10264-56-9; **22**, 115420-41-2; $H_3CCOCH{=}CH_2$, 78-94-4; $H_3C(CH_2)_3MgCl$, 693-04-9; $(H_3C)_2CHMgCl$, 1068-55-9; $C_6H_5MgCl$, 100-59-4; 2-cyclohexen-1-one, 930-68-7; 2-cyclopenten-1-one, 930-30-3; isopropylmagnesium bromide, 920-39-8.

## A Convenient Synthesis of 4-*tert*-Butyl-5-benzofuranols and Dihydrobenzofuranols

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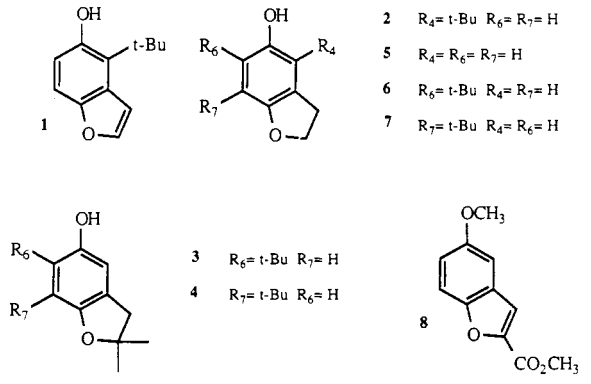
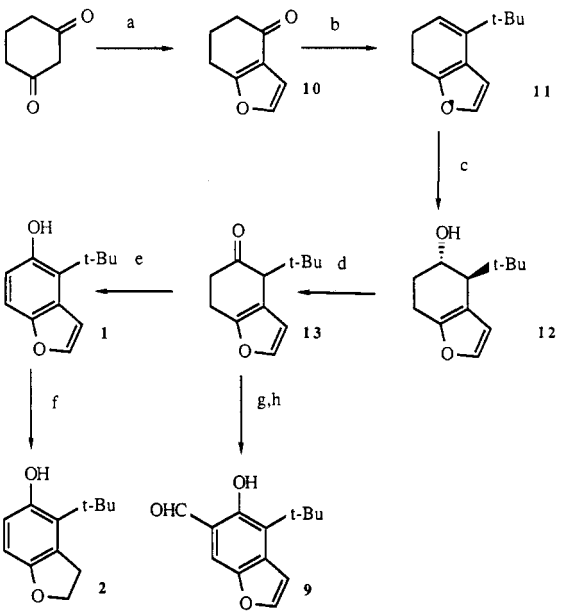
We recently described a novel series of 6-substituted 2,3-dihydro-5-benzofuranols as antioxidant based inhibitors of 5-lipoxygenase.[1,2] As part of an effort to improve the systemic activity of these agents, we required a convenient synthesis of 4-*tert*-butyl-5-benzofuranol (**1**) and 4-*tert*-butyl-2,3-dihydro-5-benzofuranol (**2**). The only previously described *tert*-butyl-2,3-dihydro-5-benzofuranols were the 2,2-dimethyl compounds **3** and **4**,[3] minor products of the photolysis of 2,5-di-*tert*-butylbenzoquinone and 2,6-*di*-*tert*-butylbenzoquinone, respectively. In our hands, direct *tert*-butylation ($H_2SO_4$, *t*-BuOH, benzene) of 2,3-dihydro-5-benzofuranol (**5**), afforded a mixture of **6** and **7** with no trace of the desired 4-*tert*-butyl isomer **2**. Attempted *tert*-butylation (*t*-BuCl, $TiCl_4$, methylene chloride) of the benzofuran **8**, a compound known to undergo electrophilic substitution at the 4-position,[4] was completely unsuccessful. We would now like to report a convenient synthesis of **1** and **2**, along with the corresponding 6-aldehyde **9**, allowing synthetic access to a variety of 4-*tert*-butyl-5-benzofuranols and dihydrobenzofuranols.




The synthesis of **1** makes use of an alkylative 1,2-carbonyl transposition[5,6] on ketone **10** followed by dehydrogenation (Scheme I). Addition of chloroacetaldehyde to 1,3-cyclohexanedione by the method of Tochtermann and Kohn[7] afforded ketone **10** in 30–35% yield. The yield of **10** was increased to 58% by the addition of 20 mol % potassium iodide to the reaction mixture.[8] Introduction of the *tert*-butyl group was achieved by the addition of **10** in 4:1 hexane/ether solution to a solution of *tert*-butyllithium in pentane at −78 °C.[9] The minimum amount of ether necessary to keep the reaction mixture homogeneous was used. The reaction mixture was then quenched and allowed to stir with dilute HCl until disappearance of the intermediate carbinol was complete (TLC). Vacuum distillation gave a constant boiling fraction which proved to be a 2:1 mixture (NMR) of **11** and **10**. Chromatographic purification afforded **11** (47%).

**Scheme I**[a]




[a] Reagents: (a) $ClCH_2CHO$, NaOH, KI, $H_2O$, 25 °C, 58%; (b) *t*-BuLi, ether/hexane, −78 to 5 °C, 47%; (c) $BH_3$, THF, 4 °C, then NaOH, $H_2O_2$, 50 °C, 82%; (d) $(COCl)_2$, DMSO, $Et_3N$, −78 to 25 °C, 82%; (e) $S_8$, 225 °C, 2 h, 52%; (f) $H_2$, 40 psi, 10% Pd/C, HOAc, 25 °C, 77%; (g) NaH, ethyl formate, toluene, 90 min, 25 °C; (h) DDQ, benzene, 25 °C, 45 min, 66%.

Hydroboration/oxidation of **11** using 1 equiv of borane in tetrahydrofuran[10] proceeded uneventfully to afford the trans-carbinol **12** as a crystalline solid in 82% yield. The NMR spectrum of **12** was initially surprising. If the *tert*-butyl substituent in **12** adopts a pseudoequatorial orientation, then the hydrogen at carbon 5 should be axial and its NMR resonance should be broadened due to the presence of two large (approximately 11 Hz) trans-diaxial couplings.[11] In fact, the observed resonance is multiplet with a peak width of only 8.8 Hz, suggesting that only equatorial–equatorial and equatorial–axial couplings are present. Since the stereochemical outcome of the hydroboration/oxidation sequence leading to **12** is well-known,[12] we must conclude that the *tert*-butyl substituent in **12**

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adopts a pseudoaxial orientation. An inspection of molecular models indicates that such a conformation is reasonable due to a severe steric interaction between an equatorial 4-*tert*-butyl substituent and the hydrogen at carbon 3.

Oxidation of **12** using chromium trioxide–pyridine under either Sarett[13] or Collins[14] conditions afforded the ketone **13** in 50–55% yield. Swern[15] oxidation proved to be more successful, affording **13** in greater than 80% yield. Several conditions were examined for the aromatization of **13**. Treatment of **13** with DDQ,[16] either in the presence or absence of acid, gave only decomposition. Dehydrogenation of **13** with palladium-on-carbon in cymene at 205 °C gave a mixture of **1** and **2** in 47% yield. The most convenient method found for the dehydrogenation of **13** was simply heating with sulfur[17] in a sealed tube at 225 °C, which afforded the desired 4-*tert*-butyl-5-benzofuranol (**1**) in 52% yield. Hydrogenation of **1** over palladium-on-carbon afforded **2** in 77% yield as a stable crystalline solid. Direct access to 6-substituted derivatives of **1** is easily achieved via Claisen condensation[18] of ketone **13** with ethyl formate followed by direct oxidation of the crude product with DDQ. In this way the aldehyde **9** was isolated in 66% overall yield from ketone **13**.

In summary we have described a nonelectrophilic method for the regiospecific synthesis of *o*-*tert*-butylphenols. The synthesis of **9** demonstrates a general solution to the problem of preparing 6-substituted 4-*tert*-butyl-5-benzofuranols.

## Experimental Section

**General.** All reagents and solvents were analytical reagent grade and were used without further purification unless otherwise noted. Dry tetrahydrofuran refers to solvent freshly distilled from sodium benzophenone ketyl. Routine $^1$H nuclear magnetic resonance (NMR) spectra were obtained on a Varian XL-200 instrument as solutions in deuterochloroform with tetramethylsilane (TMS, $\delta$ 0.00) as internal standard. Infrared (IR) spectra were generally obtained as solutions in chloroform on a Perkin-Elmer 1310 spectrophotometer. Low-resolution mass spectra (LRMS) were obtained on an LKB Model 9000 mass spectrometer at an ionizing voltage of 70 eV. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed at the Merck analytical laboratory. Flash chromatography was performed essentially as described in the literature[19] by using Kieselgel 60 (EM Science, 230–400 mesh) as stationary phase. Preparative HPLC refers to separations performed on a Waters PrepLC 500A instrument using Waters PrepPAK-500/SILICA cartridges as stationary phase. Analytical thin-layer chromatography (TLC) was performed with silica gel GHLF plates of 0.25-mm thickness obtained from Analtech Inc.

**6-*tert*-Butyl-2,3-dihydro-5-benzofuranol (6) and 7-*tert*-Butyl-2,3-dihydro-5-benzofuranol (7).** To a solution of **5** (1.00 g, 7.35 mmol) and *tert*-butyl alcohol (0.82 g, 11.0 mmol) in benzene (20 mL) was added concentrated $H_2SO_4$ (0.20 mL) and the mixture heated to 60 °C. After 1 h an additional portion of *tert*-butyl alcohol (0.82 g, 11.0 mmol) and concentrated $H_2SO_4$ (0.2 mL) was added and heating continued for another 1.5 h. At this point starting material had been consumed and two products were apparent by TLC (3:1 methylene chloride/hexane). The reaction mixture was diluted with ether (30 mL) and quenched with 5% $NaHCO_3$ (100 mL). The layers were separated, and the aqueous phase was back-extracted with an additional portion of ether (25 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. Purification by flash chromatography using 3:1 methylene chloride/hexane as eluant afforded in order of elution **6** (0.600 g, 43%) and **7** (0.350 g, 25%). **6**: mp 146.5–148 °C; $^1$H NMR $\delta$ 6.74 (s, 1 H), 6.55 (s, 1 H), 4.50 (t, 2 H, $J$ = 8.4 Hz, H-2,2′), 4.39 (s, 1 H, OH), 3.12 (t, 2 H, $J$ = 8.4 Hz, H-3,3′), 1.37 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3600, 3430 cm$^{-1}$; LRMS, *m/e* 192 (M), 177, 149. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.25; H, 8.04. **7**: mp 107–109 °C; $^1$H NMR $\delta$ 6.54 (br s, 2 H, H-4, H-6), 4.50 (t, 2 H, $J$ = 8.4 Hz, H-2,2′), 4.30 (s, 1 H, OH), 3.09 (t, 2 H, $J$ = 8.4 Hz, H-3,3′), 1.31 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3595, 3430 cm$^{-1}$; LRMS, *m/e* 192 (M), 177, 149. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.06; H, 8.43.

**4,5,6,7-Tetrahydro-4-benzofuranone (10).** To a mechanically stirred ice-cooled suspension of 1,3-cyclohexanedione (67.8 g, 605 mmol) in water (230 mL) was added a solution of potassium hydroxide (42.0 g, 758 mmol) in water (230 mL) at a rate such that the temperature of the reaction mixture did not exceed 12 °C. Upon completion of the addition, potassium iodide (20.0 g, 121 mmol) was added to the resulting clear amber solution followed by the dropwise addition of 50% aqueous chloroacetaldehyde (Fluka Chemical used as received, 80 mL) over 25 min. The reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the dropwise addition of 2 N HCl until acid to pH paper, and then methylene chloride (300 mL) was added. After filtering to clarify the emulsion, the organic layer was separated and the aqueous layer extracted with two additional portions of methylene chloride (75 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and vacuum distilled to afford **10** (48.5 g, 58%): bp 85 °C (0.5 mmHg) [lit.[20] bp 118–122 °C (2 mmHg)]; $^1$H NMR $\delta$ 7.31 (d, 1 H, $J$ = 1.8 Hz, H-2), 6.67 (d, 1 H, $J$ = 1.8 Hz, H-3), 2.88 (t, 2 H, $J$ = 6.2 Hz), 2.52 (t, 2 H, $J$ = 6.5 Hz), 2.16 (quintet, 2 H, $J$ = 6.0 Hz, H-6,6′); IR ($CHCl_3$) 1670 cm$^{-1}$; LRMS, *m/e* 136 (M), 108, 80.

**4-*tert*-Butyl-6,7-dihydrobenzofuran (11).** A 2000-mL three-neck flask fitted with a nitrogen inlet, low-temperature thermometer, and 500-mL pressure-equilibrated dropping funnel was flame-dried and charged with dry hexane (freshly distilled from calcium hydride, 200 mL). The flask was cooled with an external dry ice/acetone bath, and then *tert*-butyllithium (1.7 M in pentane, 200 mL, 340 mmol) was added via double-ended needle transfer. The resulting solution was cooled to −65 °C internal temperature then a solution of **10** (40.00 g, 294 mmol) in a mixture of ether (100 mL) and hexane (300 mL) was added dropwise over 1 h at a rate such that the reaction temperature did not exceed −55 °C. Upon completion of the addition the reaction mixture was stirred with dry ice/acetone cooling for 10 min, the cooling bath was removed, and the reaction was allowed to gradually warm. After 1 h the temperature had reached 5 °C. The reaction was quenched by the dropwise addition of water (40 mL), followed immediately by 2 N HCl (200 mL) and tetrahydrofuran (200 mL). The reaction mixture was then poured into a 4000-mL Erlenmeyer flask containing 2 N HCl (200 mL) and the resulting mixture diluted to a total volume of 2800 mL with tetrahydrofuran. The elimination was allowed to proceed for 2.5 h, then 20% NaCl (500 mL) was added, and the layers were separated. The aqueous layer was reextracted with ether (500 mL), and the combined organic layers were washed with 20% NaCl (500 mL), dried ($Na_2SO_4$), and concentrated to a reddish oil (48.7 g), which was distilled. A constant boiling fraction [bp 58 °C (0.2 mmHg)] proved to be an azeotropic mixture of **10** and **11**. Consequently the total distillate was combined and chromatographed (Waters Prep 500A) with hexane as eluant to afford **11** (24.26 g, 47%) as a colorless liquid. **11**: bp 59 °C (0.1 mmHg); $^1$H NMR $\delta$ 7.26 (d, 1 H, $J$ = 1.6 Hz, H-2), 6.52 (d, 1 H, $J$ = 1.6 Hz, H-3), 5.39 (t, 1 H, $J$ = 4.4 Hz, H-5), 2.70 (t, 2 H, $J$ = 8.4 Hz, H-7,7′), 2.50–2.34 (m, 2, H, H-6,6′), 1.18 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 1615, 1570 cm$^{-1}$; LRMS, *m/e* 176 (M), 119. Anal. Calcd for $C_{12}H_{16}O$: C, 81.79; H, 9.15. Found: C, 81.84; H, 9.15.

***trans*-4-*tert*-Butyl-4,5,6,7-tetrahydro-5-benzofuranol (12).** A flame-dried 2000-mL three-neck flask fitted with a 250-mL pressure-equilibrated dropping funnel, an internal thermometer,

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and nitrogen inlet was charged with a solution of **11** (24.26 g, 137.8 mmol) in dry tetrahydrofuran (300 mL). The solution was cooled to 4 °C, and then a solution of borane (1 M in tetrahydrofuran, 142 mL) was added dropwise over 20 min such that the internal temperature did not exceed 5 °C during the addition. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature and stir for 2.5 h. The reaction was then quenched by the dropwise addition of water (9.5 mL) followed (after hydrogen evolution was complete) by the addition of 2.5 N NaOH (280 mL). Hydrogen peroxide (30% aqueous solution, 16 mL) was carefully added dropwise such that the reaction temperature was 45 °C upon completion of the addition. An oil bath was added and the reaction mixture maintained at 45–50 °C for 1 h. The reaction mixture was allowed to cool and then diluted with 20% NaCl (500 mL). The layers were separated, and the aqueous layer was extracted with an additional portion of tetrahydrofuran (300 mL). The combined organic extracts were washed with 20% NaCl (500 mL), dried ($MgSO_4$), and concentrated. Trituration with hexane afforded 11.65 g of **12**. The mother liquors were chromatographed (Waters Prep500A) with 10% ethyl acetate in hexane as eluant to afford an additional 10.20 g (total yield 82%) of **12**: mp 81–83 °C; $^1H$ NMR $\delta$ 7.24 (m, 1 H, H-2), 6.23 (d, 1 H, $J$ = 1.6 Hz, H-3), 4.23 (br, m, 1 H, $W_{0.5}$ = 8.8 Hz, H-5), 2.68–2.55 (m, 2 H, H-7,7′), 2.43 (br s, 1 H, $W_{0.5}$ = 4.4 Hz, H-4), 2.04–1.92 (m, 2 H, H-6,6′), 0.99 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3570, 3420 $cm^{-1}$; LRMS, $m/e$ 194 (M), 137 (base). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.21; H, 9.34. Found: C, 73.92; H, 9.11.

**4-*tert*-Butyl-4,5,6,7-tetrahydro-5-benzofuranone (13).** A 1000-mL three-neck flask fitted with a 250-mL dropping funnel, mechanical stirrer, and an internal thermometer was flame-dried, then charged with a solution of oxalyl chloride (13.4 mL, 19.5 g, 130 mmol) in methylene chloride (240 mL), and cooled to −78 °C with a dry ice/acetone bath. A solution of dimethyl sulfoxide (21.3 mL, 23.5 g, 300 mmol) in methylene chloride (55 mL) was added dropwise over 15 min while the reaction temperature was maintained below −70 °C. The mixture was allowed to stir for an additional 20 min, and then a solution of **12** (21.85 g, 112.5 mmol) was added dropwise over about 15 min. The mixture was stirred at −78 °C for 1 h, and then triethylamine (freshly distilled from $CaH_2$, 87 mL, 625 mmol) was added dropwise over about 20 min. During the addition the reaction temperature increased to −50 °C. The cooling bath was removed and the white suspension allowed to warm to room temperature over 1 h. The reaction was then poured into water (900 mL), and the layers were separated. The aqueous layer was reextracted with methylene chloride (300 mL), and the combined organic layers were extracted sequentially with 2 N HCl (500 mL), 5% $NaHCO_3$ (1000 mL) and 20% NaCl (1000 mL), dried ($MgSO_4$), and concentrated to a dark oil. Chromatography (Waters Prep 500A) with 10% ethyl acetate in hexane as eluant afforded **13** (17.70 g, 81.8%) as a pale yellow oil, which slowly darkened upon prolonged standing. **13**: bp 100–105 °C (0.2 mmHg); $^1H$ NMR $\delta$ 7.35 (d, 1 H, $J$ = 1.8 Hz, H-2), 6.27 (d, 1 H, $J$ = 1.8 Hz, H-3), 3.22–2.52 (m, 5 H, H-4,6,6′,7,7′), 1.02 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 1710 $cm^{-1}$; LRMS, $m/e$ 192 (M), 136 (base). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39. Found C, 75.01; H, 8.55.

**4-*tert*-Butyl-5-benzofuranol (1).** A mixture of **13** (1.00 g, 5.2 mmol) and sulfur (0.167 g, 1 equiv) in a sealable tube was flushed with nitrogen, sealed, and heated to 225 °C for 30 min. An additional portion of sulfur (0.030 g) was then added and the mixture heated an additional 15 min. After cooling the total reaction mixture was taken up in a small portion of methylene chloride and applied directly to a flash silica gel column. Elution with 5% ethyl acetate in hexane gave **1** (0.520 g, 52%). An analytical sample was prepared by sublimation at 55 °C and 0.2 mmHg. **1**: mp 53–56 °C; $^1H$ NMR $\delta$ 7.52 (d, 1 H, $J$ = 2.1 Hz, H-2), 7.20 (dd, 1 H, $J$ = 8.5, 1.0 Hz, H-7), 7.10 (dd, 1 H, $J$ = 2.1, 1.0 Hz, H-3), 6.65 (d, 1H, $J$ = 8.5 Hz, H-6), 4.69 (s, 1 H, OH), 1.59 (s, 9 H, $C(CH_3)_3$); IR ($CCl_4$) 3530 $cm^{-1}$; LRMS, $m/e$ 190 (M), 175 (base), 147. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.42; H, 7.71.

**4-*tert*-Butyl-2,3-dihydro-5-benzofuranol (2).** To a solution of **1** (0.660 g, 3.47 mmol) in acetic acid (20 mL) was added 10% palladium-on-carbon (0.130 g) and the mixture hydrogenated overnight at 40 psi. The reaction mixture was taken up in ether (25 mL) and filtered through a bed of Celite to remove the catalyst. The filtrate and washings were diluted with water (100 mL) and ether (50 mL) and the layers separated. The aqueous layer was washed with an additional portion of ether (50 mL), and the combined extracts were washed sequentially with 5% $NaHCO_3$ (3 × 50 mL), water (50 mL), and 20% NaCl (50 mL), and then dried ($MgSO_4$), and concentrated. Purification by flash chromatography with 5% ethyl acetate in hexane as eluant gave pure **2** (0.515 g, 77%): mp 184–185 °C; $^1H$ NMR $\delta$ 6.52 (d, 1 H, $J$ = 8.2 Hz, H-6(7)), 6.46 (d, 1 H, $J$ = 8.2 Hz, H-7(6)), 4.43 (t, 2 H, $J$ = 8.5 Hz, H-2,2′), 4.40 (s, 1 H, OH), 3.44 (t, 2 H, $J$ = 8.5 Hz, H-3,3′), 1.48 (9 H, s, $C(CH_3)_3$); IR ($CHCl_3$) 3600, 3500–3250 $cm^{-1}$; LRMS, $m/e$ 192 (M), 177 (base), 150, 149, 135. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.05; H, 8.42.

**4-*tert*-Butyl-5-benzofuranol-6-carboxaldehyde (9).** To a solution of ethyl formate (28.8 g, 389 mmol) in toluene (185 mL) was added sodium hydride (97%, 4.66 g, 194 mmol), and to the resulting suspension was added dropwise a solution of **13** (12.5 g, 65.0 mmol) over 30 min (gas evolution). The mixture was allowed to stir at room temperature for 90 min and then quenched by the dropwise addition of 5% $H_2SO_4$ (160 mL). The mixture was diluted with ether (200 mL), and the layers were separated. The aqueous layer was extracted with ether (2 × 100 mL), and the combined organic layers were washed with 20% NaCl (500 mL), dried ($MgSO_4$), and concentrated to a dark oil. The residue was taken up in benzene (240 mL) and DDQ (15.79 g, 69.55 mmol) was added in portions. The mixture was allowed to stir for 45 min at room temperature at which point a precipitate had separated. The reaction mixture was filtered and concentrated to a black tar. The tar was taken up in chloroform (50 mL) and diluted with hexane (100 mL). The tarry solid which separated was removed by filtration and the filtrate concentrated and chromatographed (Waters Prep 500A, 5% ethyl acetate in hexane as eluant) to afford **9** as a yellow solid (9.4 g, 66%): mp 77–78 °C; $^1H$ NMR $\delta$ 11.65 (s, 1 H, OH), 9.88 (s, 1 H, CHO), 7.72 (d, 1 H, $J$ = 2.4 Hz, H-2), 7.52 (d, 1 H, $J$ = 0.8 Hz, H-7), 7.21 (dd, 1 H, $J$ = 2.4, 0.8 Hz, H-3), 1.63 (s, 9 H, $C(CH_3)_3$); IR ($CHCl_3$) 3080, 1645, 1625 $cm^{-1}$; LRMS, $m/e$ 218 (M), 203 (base), 175, 147, 136, 108. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.56; H, 6.47. Found: C, 71.32; H, 6.49.

## Addition and Substitution Reactions of Chloropyrimidines with Lithium Reagents

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Pyrimidines bearing halogeno substituents at activated positions 2, 4, and 6 are a cornerstone to diverse modifications of the pyrimidine ring. The polyhalogenated compounds undergo regioselective and stepwise substitutions with common nucleophiles such as hydroxide ion, alkoxides, mercaptides, and amines.[1] These reactions have produced many biologically active derivatives including compounds, synthesized in this laboratory, that enhance the activity of known anticancer agents.[2]

Halogenopyrimidines are normally obtained from hydroxypyrimidines; several other less convenient methods are also known.[1a] Few studies have been devoted to the synthesis of substituted halogenopyrimidines via the dis-

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