mL (2.3 mmol) of dry pyridine gave 0.3 g (0.9 mmol, 41%) of **4b** (Kugelrohr distillation, bp 182–187 °C, 5 mmHg): ^{1}H NMR ($CDCl_3$) δ 0.9–1.2 (d, 1 H), 2.4 (d, 1 H), 3.9 (d, 1 H), and 7.2 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.0 (q), 19.8 (q), 38.2 (s), 52.5 (d), 71.0 (d), 128.3 (d), 129.0 (d), 133.1 (d), and 137.0 ppm (s); IR (neat) 3100, 2980, 1465, 1450, 1375, and 660 cm^{-1}; mass spectrum (*m/z*, rel intensity) 284 (43, P + 2), 282 (30, P), 205 (87), 189 (23), 161 (41), 149 (54), 109 (57), 95 (100), 77 (83), and 69 (72).

Reaction with Lithium Dialkylcuprates. A solution of 2 equiv of the appropriate lithium dialkylcuprate in anhydrous ether was treated with the appropriate bromide at −20 °C and stirred for 15 h. The reaction was quenched with water and filtered through a 0.25-in. pad of Celite. Separation of the phases was followed by drying the ether phase ($MgSO_4$) and removal of solvents under reduced pressure. The products were purified by chromatography on silica gel with pentane.

In each case a "standard" concentration of dialkylcuprate was used. A solution of 13.4 mL of 2.4 M *n*-butyllithium in 30 mL of ether was treated with 2.3 g (16.1 mmol) of CuBr at −78 °C, warmed to −40 °C for 15 min, and treated with bromide. The reaction was then warmed to −20 °C. Similarly, a solution of 5.9 mL of 1.4 M methyllithium was treated with 0.6 g (4.1 mmol) of CuBr at −78 °C and warmed to 0 °C for 10 min. The slurry was cooled to −20 °C and treated with bromide. The diphenylcuprate was prepared similarly by reaction of 15 mL of 1.1 M phenyllithium and 2.93 g (20.4 mmol) of CuBr. Reaction of 13.0 mL of 1.2 M *tert*-butyllithium and 1.75 g (12.2 mmol) of CuBr at −78 °C for 30 min was followed by treatment with bromide at −78 °C, stirring for 1 h, and slow warming to −20 °C.

4-(Phenylthio)-3-decene (5a). Reaction of 0.5 g (1.8 mmol) of **4a** with the lithium di-*n*-butylcuprate slurry gave 0.27 g (1.1 mmol, 66%) of **5a** as a colorless oil (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 1.1 (t, 6 H), 0.9–1.5 (m, 8 H), 2.3 (m, 4 H), 5.9 (t, 1 H), and 7.2 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.6 (t), 14.1 (t), 22.2 (d), 22.9 (d), 32.9 (d), 35.6 (d), 43.5 (d), 125.8 (d), 128.8 (d), 129.3 (d), 127.0 (s), and 154.0 ppm (s); IR (neat) 3100, 2980, 1465, 1450, 1375, and 660 cm^{-1}; mass spectrum (*m/z*, rel intensity) 248 (10, P), 246 (100), 203 (25), 189 (30), 147 (30), 136 (20), 97 (80), 79 (75), and 41 (80). Anal. Calcd for $C_{16}H_{24}S$ *m/z* 248.1600, obsd *m/z* 248.1606 (±1.2 mmu).

Capillary GC/MS analysis revealed **5a** to be a 53:47 mixture of *E*:*Z* isomers.

4-(Phenylthio)-3-heptene (5b). Reaction of 0.3 g (1.0 mmol) of **4a** and the lithium dimethylcuprate slurry gave 0.12 g (0.6 mmol, 55%) of **5b** as a 70:30 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 1.1 (t, 6 H), 1.0–2.7 (m, 4 H), 5.9 (t, 1 H), and 7.0–7.2 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.5 (q), 18.0 (q), 22.9 (t), 30.7 (t), 125.8 (d), 127.6, 128.0 (d), 128.9 (d), 129.0 (d), 132.0 (s), and 153 ppm (s); IR (neat) 3100, 2950, 2810, 1600, 1495, 1450, 1375, 700, and 650 cm^{-1}; mass spectrum (*m/z*, rel intensity) 206 (20, P), 204 (60), 189 (21), 175 (32), 134 (35), 110 (70), 79 (85), and 67 (100). Anal. Calcd for $C_{13}H_{18}S$ *m/z* 206.1129, obsd *m/z* 206.1121 (±1.0 mmu).

3-Phenyl-4-(phenylthio)-3-hexene (5c). Reaction of 0.7 g (2.5 mmol) of **4a** and the lithium diphenylcuprate slurry gave 0.38 g (1.4 mmol, 57%) of **5c** as a 55:45 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3 H), 2.0–3.2 (m, 4 H), 4.1 (m, 2 H), 5.7 (t, 1 H), and 6.9–7.5 ppm (m, 10 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 31.2 (t), 37.5 (t), 48.0 (t), 97.0 (d), 126.0 (d), 127.1 (d), 127.5 (d), 128.4 (d), 129.4 (d), 140.0 (s), 140.0 (s), and 155.0 ppm (s); IR (neat) 3150, 2900, 1600, 1500, 1450, 1370, and 710 cm^{-1}; mass spectrum (*m/z*, rel intensity) 268 (3, P), 266 (25), 237 (27), 159 (50), 128 (100), 116 (50), 91 (40), 77 (50), and 51 (20). Anal. Calcd for $C_{18}H_{20}S$ *m/z* 268.1281, obsd *m/z* 268.1277 (±1.3 mmu).

7,7-Dimethyl-4-(phenylthio)-3-octene (5d). Reaction of 0.3 g (1.1 mmol) of **4a** and the lithium di-*tert*-butylcuprate slurry gave 0.13 g (0.5 mmol, 48%) of **5d** as a 60:40 *E*:*Z* mixture of isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 0.9–1.5 (m, 12 H), 2.3 (m, 4 H), 5.8 (t, 1 H), and 7.0–7.5 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 11.6 (q), 22.6 (d), 26.3 (q), 32.6 (s), 35.6 (t), 123.0 (d), 125.1 (d), 128.0 (d), 129.2 (d), 139.1 (s), and 155.0 ppm (s); IR (neat) 3150, 2950, 1600, 1500, 1470, 1350, and 700 cm^{-1}; mass spectrum (*m/z*, rel intensity) 248 (7, P), 246 (60), 231 (8), 217 (7), 191 (11), 137 (15), 121 (90), and 57 (100). Anal. Calcd for $C_{16}H_{24}S$ *m/z* 248.1599, obsd *m/z* 248.1590 (±1.2 mmu).

2-Methyl-4-(phenylthio)-3-decene (5e). Reaction of 0.5 g (1.6 mmol) of **4b** and the lithium di-*n*-butylcuprate slurry gave 0.28 g (1.1 mmol, 71%) of **5e** as a 70:30 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3 H), 1.0 (d, 6 H), 1.0–2.6 (m, 10 H), 2.7 (m, 1 H), 5.7 (d, 1 H), and 7.2 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.5 (q), 20.7 (q), 22.8 (q), 28.2 (d), 29.4 (d), 32.9 (d), 33.5 (d), 42.7 (d), 123.4 (d), 125.8 (d), 128.8 (d), 129.3 (d), 132.0 (s), and 154.0 ppm (s); IR (neat) 3150, 2950, 2800, 1600, 1450, 1350, and 700 cm^{-1}; mass spectrum (*m/z*, rel intensity) 262 (5, P), 260 (55), 217 (15), 183 (16), 161 (14), 147 (5), 109 (80), and 95 (100). Anal. Calcd for $C_{17}H_{26}S$ *m/z* 262.1757, obsd *m/z* 262.1747 (±1.3 mmu).

2-Methyl-4-(phenylthio)-3-heptene (5f). Reaction of 0.3 g (0.9 mmol) of **4b** and the lithium dimethylcuprate slurry gave 0.09 g (0.4 mmol, 50%) of **5f** as an 80:20 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 0.9–1.0 (t, 6 H), 1.1 (t, 3 H), 1.8–3.0 (m, 5 H), 5.6 (d, 1 H), and 7.1–7.5 ppm (7, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.7 (q), 18.5 (q), 19.8 (q), 22.6 (t), 29.4 (t), 29.5 (d), 125.1 (d), 126.3 (d), 129.1 (d), 133.0 (s), and 153.2 (s); IR (neat) 3100, 2950, 1600, 1500, 1470, 1350, 700, and 650 cm^{-1}; mass spectrum (*m/z*, rel intensity) 220 (3, P), 218 (80), 208 (10), 189 (5), 161 (20), 141 (50), 109 (100), 98 (80), 77 (50), and 67 (95). Anal. Calcd for $C_{14}H_{20}S$ *m/z* 220.1287, obsd *m/z* 220.1287 (±1.1 mmu).

2-Methyl-6-phenyl-4-(phenylthio)-3-hexene (5g). Reaction of 0.4 g (1.2 mmol) of **4b** and the lithium diphenylcuprate slurry gave 0.2 g (0.76 mmol, 64%) of **5g** as a 95:5 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 6 H), 2.2 (m, 2 H), 2.4 (m, 1 H), 2.6 (t, 2 H), 5.8 (d, 1 H), and 7.0–7.5 ppm (m, 10 H). ^{13}C NMR ($CDCl_3$) δ 21.9 (q), 22.0 (q), 29.4 (d), 125.3 (d), 125.6 (d), 126.0 (d)8, 127.1 (d), 125.5 (d), 128.0 (d), 128.5 (d), 129.3 (d), 139.0 (s), 141.2 (s), and 154.1 ppm (s); IR (neat) 3150, 2900, 2850, 1600, 1500, 1450, 1370, and 700 cm^{-1}; mass spectrum (*m/z*, rel intensity) 282 (7, P), 280 (60), 237 (100), 204 (10), 189 (9), 159 (90), 128 (95), 91 (40), and 77 (30). Anal. Calcd for $C_{19}H_{22}S$ *m/z* 282.1446, obsd *m/z* 282.1440 (±1.4 mmu).

4-(Phenylthio)-2,7,7-trimethyl-3-octene (5h). Reaction of 0.3 g (1.2 mmol) of **4b** with the lithium di-*tert*-butylcuprate slurry gave 0.2 g (0.8 mmol, 66%) of **5h** as a 90:10 mixture of *E*:*Z* isomers (R_f, 0.5): ^{1}H NMR ($CDCl_3$) δ 0.9–2.8 (m, 19 H), 5.7 (d, 1 H), and 7.1–7.5 ppm (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 18.9 (q), 19.0 (q), 26.1 (q), 26.2 (q), 26.3 (q), 28.8 (d), 29.4 (t), 29.5 (t), 125.8 (d), 126.5 (d), 128.0 (d), 129.1 (d), 132.1 (s), and 152.0 (s); IR (neat) 3150, 2950, 1650, 1600, 1500, 1450, 1370, and 700 cm^{-1}; mass spectrum (*m/z*, rel intensity) 262 (3, P), 260 (58), 203 (10), 161 (10), 151 (45), 135 (100), 109 (70), 95 (50), and 57 (80). Anal. Calcd for $C_{17}H_{26}S$ *m/z* 262.1757, obsd *m/z* 262.1744 (±1.3 mmu).

Convenient Approaches to Ketals from Phthalide: Monosubstituted Isobenzofurans

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Two new methods for the formation of ketals from phthalide are described. The ketals are readily converted to monosubstituted isobenzofurans (IBFs),[1] making these among the most easily prepared members of this family of reactive dienes.

The use of phthalide (**1**) for the preparation of the parent IBF was developed in this laboratory some time ago.[2] Procedural improvements[3] and modifications have

(1) The formation of IBFs via ketals, usually with both as proposed reactive intermediates, is discussed in two recent reviews: (a) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (b) Rickborn, B. In *Advances in Theoretically Interesting Molecules*; Thummel, R. P., Ed.; JAI Press, Inc.: Greenwich, CT, in press; Vol. I, Chapter I (Isobenzofurans).

(2) Makhlouf, M. A.; Rickborn, B. *J. Org. Chem.* **1981**, *46*, 2734. See also: Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061.

(3) Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1982**, *47*, 5391.

0022-3263/89/1954-4253$01.50/0

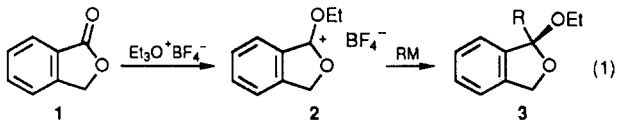
Table I. Yields of Ketals

		reactions of 2			reactions of 1
ketal	R	R_2Mg	RLi	$R_2Cu(CN)Li_2$	RLi
3a	Me	50[a]	55;[a] 66[b]	55[a]	76[b]
3b	*n*-Bu	–	48[a]	<10[a]	61[b]
3c	Ph	0	10[b]	49[b]	58[b]
3d	4-pentenyl	–	50[a]	–	–

[a] Yield after vacuum distillation. [b] Yield after column chromatography.

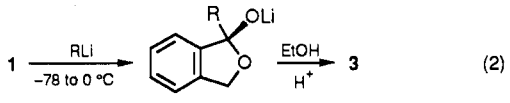
demonstrated the generality of this approach for preparation of 1-alkoxy-IBF,[2] and 1-monoalkyl(aryl)-IBFs from the corresponding 3-alkyl(aryl)phthalides.[4] In each instance O-ethylation of phthalide[5] to yield **2** (or a 3-substituted analogue) is followed either by hydride reduction to give an acetal or by reaction with alkoxide[5,6] to yield an ortho ester. It appeared that ketals could be similarly formed by the reaction of **2** with organometalics. Somewhat surprisingly, the literature contains no mention of such reactions even though **2** is easily prepared and has been known for over 30 years. In fact, there are very few references to reactions of other dioxacarbenium ions with organometalics,[7] in spite of the potential for such reactions to form carbonyl compounds in protected form.

The sequence outlined in eq 1 does indeed furnish ketals (**3**) in moderate yields with the proper choice of organometallic reagent and conditions, as outlined in Table I.



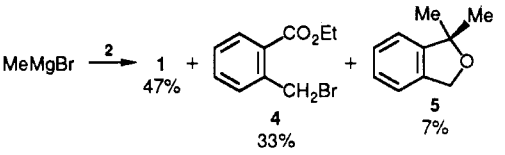
(1)

An even more convenient preparation of **3** was developed when it was found that the reaction of **1** with organolithium reagents could be halted at the monoaddition stage. Workup by addition of acidic ethanol then affords the ethoxy ketal directly. The results of this procedure (eq 2) are also displayed in Table I.



(2)

Reactions of 2. In contrast to the lone literature example[7] of ketal formation from PhMgBr and an isolated dioxacarbenium ion, Grignard reagents fail to yield ketals when mixed with **2**. Both MeMgBr and PhMgBr were examined, and no sign of ketal was detected with either reagent. The addition of **2** to an ethereal solution of MeMgBr led to rapid reaction, as evidenced by the formation of a yellow precipitate which darkened over time. Treatment of the liquid phase with water gave negligible gas evolution, while the precipitate gave some gas evolution on addition of water. The ether phase was worked up under mildly basic conditions to give phthalide (**1**), the bromo ester **4**, and 1,1-dimethylphthalan (**5**) in the chromatographed yields shown in eq 3. The bromo ester



(3)

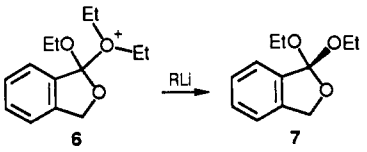
clearly arises from attack of bromide ion at the 3-position of **2**, and it appears that phthalide is similarly formed by bromide displacement of the ethyl group. Although phthalide would be expected from hydrolysis of unreacted **2**, this reaction also gives, in ca. 1/1 ratio,[6] the hydroxy ester analogue of **4** (hydroxyl in place of bromo). Since hydroxy ester was not observed, all of **2** must have been consumed prior to aqueous treatment. The dimethylphthalan (**5**) is believed to arise from further reaction of the desired ketal. It is not formed by dehydration of the corresponding diol, which was shown to be stable to these reaction and workup conditions.

Me_2Mg[8] is suitable for ketal formation, giving compound **3a** in 50% yield. An attempt to prepare and use Ph_2Mg in similar fashion gave no ketal, resulting instead in the formation of unidentified material with an NMR spectrum rich in aromatic proton absorptions.

The preferred procedure for conversion of the phthalidium salt **2** to ketals involves addition of the solid to RLi solutions at −78 °C, followed by gradual warming to room temperature with stirring over a period of 12–20 h. Crude yields which ranged from 90 to 100% of estimated (NMR) ≥90% pure **3a** were obtained in this way. However, significant losses occurred when the ketals were purified by either vacuum distillation or column chromatography, as reflected in the yields shown in Table I. The RLi procedure also proved suitable for the preparation of the *n*-butyl ketal **3b** and the 4-pentenyl ketal **3d**, but a much poorer yield of the phenyl analogue **3c** was realized from similar reaction of **2** with PhLi.

The salt **2** has limited solubility in ether, and at −78 °C essentially no reaction with MeLi takes place, as demonstrated by addition of water to a mixture which had been maintained at −78 °C for 12 h. No ketal was formed; instead a ca. 1:1 mixture of phthalide and hydroxy ester[6] was isolated, signifying hydrolysis of unreacted **2**. The addition of **2** to MeLi in ether at 0 °C was also examined. Although ketal is formed under these conditions, it is accompanied by a significant amount (up to 30%) of the ortho ester **7**. The mechanism of formation of this unexpected product has not been determined, but an interesting possibility involves RLi cleavage (possibly by β-elimination) of the oxonium salt **6**, as shown in eq 4. Alternatively, initially formed ketal may serve as the source of ethoxide for reaction with **2** to form **7**. An attempt to avoid ortho ester formation by the use of hexane solvent with *n*-BuLi gave no reaction (24 h, 0 °C), presumably because of insolubility.

(4) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849.
(5) Merrwein, H.; Borner, P.; Fuchs, O.; Sasse, H. J.; Schrodt, H.; Spille, J. *Chem. Ber.* **1956**, *89*, 2060.
(6) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 1477.
(7) The only definite claim of ketal formation is found in the work of Dimroth et al. (Dimroth, K.; Heinrich, P.; Schromm, K. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 873), who reported that PhMgBr and 4,5-benzo-2-phenyl-1,3-dioxolan-2-ylium tetrafluoroborate gave such reaction; neither conditions nor yield are given. Possibly related reactions of 1,3-dioxolan-2-ylium ions are mentioned (without details) by Raber and Guida (Raber, D. J.; Guida, W. C. *Synthesis* **1974**, 808). The Boudroux–Chichibabin reaction (RMgX + ortho ester to form acetal) is believed to involve the formation of a dioxacarbenium ion intermediate. DeWolfe's monograph (DeWolfe, R. H. *Carboxylic Ortho Acid Derivatives*; Academic Press: New York, 1970; pp 224–230) provides a useful overview of this literature. Itoh et al. (Itoh, O.; Iwakashi, N.; Saitoh, R.; Katano, H.; Fujisawa, Y.; Hasegawa, Y.; Sugita, T.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 177) have described low-yield coupling reactions of 1,3-dioxan-2-ylium ions with the sodium enolates of some 1,3-dicarbonyl compounds. The enolate of cyclohexanone may be implicated in a novel reaction with diethoxycarbenium tetrafluoroborate described by Mock and Tsou (Mock, W. L.; Tsou, H. *J. Org. Chem.* **1981**, *46*, 2557).
(8) Noller, C. R.; White, W. R. *J. Am. Chem. Soc.* **1937**, *59*, 1354.

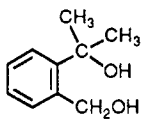


6 7 (4)

The ortho ester **7** is a potentially troublesome impurity since it will form 1-ethoxyisobenzofuran under the same conditions needed to form 1-alkyl(aryl)isobenzofuran from the ketal. Fortunately, low-temperature mixing of **2** with the RLi solution largely avoids this side reaction.

The yield of the phenyl ketal **3c** was improved by the use of the cuprate generated from PhLi and CuCN. However, attempts to prepare the *n*-butyl ketal **3b** in this manner resulted in very low yields, apparently because of further reaction of **3b** leading to 1,1-dibutylphthalan. In the analogous reaction to form the methyl ketal **3a**, it was found that the yield decreased with longer reaction times or temperatures above 0 °C, with concurrent increases in the yield of 1,1-dimethylphthalan (**5**). The organocopper reagent alone does not cause the conversion of **3a** to **5**, as shown by a control experiment in which isolated **3a** was added to the organometalic (6 h, 24 °C). The fluoroborate salt thus appears to be critical for further reaction, possibly by providing a source of BF_3, which is known to catalyze similar reactions of acetals.[9] The difference between the methyl and *n*-butyl reactions is attributed to the greater reactivity of the latter organocopper reagent.[10] Over-reaction of **3a** was easily prevented by terminating the reaction below 0 °C, whereas poor yields of **3b** were obtained even from reactions quenched at −20 °C.

Reactions of 1. It is generally believed that it is difficult to intercept the reaction of a Grignard reagent with a lactone at the monoaddition (lactol) stage, and indeed the literature dealing with RMgX reactions of phthalide suggested that this generalization would hold, except for highly substituted derivatives.[11] This expectation was confirmed when 1 equiv of MeMgBr was added to a solution of **1** at −78 °C followed by slow warming to ambient temperature. A ca. 1:1 mixture of diol **8** and recovered phthalide was isolated, clearly illustrating the difficulty of stopping the reaction at the monoaddition stage.

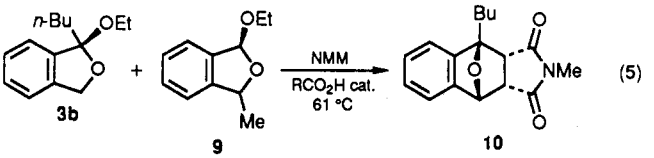


8

In contrast to Grignard/lactone reactions, several examples of halting organolithium/lactone reactions at the lactol stage have been documented, although most involve atypical organolithium reagents (e.g. acetylenic or dithiane derivatives) or substrates (sugar derivatives) which do not allow easy generalization.[12]

We were pleased to find that treatment of phthalide with 1 equiv of MeLi at −78 °C followed by acidic ethanol workup gave ketal **3a** in excellent yield (76% after chromatography). Good yields of the *n*-butyl and phenyl ketals **3b** and **3c** were also obtained using this approach (see Table I). *This is the procedure of choice for preparing ketals from phthalide.*

Isobenzofuran Applications. The ketals in Table I are efficient precursors for monosubstituted IBFs when subjected to base-induced 1,4-elimination,[13] and ketals have also been invoked as intermediates in acid-catalyzed procedures for generating IBFs.[1] Mechanistic considerations[1b] suggest that IBFs will be formed more rapidly from ketals than from the analogous (3-alkyl or aryl) acetals, under either base-induced or acid-catalyzed conditions. Stereochemical constraints and the need to remove a tertiary proton tend to slow the base-induced reaction of e.g. the acetal **9** derived from 3-methylphthalide.[4] The significantly greater reactivity of ketal relative to acetal under acid-catalyzed conditions has now been demonstrated, by the following experiment. A mixture of the ketal **3b** (1 equiv) and acetal **9** (1 equiv), in refluxing chloroform solution with <1 equiv of *N*-methylmaleimide (NMM) and mesitoic acid catalyst, gave *only* the cycloadduct **10**[13] derived from the ketal, as shown in eq 5.



3b 9 10 (5)

A limit of ≤0.5% was established by NMR for the amount of the known 1-methyl-IBF NMM cycloadduct[4] present in the crude product mixture. Since it has been shown that 1-methyl- and 1-butyl-IBF have nearly identical rates of reaction with NMM,[13] it follows that the reaction of ketal **3b** to form the isobenzofuran must be ≥200 times faster than the analogous reaction of **9**. This order is also qualitatively evident from the relatively low temperature needed for the conversion of **3a** to **10**.

Experimental Section

All reactions were carried out under an atmosphere of N_2 in oven-dried glassware. Ether was distilled from $LiAlH_4$ immediately before use. ^1H NMR spectra of $CDCl_3$ solutions were recorded on a Nicolet NT-300 instrument. MS data were obtained by Dr. Hugh Webb on a VG 70-250 spectrometer. Combustion analyses were performed by MicAnal (now Desert Analytics), Tucson, AZ. The *O*-ethylphthalidium salt **2** was prepared as described by Meerwein et al.[5] and stored at −20 °C between uses.

Reaction of MeMgBr with 2. The salt **2** (1.0 g, 4.0 mmol) was added in one portion to a flask containing 4.8 mmol of MeMgBr (1.75 mL of 2.75 M solution) in 20 mL of ether at 0 °C. The ice bath was removed, and the mixture was stirred for 11 h. The color changed from pale to deep orange and then to red-brown within the first hour. Saturated $NaHCO_3$ solution (50 mL) was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine, dried over K_2CO_3, and rotary evaporated to give 670 mg of crude product, which by NMR examination appeared to contain mainly phthalide and the bromo ester. This mixture was chromatographed (silica gel, 25% ether/hexanes to neat ether) to afford: (a) 42 mg (7%) of 1,3-dihydro-1,1-dimethylisobenzofuran (**5**);[14] ^1H NMR (60 MHz) δ 1.51 (s, 6 H), 5.10 (s, 2 H), and 7.0–7.4 ppm (m, 4 H); (b) 322 mg (33%) of the ethyl 2-(bromomethyl)benzoate (**5**); bp 100–105 °C (2 Torr); NMR spectrum in accord with the literature;[15] and (c) 254 mg (47%) of phthalide.

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Ketal Preparations. The procedures used to obtain the data in Table I were uniform for all the substrates. Representative examples are given of the better yield methods.

1,3-Dihydro-1-ethoxy-1-methylisobenzofuran (3a). (a) Reaction of 2 with Me_2Mg. Dimethylmagnesium was prepared by the dropwise addition of 34 mL of dioxane in 60 mL of ether to 109 mL of 2.75 M MeMgBr in ether, in a Schlenk flask at ambient temperature. After 20 h of stirring, the white solid was removed by filtration. An aliquot of the solution was titrated with 0.1 M HCl and found to be 0.65 M in Me_2Mg (83%). To a portion (15.5 mL, 10.0 mmol) of this solution at -78 °C was added 1.0 g (4.0 mmol) of **2** in one portion. The resulting slurry was allowed to warm gradually to 0 °C over 1.75 h and then quenched with $NaHCO_3$ solution. The usual workup gave 803 mg of crude material, which was chromatographed on basic alumina, using hexanes containing 0.5% Et_3N, to afford 355 mg (50%) of pure **3a**: ^1H NMR δ 1.11 (t, 3 H, J = 7 Hz), 1.72 (s, 3 H), 2.93-3.05 (m, 1 H), 3.33-3.45 (m, 1 H), 5.04 (d, 1 H, J = 13 Hz), 5.15 (d, 1 H, J = 13 Hz), 7.21-7.27 (m, 1 H), and 7.28-7.40 ppm (m, 3 H). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.88; H, 7.81.

(b) Reaction of 2 with MeLi. Commercial low halide MeLi (120 mL of 0.31 M in ether, 37.2 mmol) was placed in a 200-mL round-bottom flask with a stir bar and cooled to -78 °C. The salt **2** (7.5 g, 30.0 mmol) was added in one portion, and the resulting slurry was allowed to warm gradually to -10 °C, with stirring over a period of 26 h. It was then quenched by careful addition of 50 mL of saturated $NaHCO_3$ solution. The usual treatment gave 5.2 g of crude product as a yellow oil, which was distilled to give 2.96 g (55%) of pure **3a**, bp 54-57 °C (0.3 Torr).

(c) Reaction of Phthalide with MeLi. To 1.007 g (7.51 mmol) of phthalide in 50 mL of ether at -78 °C was added 5.9 mL (8.25 mmol) of MeLi (1.4 M in ether). After this mixture was stirred in the dry ice bath for 4 h, 5 mL of EtOH was added, and the majority of the solvent was removed by rotary evaporation. An additional 30 mL of EtOH was added, followed by 3 mL of glacial HOAc. This colorless solution was stirred at room temperature for 5 h, poured into 150 mL of saturated $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 5 mL). The usual brine wash, drying, and evaporation gave 1.29 g of crude material. Chromatography as in (a) gave 1.02 g (76%) of pure **3a**.

1-Butyl-1,3-dihydro-1-ethoxyisobenzofuran (3b). (a) Reaction of 2 with *n*-BuLi. Commercial *n*-BuLi (18.75 mL, 1.6 M in hexane, 30 mmol) was placed in a round-bottom flask, and the hexane was removed under vacuum. Diethyl ether (80 mL) was added. After cooling as in (b) above, **2** (5.1 g, 20.4 mmol) was added, and the stirred mixture was allowed to warm to -10 °C over a period of 16 h. The usual workup gave 4.4 g of crude product. Short path distillation gave 180 mg (4%) of the diethyl ortho ester **7**, followed by 2.14 g (48%) of **3b**: colorless oil; bp 69-71 °C (0.07 Torr); ^1H NMR δ 0.84 (t, 3 H, J = 7 Hz), 0.96-1.42 (m, 4 H), 1.09 (t, 3 H, J = 7 Hz), 1.93-2.13 (m, 2 H), 2.93 (dq, 1 H, J = 9 and 7 Hz), 3.36 (dq, 1 H, J = 9 and 7 Hz), 5.03 (d, 1 H, J = 13 Hz), 5.16 (d, 1 H, J = 13 Hz), and 7.20-7.40 ppm (m, 4 H). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.42; H, 9.23.

(b) Reaction of Phthalide with *n*-BuLi. A solution of 1.01 g (7.51 mmol) of phthalide in 50 mL of ether at -70 °C was treated with 5.1 mL (8.26 mmol) of *n*-BuLi in hexane. Subsequent treatment was the same as in (c) above; chromatography gave 1.01 g (61%) of pure **3b**.

1,3-Dihydro-1-ethoxy-1-phenylisobenzofuran (3c). (a) Reaction of 2 with $Ph_2CuCNLi_2$. The homogeneous reagent prepared from 790 mg (8.8 mmol) of CuCN and 10.4 mL (17.6 mmol) of PhLi (1.7 M in cyclohexane/ether) in 50 mL of ether was cooled in the usual way, and 2.0 g (8.0 mmol) of **2** was added on one portion. This slurry was stirred for 20 h while warming to 20 °C. Saturated NH_4Cl solution, brought to pH 8 by the addition of concentrated NH_4OH, was added. The layers were separated, and the aqueous phase was extracted with ether (3 × 30 mL). The usual treatment gave 2.02 g of crude product, which was chromatographed as above to furnish 938 mg (49%) of pure **3c** as a colorless oil: ^1H NMR δ 1.20 (t, 3 H, J = 7 Hz), 3.31 (dq, 1 H, J = 9 and 7 Hz), 3.50 (dq, 1 H, J = 9 and 7 Hz), 5.25 (d, 1 H, J = 13 Hz), 5.34 (d, 1 H, J = 13 Hz), 7.20-7.38 (m, 7 H), and 7.58-7.63 ppm (m, 2 H). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.87; H, 6.62.

(b) Reaction of Phthalide with PhLi. The reaction was done on the same scale and in the same manner as for the aliphatic derivatives above, except for the use of PhLi. Chromatography gave 1.034 g (58%) of pure **3c**.

1,3-Dihydro-1-ethoxy-1-(4-pentenyl)isobenzofuran (3d). The method of Perry et al.[16] was used to convert commercial 4-penten-1-ol to 1-bromo-4-pentene. A solution of 12.5 g (0.084 mol) of the bromide in 10 mL of ether was added via syringe pump (0.5 h) to 2.4 g (0.35 mol) of finely dispersed Li in 35 mL of ether held in an ice bath. After 2 h of stirring at this temperature, the mixture was filtered under N_2 through Celite to give a clear solution of titre 0.85 M (56%). A portion of this material (48 mL, 40.8 mmol) and an additional 80 mL of ether was brought to -70 °C and treated with 8.0 g (32 mmol) of **2** in the usual way. Gradual warming to -10 °C over 12 h followed by the usual workup gave 8.6 g of yellow oil. Short-path distillation gave 4.20 g (56%) of ca. 90% pure **3d**: bp 73-75 °C (0.05 Torr); ^1H NMR δ 1.09 (t, 3 H, J = 7 Hz), 1.12-1.25 (m, 1 H), 1.41-1.56 (m, 1 H), 1.93-2.14 (m, 4 H), 2.88-2.98 (m, 1 H), 3.30-3.40 (m, 1 H), 4.87-4.99 (m, 2 H), 5.11 (d, 1 H, J = 13 Hz), 5.16 (d, 1 H, J = 13 Hz), 5.66-5.80 (m, 1 H), and 7.21-7.39 ppm (m, 4 H); MS calcd for $C_{15}H_{19}O_2$ (P-H) 231.1347, found, 231.1366.

Efforts to purify this material further by repeating the distillation and by chromatography were unsuccessful. Reactions of **3d** which assure the correctness of this structure have been reported previously.[13]

2-(2-(Hydroxymethyl)phenyl)-2-propanol (8). This diol was formed in essentially quantitative yield by the treatment of phthalide with excess MeMgBr or MeLi and constituted half of the material recovered from treatment of phthalide with 1 equiv of MeMgBr, as described in the text. It was characterized by ^1H NMR (60 MHz) δ 1.63 (s, 6 H), 3.80 (br s, 2 O-*H*), 4.74 (s, 2 H), and 7.23 (br s, 4 H).

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Varamines A and B, New Cytotoxic Thioalkaloids from *Lissoclinum vareau*

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The prolific variety of nitrogenous natural products obtained from tunicates (ascidians) portrays these marine animals as specialists in the production of unusual alkaloids. It is noteworthy that some 90% of reported tunicate secondary metabolites are nitrogenous,[1] most having highly modified amino acid or peptide structures.[2] Our interest in the chemistry of tunicates is drawn to these uncommon alkaloids, many with remarkable bioactivity. We report two new cytotoxic alkaloids, varamines A (**1**) and B (**2**).

Lissoclinum vareau (Monniot and Monniot, 1987), a bright red, thinly encrusting tunicate, was collected in shallow waters off the Yasawa island chain, in the Fiji Island group. Assay of the crude methanol extract of this tunicate revealed potent antifungal activity (zone of inhibition of 35 mm in a disk diffusion assay) and cytotox-

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