enone (1.18 mmol). The mixture was stirred for 5 min, and boron trifluoride etherate (0.21 mL, 1.71 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min followed by the addition of 50 mL of a 1:1 concentrated NH_4OH/saturated NH_4Cl solution. The mixture was extracted with methylene chloride, and the combined organic extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed in vacuo to give the crude product, which was purified by flash chromatography.

6-[(Methoxymethoxy)methyl]-2,2-dimethyl-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one: ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 3 H), 1.35 (s, 3 H), 2.04 and 2.69 (ABX, J_{AB} = 18.02 Hz, J_{AX} = 9.25 Hz, J_{BX} = 1.71 Hz, 2 H), 2.53 (m, 1 H), 3.22 (s, 3 H), 3.55 (ABX, J_{AB} = 9.30 Hz, J_{AX} = 2.87 Hz, J_{BX} = 3.24 Hz, 2 H), 4.18 (d, J = 5.20 Hz, 1 H), 4.46 (AB q, J = 6.61 Hz, $\Delta\nu_{AB}$ = 11.4 Hz, 2 H), 4.60 (d, J = 5.33 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.40, 26.52, 36.98, 37.24, 55.27, 68.99, 78.70, 81.32, 96.26, 111.10, 212.74. Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.22; H, 8.07.

3-[(Methoxymethoxy)methyl]cyclohexanone: ^{1}H NMR ($CDCl_3$) δ 1.30–1.64 (m, 2 H), 1.75–2.34 (m, 7 H), 3.22 (s, 3 H), 3.32 (d, J = 5.45 Hz, 2 H), 4.48 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 24.61, 27.80, 38.84, 41.05, 44.45, 54.18, 71.27, 96.18, 210.6. Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.92; H, 9.18.

***trans*-1-Acetyl-2-[(methoxymethoxy)methyl]cyclohexane**: ^{1}H NMR ($CDCl_3$) δ 1.20–1.88 (m, 8 H), 2.11 (s, 3 H), 2.28 (m, 1 H), 2.61 (m, 1 H), 3.27 (s, 3 H), 3.44 (d, J = 7.26 Hz, 2 H), 4.48 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 22.47, 24.04, 24.09, 27.35, 28.78, 37.45, 50.76, 55.14, 67.93, 96.48, 210.93. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.06. Found: C, 66.18; H, 10.20.

Acknowledgment. This work was supported by a grant (CHE 86-07956) from the National Science Foundation and a graduate assistantship award from the office of the Vice-President for Research, Wayne State University.

Registry No. 1, 27490-33-1; 5, 100045-83-8; Bu_3SnH, 688-73-3; $CH_2(COH_3)_2$, 109-87-5; $CH_3OCH_2OCH_2OCH_2SnBu_3$, 115384-51-5; $PhC(O)CH(CH_3)_2$, 611-70-1; $PhCH_2C(O)CH_2CH_3$, 1007-32-5; PhCHO, 100-52-7; $PhC(OH)(CH_2OCH_2OCH_3)CH(CH_3)_2$, 115384-54-8; $PhCH_2C(OH)(CH_2OCH_2OCH_3)CH_2CH_3$, 115384-55-9; $PhCH(OH)CH_2OCH_2OCH_3$, 115384-56-0; $CuBrMe_2S$, 54678-23-8; $LiCH_2OCH_2OCH_3$, 115384-62-8; cycloheptanone, 502-42-1; 2-methylcyclohexanone, 583-60-8; *cis*-3a,6a-dihydro-2,2-dimethyl-4*H*-cyclopenta-1,3-dioxol-4-one, 40269-54-3; 2-cyclohexene-1-one, 930-68-7; 1-(1-cyclohexen-1-yl)ethanone, 932-66-1; 1-[(methoxymethoxy)methyl]cycloheptanol, 115384-52-6; 1-[(methoxymethoxy)methyl]-2-methylcyclohexanol (isomer 1), 115384-53-7; 2,2-dimethyl-4-[(methoxymethoxy)methyl]-3aβ,6aβ-dihydro-4*H*-cyclopenta-1,3-dioxol-4α-ol, 115384-57-1; 6-[(methoxymethoxy)methyl]-2,2-dimethyl-3aβ,5,6α,6aβ-tetrahydro-4*H*-cyclopenta-1,3-dioxol-4-one, 115384-58-2; 3-[(methoxymethoxy)methyl]cyclohexanone, 115384-59-3; *trans*-1-acetyl-2-[(methoxymethoxy)methyl]cyclohexane, 115384-60-6; 1-[(methoxymethoxy)methyl]-2-methylcyclohexanol (isomer 2), 115384-61-7.

Regiospecific 1,4-Addition with Grignard-Derived Mixed Triorganozincate Reagents

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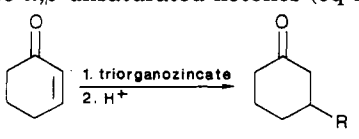
It has been previously reported that "triorganozincate" type reagents are convenient and synthetically useful reagents for transferring various organic moieties in a 1,4-fashion to α,β-unsaturated ketones (eq 1).[1-4] These



(1)

reports have involved four types of triorganozincate reagents[5]—R_3ZnLi,[1] RR'_2ZnLi,[2,3] R_3ZnMgX,[3,4] and RR'_2ZnMgX.[3] Methyl has been shown to be especially effective as the nontransferring or "dummy ligand" (R') in "mixed" (RR'_2) triorganozincates.[2,3]

We describe herein the results of our study of the 1,4-addition reactions with Grignard-derived mixed triorganozincate reagents. Although RMe_2ZnMgX type reagents were reported by Oshima and co-workers[3] during the course of our study, we are now prompted to publish our findings in view of the following differences. Our experiments were carried out at 0 °C rather than −78 °C, thus demonstrating one of the advantages of these reagents—thermal convenience. Also, our report includes enones other than 2-cyclohexene-1-one, and the yields of 1,2-addition products are given. Furthermore, the Grignard-derived mixed triorganozincates in the Oshima report were prepared by a procedure that involves two volumetric measurements (hexane/Me_2Zn solution[6] and Grignard solution) and which consequently requires prior knowledge of two concentrations. The Grignard-derived mixed triorganozincates reported herein were prepared from crystalline $ZnCl_2$·TMEDA (TMEDA = $Me_2NCH_2CH_2NMe_2$) by a procedure that involves only one volumetric measurement (the Grignard solution) and which consequently requires prior knowledge of only one concentration.

To further clarify this last point, it had been previously shown that triphenylmethane can be used to signal the end point in the formation of lithium triorganozincates (R_3ZnLi) by the addition of RLi to $ZnCl_2$ or $ZnCl_2$·TMEDA.[1] Disappointly, we had found that, when a Grignard reagent is used in place of an alkyllithium (i.e. in the preparation of R_3ZnMgX type reagents), the color change appears gradually during the addition of the 3 equiv of RMgX rather than sharply at the end of the addition of the third equivalent.[4] When preparing the Grignard-derived mixed triorganozincate reagents, we again faced this gradual color change. In order to take advantage of at least part of the convenience and accuracy of using an indicator, we arrived at the following procedure. An indicator (triphenylmethane) was used to prepare $^2/_3$ mmol of Me_3ZnLi, which was then converted to 1 mmol of Me_2Zn by adding $^1/_3$ mmol of $ZnCl_2$·TMEDA. This was followed by the addition of 1 mmol of RMgCl to give 1 mmol of the desired reagent (eq 2).

$$^2/_3ZnCl_2\cdot TMEDA \xrightarrow{2MeLi} {}^2/_3Me_3ZnLi \xrightarrow{^1/_3ZnCl_2\cdot TMEDA} Me_2Zn \xrightarrow{RMgCl} RMe_2ZnM\ (M = MgCl/Li) \quad (2)$$

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(3) Tuckmantel, W.; Oshima, K.; Hozaki, N. *Chem. Ber.* **1986**, *119*, 1581-1593.

(4) Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993-3996, and presented in part at the 19th Great Lakes Regional Meeting of the American Chemical Society, West Lafayette, IN, June 1985, No. 278.

(5) None of the experiments in this or any of the above referenced papers prove the existence of a discrete triorganozincate species. Formulas such as RMe_2ZnLi or $R_3ZnMgCl$ at the very least then, represent the stoichiometry involved in preparing the reagents. Spectroscopic evidence of one particular R_3ZnLi type species, however, has been reported, see: Waack, R.; Doran, M. A. *J. Am. Chem. Soc.* **1963**, *85*, 2861-2863.

(6) Solutions of Me_2Zn in ether, hexane, or any other solvent are not commercially available in the USA. Neat Me_2Zn (95%) is available from Alfa for $450/25 g. Two other companies offer higher purity material but at substantially higher prices. (Based on information given in *Chem Sources-USA*; Directories Publishing: Clemson, SC, 1987; and telephone calls to the companies listed.)

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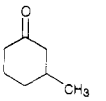
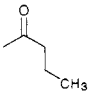
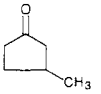
Table I. Reactions of α,β-Unsaturated Ketones with Mixed Triorganozincates (RMe_2ZnM, M = Metal) Derived from $ZnCl_2$•TMEDA, CH_3Li, and RMgCl

entry	α,β-unsaturated ketone	R	products (compound number, % yield[a]) 1,4-addn of R	1,2-addn of R	1,4-addn of CH_3	1,2-addn of CH_3
						
1		*n*-butyl	**1**, 89	**2**, 0	**3**, 3	**4**, 5
2		isopropyl	**5**, 85	**6**, 0	**3**, 0–2	**4**, 0–2
3		phenyl	**7**, 18	**8**, 48	**3**, 7	**4**, 11
						
4		*n*-butyl	**9**, 62	**10**, trace	**11**, trace	**12**, trace
5		isopropyl	**13**, 83	**14**, 0	**11**, trace	**12**, trace
6		phenyl	**15**, 20	**16**, 4	**11**, trace	**12**, trace
						
7		*n*-butyl	**17**, 70	**18**, 0	**19**, 4	**20**, 1
8		isopropyl	**21**, 93	**22**, 0	**19**, trace	**20**, trace

[a] Determined by GC.

Our results are summarized in Table I. We found that 4-methyl-3-penten-2-one (not in the table) failed to give much, if any, of the 1,4-addition products. Thus it appears that β-disubstitution strongly discourages 1,4-addition with these reagents.

Although the mixed triorganozincates in this report are "Grignard-derived", both lithium(I) and magnesium(II) are present. Thus, it is not known if our reagents are lithium or magnesium triorganozincates or a mixture of the two. One observation, however, does merit attention. The *magnesium* phenyl zincates $PhMe_2ZnMgBr$[3] and $Ph_3ZnMgCl$[4] react with 2-cyclohexen-1-one to give 3-phenylcyclohexanone in 62%[3] and 64%[4] yield, respectively, whereas the Grignard-derived mixed reagent $PhMe_2ZnM$ (M = metal) (entries 3 and 6) and the *lithium* phenyl zincates $PhMe_2ZnLi$[2] and Ph_3ZnLi[1] give only very low yields of that same 1,4-addition product.[2,1] That is, the reactivity of the PhMgCl/MeLi derived reagent mimics the reactivity of the *lithium* phenyl zincates rather than that of the *magnesium* phenyl zincates. Even when the temperature and reaction times were varied, the phenyl group failed to transfer efficiently (entries 3 and 6).

Experimental Section

^1H NMR spectra were recorded on a Varian T-60. A Varian Aerograph 90-P with a $^1/_4$ in. × 6 ft column packed with 3% SE-30 on 100/120 Varapact No. 30 was used for preparative GC. Analytical GC was performed on a Varian 3300 equipped with a stainless steep $^1/_8$ in. × 6 ft column packed with 10% OV-1 on WHP 80/100. Recording and integration were done with a Shimadzu C-R3A Chromatopac.

Chemicals. Tetrahydrofuran (THF) was stored under reflux with sodium and benzophenone. The α,β-unsaturated ketones were obtained commercially and, except for 2-cyclopenten-1-one, were distilled prior to use. The Grignard reagents were prepared in diethyl ether by standard methods from the corresponding organohalides and magnesium. The concentration of each Grignard reaent was determined by the procedure described in the R_3ZnMgX paper.[4]

$ZnCl_2$•TMEDA was prepared by Isobe's method,[1] i.e. 19 mL of saturated $ZnCl_2$/THF solution and 5 mL of TMEDA were mixed and allowed to stand several hours at 25 °C. The crude crystals were separated and recrystallized from THF: white needles, mp 176–177 °C.

General Procedure. To a stirring solution of 0.667 mmol (168 mg) of $ZnCl_2$•TMEDA and 2 mg of triphenylmethane in 5 mL of THF at 0 °C under an atmosphere of dry N_2 was added enough methyllithium (Alfa) to produce a persistent light red color. This was followed by the addition of 0.333 mmol (84.0 mg) of $ZnCl_2$•TMEDA. The ice bath was removed, and the solution was allowed to stir for about 15 min. The solution was once again cooled with the ice bath, and then 1.00 mmol of Grignard reagent was added via syringe followed immediately by 1.00 mmol of α,β-unsaturated ketone. After 15 min, the ice bath was removed and stirring was continued for another 15 min. The reaction mixture was diluted with 5 mL of diethyl ether and 5 mL of 10% aqueous NH_4Cl. The layers were separated, the aqueous phase was extracted with 5 mL of ether, and the combined organic phase was washed with 5 mL of H_2O, dried with Na_2SO_4, and then evaporated to give the crude product, sometimes contaminated with a small amount of $ZnCl_2$•TMEDA. When the yields were determined by GC, an internal standard was added after the aqueous NH_4Cl, and the organic phase was not evaporated. Since the GC retention times of compounds **11** and **12** were very close to that of THF, it was necessary to employ the following minor modifications in the workup procedure when determining the yield of these two compounds: prior to the addition of ether and aqueous NH_4Cl, the reaction mixture was cooled with an ice water bath and the solvent was completely removed under vacuum.

Identification of Products. The identity of each of the 1,4- and 1,2-addition products listed in the table was confirmed by comparing the GC retention time (coinjection) and, for compounds **1**, **3–5**, **7–9**, **13**, **15**, **17**, and **21**, the ^1H NMR spectrum with that of authentic material. The sources of the authentic materials are as follows: compounds **3**, **9**, **11–13**, **15**, and **19** were obtained commercially; allylic alcohols **10**, **14**, and **16** were prepared from vinylmagnesium bromide and the corresponding methyl ketone; 1,4-addition products **1**, **5**, **7**, **17**, and **21** were prepared by the reaction of a triorganozincate or diorganocuprate with the appropriate α,β-unsaturated ketone; 1,2-addition products **2**, **4**, **8**, **18**, and **20** were prepared by the reaction of *n*-butyllithium, methyllithium, or phenyllithium with the appropriate α,β-unsaturated ketone; 1,2-addition products **6** and **22** were prepared by the reaction of isopropylmagnesium bromide with an α,β-unsaturated ketone and purified by preparative GC.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1, 39178-69-3; **2**, 88116-46-5; **3**, 591-24-2; **4**, 23758-27-2; **5**, 23396-36-3; **6**, 102936-19-6; **7**, 20795-53-3; **8**, 60174-90-5; **9**, 111-13-7; **13**, 110-12-3; **15**, 2550-26-7; **16**, 6051-52-1; **17**, 57283-81-5; **18**, 53253-12-6; **19**, 1757-42-2; **20**, 40459-88-9; **21**,

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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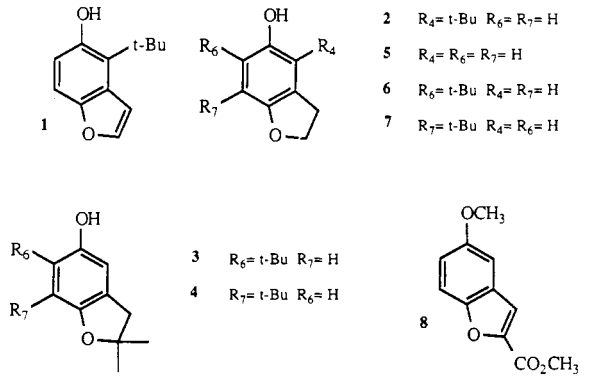
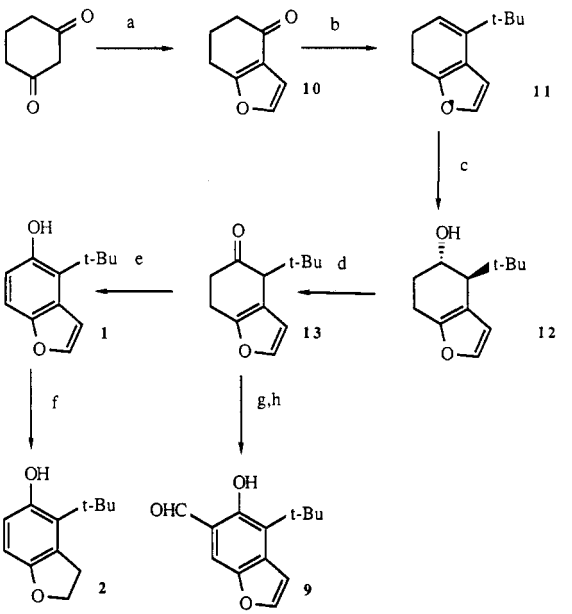
We recently described a novel series of 6-substituted 2,3-dihydro-5-benzofuranols as antioxidant based inhibitors of 5-lipoxygenase.[1,2] As part of an effort to improve the systemic activity of these agents, we required a convenient synthesis of 4-*tert*-butyl-5-benzofuranol (**1**) and 4-*tert*-butyl-2,3-dihydro-5-benzofuranol (**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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