 146.6, 129.8, 126.1, 113.0, 112.5, 55.4, 42.3, 31.4, 29.2, 15.6; IR (neat) 3505 (overtone of CO), 3075, 1685 (CO) cm^{-1}; MS (*m*/*e*) 190 (M+) 175, 161, 148. Tetrahydro-6-methoxy-1-methyl-1-naphthol: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 (3H, s), 1.68−1.93 (4H, m), 2.75 (2H, bt), 3.78 (3H, s) 6.59 (1H, d, J = 2.6 Hz), 6.76 (1H, dd, J = 8.5, 2.8 Hz), 7.5 (1H, d, J = 8.7 Hz).

4′-Methoxypropiophenone (12b). In a dry one neck flask was placed highly dried CuCN (895 mg, 10 mmol). The flask was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (10 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium lithium bromide complex (1.5 M MeLi·LiBr, 13 mL, 20 mmol) dropwise. The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced 4′-methoxyacetophenone **11b** (150 mg, 1 mmol), and the reaction was stirred for 2 h at −78 °C. It was then allowed to warm to 25 °C gradually and stirred for 2 days more. The reaction was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the well-known 4′-methoxypropiophenone **12b** (58 mg, 0.353 mmol, 35.3%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (3H, t, J = 7.3 Hz), 2.29 (2H, q, J = 7.2 Hz), 3.87 (1H, s), 6.93 (2H, d, J = 8.8 Hz), 7.95 (2H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 163.3, 130.2, 130.0, 113.7, 55.5, 31.4, 8.5; IR (neat) 3495 (CO overtone), 3055, 1680 (CO) cm^{-1}; MS (*m*/*e*) 164 (M^+), 135, 107.

5-Methoxy-2-methyl-1-indanone (12c). In a dry one neck flask was placed highly dried CuCN (450 mg, 5 mmol). The flask was flushed with argon and then evacuated under high vacuum, the process being repeated three times, leaving the CuCN under argon. Dry THF (5 mL) was introduced via syringe, and the slurry was cooled to −78 °C. To this slowly stirring suspension was added the methyllithium (1.M MeLi, 10 mL, 10 mmol) dropwise and then LiBr (200 mg). The heterogeneous mixture was allowed to warm to 0 °C gradually until complete dissolution resulted and was then cooled to −78 °C. To this solution was introduced 5-methoxy-1-indanone **11c** (81 mg, 0.5 mmol), and the reaction was stirred for 2 h at −78 °C. It was then allowed to warm to 25 °C gradually and stirred for 2 days more. The reaction was quenched with a mixture composed of 10% concentrated NH_4OH in saturated aqueous NH_4Cl solution and allowed to stir at room temperature for 3 h. It was then extracted with ether, dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography of the residue on silica gel (25% ether in petroleum ether) gave the known[13] 5-methoxy-2-methyl-1-indanone **12c** (12 mg, 0.068 mmol, 13.6%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (3H, d, J = 7.3 Hz), 2.26−2.73 (2H, m) 3.28−3.42 (1H, dd, J = 8.5, 8.2 Hz), 3.88 (3H, s) 6.89 (2H, d, J = 8 Hz), 7.69 (1H, d, J = 8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.9, 166.0, 157.0, 129.7, 125.7, 115.3, 109.7, 55.6, 42.1, 35.1, 16.6; IR (neat) 3495 (overtone of CO), 3071, 1702 (CO) cm^{-1}; MS (*m*/*e*) 176 (M^+), 161, 133.

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Supporting Information Available: Proton NMR spectra of compounds **5**, **9**, **10a** and **10b** (and their precursors), and **12abc** and carbon NMR spectra of **5** and **12abc**. This material is available free of charge via the Internet at http://pubs.acs.org.

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