organic layer was dried with $MgSO_4$, and the solvent was removed. The residue was purified by column chromatography on silica gel (AcOEt-hexane, 1:2) to afford **31**: 1.166 g (3.48 mmol, 81% yield): IR (neat) 2950, 2875, 1735, 1700, 1500, 1410, 1360, 1305, 1260, 1194, 1160, 1027, 976, 770, 695 cm^{-1}; NMR (CCl_4) δ 1.55–2.30 (m, 4 H), 3.10–3.75 (m, 2 H), 3.63 (s, 6 H), 3.90–4.50 (m, 2 H), 5.06 (s, 2 H), 7.29 (s, 5 H). Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 61.03; H, 6.27; N, 4.19.

Preparation of 30 from 31. A solution of **31** (1.524 g, 4.55 mmol), methyl bromoacetate (1.03 g, 6.75 mmol), and sodium (175 mg, 7.6 mmol) in benzene (15 mL) was refluxed for 33.5 h. The solution was poured into water and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, the solvent was removed, and the residue was purified by column chromatography (silica gel, AcOEt-hexane, 1:2) to yield **30** (908 mg, 2.23 mmol, 49% yield).

Preparation of 32. Hydrolysis and subsequent decarboxylation were carried out by a method similar to the reported procedure.[18] A solution of **30** (3.14 g, 7.72 mmol) and sodium hydroxide (1.26 g, 31.5 mmol) in a mixture of EtOH (20 mL) and H_2O (10 mL) was heated at 60–70 °C for 6 h. The reaction mixture was acidified with dilute HCl and extracted with CH_2Cl_2. The organic layer was dried with $MgSO_4$, and then the solvent was removed in vacuo. The residue was dissolved in a mixed solvent of acetic acid (30 mL) and H_2O (20 mL) and refluxed for 13 h, and the solvent was removed in vacuo. A solution of the residue in EtOH (50 mL) containing concentrated H_2SO_4 (1 mL) was refluxed for 13 h and poured into cold aqueous Na_2CO_3. The organic layer was extracted with CH_2Cl_2 and dried with $MgSO_4$. The solvent was removed, and the residue was purified by column chromatography on silica gel (AcOEt-hexane, 1:2) to yield **32**: 1.29 g (3.4 mmol, 44% yield); IR (neat) 2980, 2890, 1730, 1705, 1503, 1452, 1410, 1360, 1260, 1180, 1117, 1030, 918, 860, 772, 748, 700 cm^{-1}; NMR (CCl_4) δ 1.22 and 1.23 (2 t, 6 H, J = 7.0 Hz), 1.58–2.18 (m, 4 H), 2.18–2.85 (m, 2 H), 3.00–3.78 (m, 3 H), 3.78–4.45 (m, 1 H), 4.04–4.07 (2 q, 4 H, J = 7.0 Hz), 5.70 (s, 2 H), 7.30 (s, 5 H). Anal. Calcd for $C_{20}H_{27}NO_6$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.76; H, 7.04; N, 3.62.

Preparation of 33 and 34. A solution of **32** (1.04 g, 3.08 mmol) in EtOH (30 mL) was placed in an autoclave with a catalytic amount of W-2 Raney Ni. The apparatus was tightly closed, filled with 15 kg/cm^2 of hydrogen, and shaken at room temperature for 15 h. After removal of the catalyst by filtration, the filtrate was condensed and distilled to yield a mixture of **33** and **34**: 79% yield (478 mg, 2.43 mmol); bp 92–134 °C (0.4 mmHg, bulb-to-bulb). Esters **33** and **34** are separable by GLC (PEG) or TLC (silica gel, AcOEt-hexane, 1:1). Ester **33** was less polar than **34** on silica gel plate and GLC (PEG). The ratio of **33** and **34** was 62:38 (by GLC).

33: IR (neat) 2975, 1730, 1700, 1420, 1375, 1337, 1262, 1190, 1098, 1038 cm^{-1}; NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.0 Hz), 1.73–2.33 (m, 4 H), 2.35–3.23 (m, 4 H), 3.23–3.80 (m, 1 H), 3.80–4.33 (m, 3 H); mass spectrum, m/e 197 (M^+), 169, 96 (base).

34: the spectroscopic data was identical with that described in the report.[12] Also, mass spectrum coincided with assigned structure.

Synthesis of 35 and 36. A solution of **33** (84 mg, 0.4264 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (53 mg, 1.4 mmol) in THF (3 mL) at room temperature. The suspension was refluxed for 6 h under an atmosphere of nitrogen. The usual workup gave **35** quantitatively [picrate mp 174–177.5 °C (lit.[19] mp 170–172, 173–174 °C)]. Transformation of **34** and **36** has been described (62% yield)[12].

Acknowledgment. T.S. is grateful for the partial financial support donated by the Asahi Glass Foundation for Industrial Technology.

Registry No. (±)-**4**, 36451-37-3; (±)-**5**, 73971-21-8; (±)-**7**, 88001-28-9; **8**, 40911-68-0; (±)-**9**, 88001-27-8; (±)-**10**, 88001-29-0; (±)-**11**, 88001-30-3; **12**, 18742-02-4; (±)-**13**, 88001-31-4; (±)-**14**, 74045-76-4; **15**, 76470-03-6; **16**, 88001-32-5; **17**, 88001-33-6; **18**, 88001-34-7; **19**, 88001-35-8; **20**, 591-12-8; **21**, 88001-36-9; **22**, 88001-37-0; **23**, 88001-38-1; **24**, 88001-39-2; **25**, 88001-40-5; **26**, 88001-41-6; **27**, 25070-74-0; (±)-**28**, 88001-42-7; **29**, 40967-67-7; (±)-**30**, 88001-43-8; (±)-**31**, 88001-44-9; **32**, 88001-45-0; (±)-**33**, 88001-46-1; (±)-**34**, 67800-68-4; (±)-**35**, 18929-91-4; (±)-**35** (picrate), 81255-00-7; (±)-**36**, 18929-90-3; $BrCH_2CO_2CH_3$, 96-32-2; 1-(methoxycarbonyl)pyrrolidine, 56475-80-0; 2-pentanone, 107-87-9; chlorotrimethylsilane, 75-77-4.

(18) Battersby, A. R.; Turner, J. C. *J. Chem. Soc.* **1960**, 717.

(19) Borch, R. F.; Ho, B. C. *J. Org. Chem.* **1977**, *42*, 1225.

1-Lithio- and 1,3-Dilithioisobenzofuran: Formation and Reactions with Electrophiles

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The acetal **1** reacts with 1 equiv of alkyllithium in the presence of catalytic diisopropylamine to form isobenzofuran (**2**), which with an additional equivalent of alkyllithium gives 1-lithioisobenzofuran (**3**). Solutions of **3** have been treated with various electrophiles and the resulting products characterized by NMR and as cycloadducts formed on addition of dienophiles. Lithiation of **2** occurs cleanly at C-1, as shown by quenching with D_2O. Both the metalation and subsequent alkylation reactions are more rapid in THF than in ether. Reaction of **3** with CH_3I gives 1-methylisobenzofuran (**6**) as the major product, accompanied by some 1,3-dialkylated material. Further treatment of **6** with alkyllithium results in specific lithiation at C-3 to give **14**, as demonstrated by deuteration and analysis of cycloadducts by ^2H NMR. Ethylation of **14** gives 1-ethyl-3-methylisobenzofuran, illustrating the feasibility of a one-pot procedure for preparing unsymmetrically disubstituted isobenzofurans. Dilithiation of **2** occurs when excess base is employed in THF, and this allows the direct formation of some symmetrical 1,3-disubstituted isobenzofurans. The 1-alkyl- and 1,3-dialkylisobenzofurans are moderately stable in neutral or mildly basic solution, resembling the parent **2** in this respect. Exchange reactions demonstrate that isobenzofuran is more acidic than both furan and diisopropylamine.

Since the earliest report of generating isobenzofuran (**2**) as a reactive intermediate by a thermolytic process, several variants have been developed which allow either the isolation or in situ formation and use of this interesting

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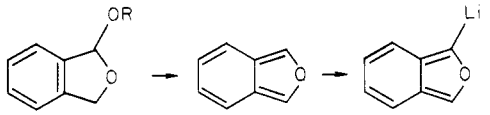
species.[1] These methods have in common the use of the cycloadduct of furan and benzyne, which after suitable derivatization gives materials which may be thermally converted to **2**. The flash vacuum pyrolysis (650 °C) approach[2] utilizing the dihydro derivative is notable for its conceptual simplicity and excellent yields, while other precursors are suitable for lower temperature generation of **2**, particularly for in situ applications. Mechanistically unrelated approaches involve the acid-catalyzed (ca. 100 °C) reaction of the acetal **1**, developed in our work[3] and a related procedure which Rodrigo has employed to advantage in syntheses of polycyclic natural products.[4]

With the exception of 1-benzylisobenzofuran, which Smith[5] has shown to be in tautomeric equilibrium with benzylidenephthalan, in general only thermal cycloreversion approaches have been used to form 1-alkyl- and 1,3-dialkylisobenzofurans. Wiersum and Mijs,[6] and Bornstein and co-workers[7] generated and isolated 1-methyl- and 1,3-dimethylisobenzofuran by the pyrolysis technique utilizing the corresponding dihydro furan–benzyne adduct precursors, while Warrener[8] has employed the diphenyl-*s*-tetrazine derivatives for in situ formation and reactions of these same species. As a general method for the preparation of substituted isobenzofurans, these approaches require access to the appropriately substituted benzynes and furans; the latter is used in excess (often as the solvent), and consequently this approach has been used only with readily available furans.

Results and Discussion

We have reported[3a] earlier that **2** can be generated at room temperature by lithium diisopropylamide (LDA) induced 1,4-elimination of acetal **1** (R = Me or Et). This



1 2 3

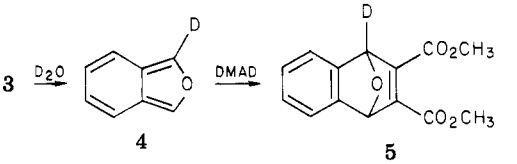
method has subsequently been used for the generation of 1-methoxyisobenzofuran[3b] (reactive, trapped in situ) and benzo[*e*]isobenzofuran (isolable solid).[9] Recently, in examining ways to effect the conversion of **1** to **2** with minimal side products, we explored the use of CH_3Li in ether with 0.05 equiv (per mol of **1**) of diisopropylamine as a prospective reagent for the elimination. Using excess CH_3Li at 0 °C, the reaction was monitored with a gas buret, and it was found that methane evolution continued until 2 equiv was formed. While gas evolution slowed with time, there was no apparent break in the plot of gas evolved vs. time after the formation of 1 equiv. The product of interest is 1-lithioisobenzofuran (**3**), as shown by the evidence discussed below.

When carried out in ether at 0 °C, the reaction requires ca. 2 h to approach completion. Subsequently it was established that negligible reaction occurs over 1 h in the absence of amine, while larger amounts speed the process. Presumably LDA acts as a recycled carrier base (catalyst) for the elimination and deprotonation. The overall reaction was also found to be more rapid in tetrahydrofuran (THF) than in ether, and since subsequent reaction of **3**, e.g., coupling with alkyl halides, is also faster in THF, this will be a solvent of choice for certain applications.

The progress of the reaction starting with **1** through **2** to **3**, was also monitored by ^1H NMR. A literature spectrum[10] of **2** in $CDCl_3$ consists of a singlet at 8.0 ppm for the furan protons and two multiplets (AA'BB') for the remaining protons at 7.50–7.25 and 7.00–6.74 ppm. Our spectra of **2** in ether/THF reproduce this pattern and spacing, and we assign the downfield singlet for use as the reference line in further discussion at 8.0 ppm[11] in these solvents.

When ca. 1.5 equiv of CH_3Li is added to **1**, the NMR spectrum is that of a mixture of **2** and **3**. Interestingly, the singlet of **3** appears downfield (8.3 ppm) from that for **2**; the appearance of two singlets not only allows determination of the extent of conversion, but also shows that **2** and **3** are not in very rapid (NMR time scale) equilibrium. Additional CH_3Li caused the disappearance of peaks due to **2** and the emergence of the features of **3**, characterized by the singlet mentioned, by broadened doublets (H-4 and H-7) with chemical shifts centered at roughly the same position as the corresponding protons of **2**, and by a multiplet for H-5 and H-6 shifted upfield (centered at 6.35 ppm) relative to their position in **2**.

Further evidence for the formation of **3** was obtained by quenching a solution with D_2O, to form 1-deuterioisobenzofuran (**4**). The ^1H NMR spectrum of **4** is essentially



4 5

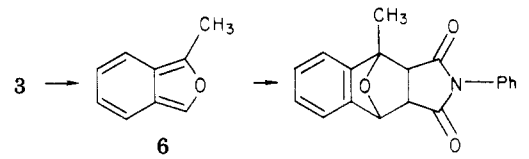
identical with that of **2**, except for the diminution of the downfield singlet to a relative area of 1 H. Direct addition of this reaction mixture to dimethyl acetylenedicarboxylate (DMAD) in ether gave **5**, which was isolated (in poor yield, we believe because a water wash and drying step was omitted) by column chromatography. The ^1H NMR spectrum of **5** was identical with that of the protio analogue, except for the anticipated lower relative area of the bridgehead benzylic singlet. The ^2H NMR (D NMR) spectrum indicated deuterium incorporation only at the position indicated, within measurement error 1 D/mol, based on cyclohexane-d_{12} used as the internal quantitative standard.

These results show that **2** is deprotonated exclusively at the 1 position. There is ample precedent for this being the most kinetically acidic site in furan[12–15] and in vinyl

(1) For a thorough review of isobenzofuran chemistry and discussion of these methods of formation, see: Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135.
(2) Recent reviews: Wiersum, U. E. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 317 and 365.
(3) (a) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061; (b) Makhlouf, M. A.; Rickborn, B. *Ibid.* **1981**, *46*, 2734.
(4) Keay, B. A.; Rodrigo, R. *J. Am. Chem. Soc.* **1982**, *104*, 4725 and references therein.
(5) Smith, J. G.; Wikman, R. T. *J. Org. Chem.* **1974**, *39*, 3648; Smith, J. G.; Welankiwar, S. S.; Shantz, B. S.; Lai, E. H.; Chu, N. G. *Ibid.* **1980**, *45*, 1817.
(6) Wiersum, U. E.; Mijs, W. J. *Chem. Commun.* **1972**, 347.
(7) Chacko, E.; Sardella, D. J.; Bornstein, J. *Tetrahedron Lett.* **1976**, 2507.
(8) Warrener, R. N.; Evans, D. A. C.; Padden-Row, M. N.; Russell, R. A. *Aust. J. Chem.* **1982**, *35*, 757.
(9) Cornejo, J.; Ghodsi, S.; Johnson, R. D.; Woodling, R.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 3869. See also: Stringer, M. B.; Wege, D. *Tetrahedron Lett.* **1980**, 21 3831, for the preparation of this material by the flash vacuum pyrolysis technique.
(10) Wege, D. *Tetrahedron Lett.* **1971**, 2337.
(11) This is in fact quite close to the true chemical shift in this solvent as shown by the ^2H NMR spectra discussed in the Experimental Section, which allow the assignment of the singlet at 8.08 ppm in ether.
(12) Gilman, H.; Breuer, F. *J. Am. Chem. Soc.* **1934**, *56*, 1123.
(13) Gilman, H.; Bebb, R. L. *J. Am. Chem. Soc.* **1939**, *61*, 109.
(14) Ramanathan, V.; Levine, R. *J. Org. Chem.* **1962**, *27*, 1216.

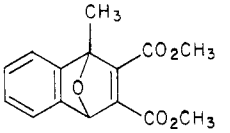
ethers generally,[16-21] but the lithiation of **2** appears to be especially facile. That this reflects a lower pK_a for **2** was shown by treatment of **1** with 2.5 equiv of LDA; the ^1H NMR spectrum closely resembled that of **3** generated by the CH_3Li (catalytic R_2NH) method, implying that **2** is more acidic than diisopropylamine. In contrast, Soderquist has reported that 1-lithio-1-methoxyethene reacts with 1 equiv of the amine to generate LDA and methyl vinyl ether.[19] Further, treatment of a solution of **3** with furan (1 equiv) gave no reaction (by ^1H NMR), while the reverse process, treatment of **2** with α-lithiofuran, effected rapid and apparently complete conversion to **3** and furan. These observations show qualitatively that **2** is more acidic than furan, and this is also reflected in the slower lithiation of furan under our conditions.[22] Very recently, pK_a values have been determined for, inter alia, diisopropylamine (35.7) and furan (35.9) in THF solvent with lithium counterion.[25] Our results indicate that **2** would have $pK_a \leq 34.5$ on this scale.[25]

With a facile method to generate **3** available, its reactions with some simple electrophiles were examined. Addition (in ether/THF solvent) of methyl iodide gave rapid formation of 1-methylisobenzofuran (**6**) along with some **2** and



1,3-dimethylisobenzofuran (see later discussion). Direct examination of the ^1H NMR spectrum showed a pattern essentially identical with that of 1-deuterioisobenzofuran **4**. It is interesting that the introduction of the methyl substituent does not appreciably alter the AA'BB' pattern which characterizes **2**, **4**, and **6**. The solution of **6** was washed with cold brine, dried over K_2CO_3, and then treated with *N*-phenylmaleimide to furnish the known[7] derivatives **7** and **8**, thus confirming the formation of 1-methylisobenzofuran.

Addition of a similarly treated solution of **6** to an ethereal solution of DMAD gave, in a rapid reaction, the cycloadduct **9** as the major product; a pure sample of **9** was



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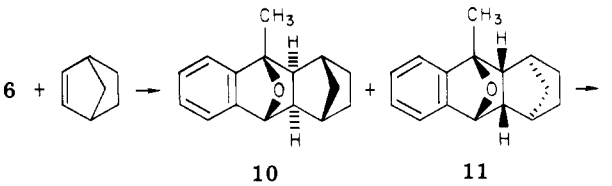
obtained as an oil by column chromatography and characterized by NMR and MS.

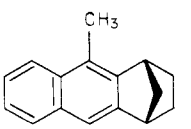
Bornstein[7] has reported that **6**, prepared by the flash vacuum pyrolysis method, decomposes rapidly in $CDCl_3$ solution near room temperature; it was also noted that addition of triethylamine retarded the decomposition somewhat, while **6** was instantly destroyed by addition of a trace of trifluoroacetic acid. We find that basic/neutral solutions of **6** are at least moderately stable, much like those of **2** prepared in the same manner. Thus it is likely that the earlier observation[7] of rapid decomposition in $CDCl_3$ was due to trace acid in the solvent. It is expected that **6** would be more susceptible to acid-catalyzed polymerization than **2**.

The relative reactivity of **6** compared to **2** as a diene in cycloaddition reactions is of interest. A rough measure of this property is possible by examing the room temperature reaction with norbornene, which can be followed by NMR. In earlier work a second-order rate constant, k (22°C) = 1.9×10^{-5} M^{-1} s^{-1}, was found for the reaction of **2**.[28] Similar treatment of a solution of **6** with norbornene gave $k = 2.5 \times 10^{-5}$ M^{-1} s^{-1}. These determinations are subject to considerable uncertainty not only because of the method of analysis but because of the unknown degree of polymerization or other side reactions of **2** and **6** under these conditions (yields of cycloadducts are substantial but not quantitative). Thus we conclude only that **2** and **6** do not exhibit large differences in cycloaddition rates with norbornene.

For preparative purposes with this modest dienophile, it was more convenient to reflux the THF solution of **6** with a slight excess of norborene; after 48 h crude product was obtained in high yield. Chromatography gave a mixture of adducts **10** and **11** (53%, pooled because of limited separation). The formation of both exo, exo and endo,



10 **11**



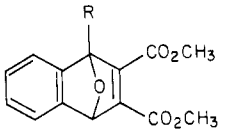
12

exo adducts in reactions of norbornene with isobenzofurans is characteristic.[3b,29] A portion of this mixture was con-

(15) Heathcock, C. H.; Gulich, L. G.; Dehlinger, T. *J. Heterocycl. Chem.* **1969**, *6*, 141.
(16) For a very useful compilation and discussion of "Heteroatom-facilitated Lithiations", see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(17) Schollkopf, U.; Hanssle, P. *Liebigs Ann. Chem.* **1972**, *763*, 208.
(18) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.
(19) Soderquist, J. A.; Hsu, G. J. *Organometallics* **1982**, *1*, 830.
(20) Sebastian and co-workers[21] have shown that *n*-butyllithium, with a small amount of TMEDA, will effect α-lithiation of some cyclic vinyl ethers, e.g., dihydropyran and dihydrofuran.
(21) Oakes, F. T.; Sebastian, J. F. *J. Org. Chem* **1980**, *45*, 4959. Oakes, F. T.; Yang, F.; Sebastian, J. F. *J. Org. Chem.* **1982**, *47*, 3094.
(22) The lithiation of furan occurs readily with 0.05 equiv of diisopropylamine in THF solvent, as shown by gas evolution and examination of the ^1H NMR spectrum. The latter exhibits, similarly to **3**, a dowfield shift of the remaining α'-proton and an upfield shift of the β'-proton. It is worth noting that CH_3Li is rarely if ever used for such lithiations,[16] perhaps because of Gilman's observations on yields of 2-furoic acid on carbonation of the mixtures formed by treating furan with different organolithium reagents.[13] This early work involved ether solvent and relatively short reaction times. The fairly rapid reaction[23] of alkyllithium reagents with THF must be taken into consideration when this solvent is employed. Methyllithium[23] appears to be more stable than *n*-butyllithium[24] in THF; the effect of lithium diisopropylamide on these reactions with solvent has however not been explored.
(23) Gilman, H.; Gaj, B. J. *J. Org. Chem.* **1957**, *22*,1165.
(24) Bates, R. B.; Kroposki, L. M. Potter, D. E.. *J. Org. Chem.* **1972**, *37*, 560.
(25) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Chem. Soc., Chem. Commun.* **1983**, 620. The pK_a values are relative to 37.8 assigned to 2-methyl-1,3-dithiane, chosen as a reference to correlate with Streitwieser's pK_a for this compound in cyclohexylamine solvent with a cesium counterion.[26] A higher pK_a for furan might be expected on the basis of Shatenshtein's H/D exchange kinetic studies; in Me_2SO solvent with KO-*t*-Bu, furan is reported to be only ca. twice as reactive as toluene (α positions of both).[27]
(26) Streitwieser, A. Jr.; Guibé, F. *J. Am. Chem. Soc.* **1978**, *100*, 4532.
(27) Shatenshtein, A. I.; Shapiro, I. O.; Ranneva, Y. I.; Kamrad, A. G.; *Reaktsionnaya Sposobnost Organ. Soedin, Tartusk, Gos. Univ.* **1964**, *1*(2), 232; *Ch. Abst.* **1965**, *62*, 11648d.
(28) Makhlouf, M. A. Ph.D. Dissertation, UCSB, 1982.

verted to the anthracene derivative **12** for further characterization.

Other electrophiles examined in reaction with **3** were ethyl bromide and iodide, trimethylsilyl chloride, and allyl bromide, all of which gave monosubstituted isobenzofurans as the major product in fair to good yield. These were further characterized by conversion to cycloadducts **13a–c** by treatment with DMAD.



13a, R = Et
b, R = $Si(CH_3)_3$
c, R = allyl

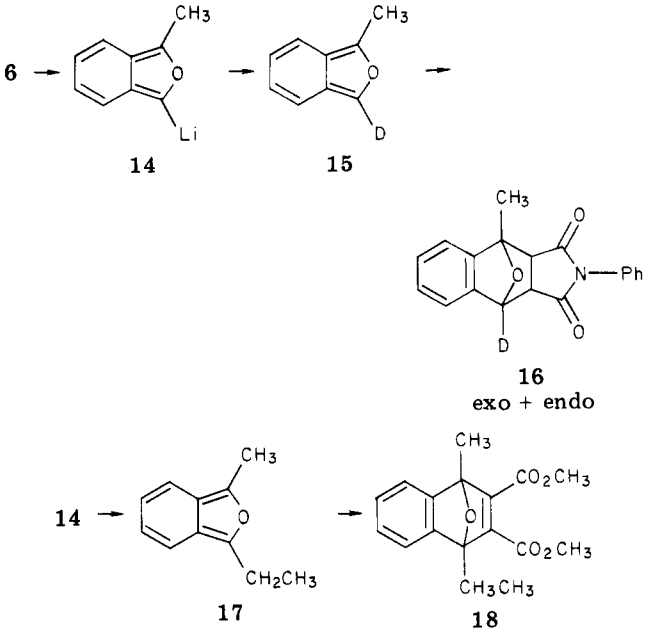
Conversely, no evidence for alkylation of **3** was obtained with benzyl bromide or chloride, even when copper-modified derivatives of the organometallic were used.[30]

The alkylated isobenzofurans were washed with a small volume of cold brine, dried over K_2CO_3, and filtered directly into an ethereal solution of DMAD; after standing a few minutes, rotary evaporation afforded the crude products. When the wash step was omitted, considerable darkening occurred on addition of the DMAD solution, and yields were adversely affected. Residual strong bases and perhaps the LiOEt formed in the initial elimination step presumably destroy the DMAD, leading to tarry residues.

Several attempts to prepare the trimethylsilyl derivative **13b** using the brine wash method gave this material in at best 28% yield. An alternative approach, using 3 equiv of Me_3SiCl, omitting the brine rinse and adding this solution directly to 1 equiv of DMAD in ether gave **13b** in 66% yield after column chromatography. This suggests that similar treatment with Me_3SiCl of other isobenzofuran derivatives may allow omission of the aqueous wash and improvement in yield.

The reaction of **6** with additional base was explored as follows. Acetal **1** was treated with 2 equiv of CH_3Li as before to generate **3**; 1 equiv of CH_3I was added and the mixture was stirred at room temperature for 0.3 h. After the mixture had cooled in an ice bath, 1.1 equiv of CH_3Li was added. After stirring for 10 min, the mixture was quenched by addition of D_2O, washed with cold brine, dried, and treated with *N*-phenylmaleimide. D NMR of the crude product **16** showed that deuterium was incorporated only at the remaining α-position of **6**, hence demonstrating the formation of **14** and **15** on treatment with D_2O. Both the ^1H and D NMR spectra of **16** indicated ≥65% D incorporation.

To examine the potential of this approach for the preparation of unsymmetrical dialkylated isobenzofurans, the sequence was repeated to generate **14**, which was treated with excess ethyl iodide. One equivalent of Me_3SiCl was added to quench the excess base, and the cold solution was added directly to DMAD in ether. Evaporation of the solvent and chromatography gave **18** as a colorless oil (45%). This result demonstrates the utility



of this one-pot procedure for formation of 1,3-disubstituted isobenzofurans; the modest yield of **18** may reflect less than optimal conditions for the six individual reaction step involved or limited stability of the various intermediates.

The observed preference for lithiation at the remaining α-position has precedent in the reaction of 2-methylfuran with organolithium reagents,[32] but extension to isobenzofuran required this experimental confirmation.

As noted earlier, procedures designed to give monosubstituted products from **3** led in some instances to formation of small amounts of unsubstituted and disubstituted materials. Three plausible explanations for the formation of these products are: (a) an equilibrium disproportionation of **3** to give **2** and dilithiated isobenzofuran; (b) the formation of dilithiated material from an (slight) excess of base used in some reactions (with formation of **2** then accounted for by adventitious proton sources reacting with **3**); or (c) an exchange reaction that occurs during alkylation, between the alkylated neutral material and **3** to give, e.g., **14** and **2**. Alternative a is not supported by the NMR evidence, since no **2** is visible in solutions of **3** prepared from **1** and the appropriate amount of base; thus if this disproportionation occurs, the position of equilibrium must strongly favor **3**. The unknown relative rates of alkylation of **3** and the dilithiated species, though, do not allow ruling out this alternative.

The possibility of formation of dilithiated material was addressed by treating **1** with 4 equiv of CH_3Li (amine catalyst). In THF/ether at 0 °C rapid evolution of slightly more than 2 equiv of gas occurred, signifying formation of **3**. The mixture was then allowed to warm to room temperature. After 2 h, additional gas (ca. 1 equiv) had evolved, the solution had darkened, and the flask contained a substantial precipitate. The ^1H NMR spectrum of this mixture resembled a very dilute solution of **3**, suggesting that most of the material with NMR absorption in the aromatic region had precipitated.[33] Quenching this mix-

(29) Mir-Mohamad-Sadeghy, B.; Rickborn, B. *J. Org. Chem.* **1983**, *48*, 2237.

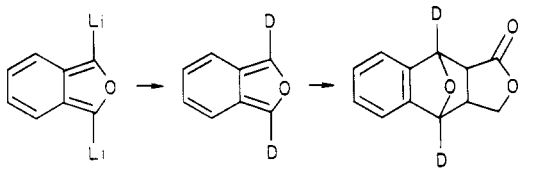
(30) In an attempt 1 equiv of CuCN was added and in another the procedure of Heathcock[31] (which allows benzylation of α-lithio methyl vinyl ether) was employed. Neither 1-benzylisobenzofuran nor its benzylidene tautomer[7] were evident by direct examination of the NMR spectra. It appears that a significant amount of **2** is regenerated in these and in the reactions of **3** with benzyl halides; bibenzyl seems not to be formed in large amounts.

(31) Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822.

(32) See, for example: Buechi, G.; Wuest, H. *J. Org. Chem.* **1966**, *31*, 977.

(33) The dilithiation of furan[34] was also examined, using our conditions and those described by Chadwick,[35] in ether solvent. In both cases darkening and precipitation were observed with the NMR resembling that of very dilute α-lithiofuran. Subsequent quenching with D_2O gave furan that was extensively 2,5-dideuterated (by ^1H NMR). The limited solubility of the dilithiated species is thus a common feature of furan and isobenzofuran.

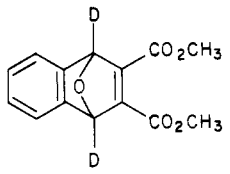
ture with D_2O, washing, drying, and treatment with 2-butenolide gave (in an apparently rather slow reaction, requiring several hours at room temperatures) adducts **21** and **22**. These were separated by column chromatography



19 **20** **21** (exo) + **22** (endo)

in yields of 13% and 22%, respectively. The ^1H NMR spectra of both indicated ca. 15% H at each bridgehead position. Thus 1,3-dilithioisobenzofuran (**19**) is formed, at least to a substantial degree, by this procedure.

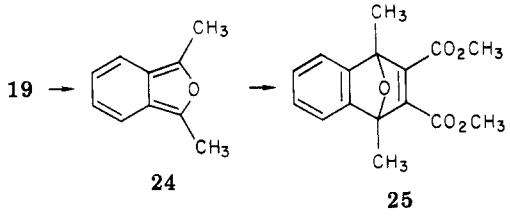
The formation of **19** was also effected by use of *n*-butyllithium (4 equiv) with 0.05 equiv of amine in a mixture of hexane and THF solvent. Precipitation was again observed in this reaction. Quenching with D_2O and workup as before gave a solution of **20** which was converted to the DMAD adduct **23**; the ^1H NMR spectrum of this product



23

indicated an H/D ratio of 8/92 (i.e., 84% dideuterated).

Compound **19** was generated in a separate experiment and treated with excess CH_3I to explore the feasibility of a one-step formation of symmetrically dialkylated isobenzofurans. The usual cold brine workup and addition of DMAD solution followed by chromatography gave cycloadduct **25** in 43% yield, along with monomethylated



24 **25**

derivative **9** (23%). Two attempts were made to form the diethyl analogue of **24** by similar treatment of **19** with ethyl iodide; a marked exotherm occurred on addition of the electrophile at 0 °C and was also noted when a solution of **19** cooled to −70 °C was treated with ethyl iodide and allowed to warm. Negligible yields of diethylated cycloadduct were formed after the usual wash and treatment with DMAD. Also, neither unsubstituted nor monoethylated derivatives formed in significant yield, as anticipated if elimination of ethyl iodide had occurred. The course of this reaction remains unclear, but these observations suggest that application of the dilithio derivative will not be as general as the stepwise approach.

These results show that dilithiation of **2** is feasible, especially in THF-containing solvent if excess base is used, dictating control of this variable when formation of **3** and monosubstitution is desired. While dilithiation may account for some of the disubstituted product observed in experiments designed to give monoalkylation, we believe the most likely pathway to be the exchange (c) described above. This view is supported by the fact that both unsubstituted and disubstituted products are observed in the same reactions, and the amounts tend to increase as the reactivity of the electrophile decreases, as seen in reactions involving ethyl bromide. The facile exchange between α-lithiofuran and **2** also implies that similar exchange between **3** and **2** (or its monoalkylated derivatives) can occur. While the problem of forming monoalkylated materials exclusively has not been overcome, these are the major products in all cases examined even with the poorer electrophiles. If the synthetic goal is the formation of an unsymmetrical 1,3-dialkylated isobenzofuran, these observations suggest that yields will be better if the more reactive alkylating agent is introduced first.

Summary

Alkyllithium reagents can be used with a catalytic amount of diisopropylamine to generate solutions of isobenzofuran **2** which are nearly free of amine. An added equiv of alkyllithium forms 1-lithioisobenzofuran (**3**), which can be coupled with various electrophiles. These products may in turn be lithiated and substituted at the 3 position in a one-pot procedure. The use of excess base in THF effects the formation of 1,3-dilithioisobenzofuran, as shown by treatment with D_2O or CH_3I. Since the precursor acetal **1** is now readily prepared in convenient amounts,[36] these procedures offer a convenient route to various substituted isobenzofurans.

We are continuing the study of the lithiation of **2** and other isobenzofurans and the reactions of these organometallics with other electrophiles.

Experimental Section

Ether and THF were distilled from $LiAlH_4$ and Na/benzophenone ketyl, respectively, immediately before use. Diisopropylamine was distilled from CaH_2 and stored under an inert atmosphere. Commercial CH_3Li (in ether) and *n*-butyllithium (in hexane) reagents were employed, with concentration checked periodically. ^1H NMR spectra were recorded on a Varian T-60, either directly on the reaction mixtures (typically ether/THF solvent, no internal standard) or in $CDCl_3$ using Me_4Si standard. ^2H NMR spectra were obtained on a Nicolet NT-300 instrument. Melting points (uncorrected) were determined in open capillary tubes on a Mel-temp apparatus. MS (EI) and MS-CI (chemically induced, methane flow gas) data were obtained from a VG Micromass ZAB-2F instrument. Combustion analyses were performed by Galbraith Laboratories, Knoxville, TN. Reactions were in general carried out under a dry N_2 atmosphere.

1-Lithioisobenzofuran (3). Typically 0.83 mL (6.1 mmol) of **1** was taken up in 10 mL of THF or ether in a 50-mL two-necked flask equipped with a magnetic stir bar and a rubber septum and attached to either a gas buret or N_2 line. Diisopropylamine (43 μL, 0.31 mmol) was added, the mixture was cooled in an ice bath, and methyllithium (12.8 mmol, e.g., 8.6 mL of 1.5 M solution in ether) was then added by syringe. Gas evolution was complete within a few minutes in THF, but slower in ether. The NMR characteristics of the pale yellow solution are described in the text.

DMAD Adduct 5. A solution of **3** was converted to 1-deuterioisobenzofuran (**4**) by addition of excess D_2O. DMAD (1 equiv) was added and the mixture was then washed with brine,

(34) Ziegler, G. R.; Hammond, G. S. *J. Am. Chem. Soc.* **1968**, *90*, 513. In a footnote, the authors state that refluxing an ethereal solution of furan with a 3-fold excess of *n*-butyllithium for 4 h, followed by D_2O quenching, gave product which was 80% dideuterated.

(35) Chadwick, D. J.; Willbe, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 887; dilithiation was promoted by TMEDA and the use of hexane, as opposed to ether, solvent. Increasing the *n*-butyllithium beyond 2.5 equiv had a deleterious effect on yield attributed to polymerization. It was also demonstrated that dilithiofuran will react with furan to generate lithiofuran.

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

dried (K_2CO_3), and evaporated to give a residue which was chromatographed on silica gel. Pure **5** was isolated in poor yield; later reactions established that yields are greatly improved if the isobenzofuran solutions are washed with brine and dried (K_2CO_3) prior to mixing with the dienophile. The cycloadduct with DMAD is itself a reactive dienophile, and addition of the isobenzofuran to ethereal solution of DMAD minimizes the formation of diadducts. The proton analogue of **5** has been previously characterized.[29] Compound **5** has an identical ^1H NMR spectrum, except for the appropriately diminished singlet at 5.9 ppm; ^2H NMR (CCl_4 containing C_6D_{12} standard) 5.86 ppm (s, 1 D/mol), no other absorption present.

1-Methylisobenzofuran (6). To a THF solution of **3** prepared as described above, 1.05 equiv of CH_3I was added at 0 °C. The NMR spectrum taken a few minutes after addition indicated consumption of **3** and formation of **6** with spectral features as described in the text.

***N*-Phenylmaleimide Adducts 7 and 8.** The solution of **6** was transferred to a cold separatory funnel and washed with ice-cooled brine (3 × 5 mL). The organic phase was dried over K_2CO_3 at −15 °C for several hours (no decomposition was evident by NMR analysis) and then filtered into an ethereal solution of *N*-phenylmaleimide (1 equiv). After warming to room temperature with stirring, the solvent was evaporated in vacuo. NMR analysis of the residue indicated 79% cycloadduct yield based on comparison of product peaks with the upfield singlet of unreacted dienophile. Silica gel chromatography effected separation of *exo*-**7**, mp 199–202 °C (lit.[7] mp 201–201.6 °C), from *endo*-**8**, mp 149–151 °C (lit.[7] mp 153–153.5 °C). NMR data are given here, since the literature descriptions[7] contain obvious (typographical) errors.

7: δ 2.0 (s, 3 H), 2.83 (d, 1 H, J = 7 Hz), 3.17 (d, 1 H, J = 7 Hz), 5.62 (s, 1 H), and 6.96–7.5 ppm (m, 9 H).

8: δ 2.03 (s, 3 H), 3.43 (d, 1 H, J = 8 Hz), 3.73–4.03 (dd, 1 H, J = 8, 6 Hz), 5.60 (d, 1 H, J = 6 Hz), 6.20–6.46 (m, 2 H), and 6.85–7.5 ppm (m, 7 H).

DMAD Adduct 9. When 3.1 mmol of **1** was used a solution of **6** was prepared as above. This was filtered into a solution of 3.1 mmol of DMAD in ether; after 0.2 h, the solvent was rotary evaporated and the residue chromatographed on silica gel using graded elution from Skelly-solv to CH_2Cl_2. Adduct **9**, 514 mg (61%), was obtained in pure form as an oil: ^1H NMR δ 2.0 (s, 3 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 5.9 (s, 1 H), and 6.9–7.5 ppm (m, 4 H); MS–CI calcd for $C_{15}H_{15}O_5$ (P + H), 275.0919; found, 275.0946.

Norbornene Adducts 10 and 11. A solution of **6** was prepared in the usual way from 3.1 mmol of **1** without an aqueous wash. Norbornene (3.4 mmol) was added, and the mixture refluxed for 48 h. The solution was taken up in additional ether (20 mL), washed with water and brine, and dried over K_2CO_3. Rotary evaporation gave crude product in high yield, which was chromatographed on silica gel with graded elution from pentane to pentane/ether (9/1). Only partial separation of the isomers was effected (combined yield 53%). Preparative TLC gave the pure materials.

10: NMR δ 0.8–1.6 (m, 6 H), 1.7 (s, 3 H), 2.3 (br s, 2 H), 5.0 (s, 1 H), and 7.1 ppm (s, 4 H). Anal. Calcd for $C_{16}H_{18}O$: C, 84.9; H, 8.02. Found: C, 84.9; H, 8.16. NMR **11**: δ −1.25 (br d, J = 12 Hz, endo H of methylene bridge), 0.2 (br d, exo H, J = 12 Hz), 0.9–1.6 (m, 4 H), 1.8 (s, 3 H), 1.9–2.2 (m, 1 H), 2.4–2.65 (m, 1 H), 5.15 (d, J = 6 Hz, 1 H), and 7.15 ppm (br s, 4 H).

1,2,3,4-Tetrahydro-1,4-methano-9-methylanthracene (12). To a stirred ice-cooled solution of **10** and **11** (155 mg) in 2 mL of benzene was added 70 μL of $TiCl_4$. After 0.5 h, water and ether were added, and the organic phase was separated and dried over K_2CO_3. The residue from evaporation was chromatographed (silica gel, Skelly-solv) to give 80 mg (56%) of liquid **12**: NMR δ 1.1–2.2 (m, 6 H), 2.6 (s, 3 H), 3.4 (br s, 1 H), 3.6 (br s, 1 H), and 7.3–8.0 ppm (m, 5 H); MS calcd for $C_{16}H_{16}$, 208.1252; found, 208.1256.

DMAD Adducts: 13a. Several reactions were carried out using ethyl bromide or iodide in an effort to maximize the yield of monoalkylated material. The reactions are slower in ether than in THF/ether mixtures. The iodide gives some what better results. Yields and proportions of mono- to dialkylated products were not markedly affected by inverse addition, excess ethyl halide, or by varying the temperature from 20 to 40 °C. In a typical experiment, **3** was prepared in ether/THF, transferred to a dropping funnel (0 °C), and added to 3 equiv of ethyl iodide in THF at 40 °C over a period of 0.3 h. The reaction was complete within 0.5 h of additional stirring. After washing and drying, the cold solution was filtered into the 1 equiv of DMAD in ether. After 0.3 h the solvent was rotary evaporated, and the residue chromatographed on silica gel with 10–50% CH_2Cl_2 in Skelly-solv. In order of elution this gave: 10% diethylated adduct, 46% of **13a**, and 3% of unsubstituted adduct.

Compound **13a** is an oil: bp 120 °C (0.7 Torr); NMR δ 1.1 (t, J = 7 Hz, 3 H), 2.2–2.6 (m, CH_2CH_3 diastereotopic protons), 3.73 (s, 3 H), 3.75 (s, 3 H), 5.8 (s, 1 H), and 6.8–7.4 ppm (m, 4 H); MS calcd for $C_{16}H_{18}O_5$, 288.0998; found, 288.1005.

13b: A solution of **3** (3.1 mmol) was added by cannula to an ice-cooled ethereal solution of trimethylsilyl chloride (3 equiv, freshly distilled from dimethylaniline). This mixture was added directly to an ethereal solution of DMAD (1 equiv) at 0 °C. The solution was stirred and allowed to come to room temperature (0.25 h), then washed with water and brine, and dried over K_2CO_3. Evaporation followed by chromatography gave 660 mg (66%) of **13** (oil) and 7.4% of unsubstituted cycloadduct. **13b**: NMR δ 0.3 (s, 9 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 5.85 (s, 1 H), 6.75–7.10 (m, 2 H), and 7.15–7.40 ppm (m, 2 H); MS-CI (negative ion) calcd for $C_{17}H_{19}O_5Si$ (P–H), 331.1001; found, 331.0980.

When Me_3SiCl was added to the solution of **3** (inverse addition), small amounts of the ditrimethylsilylated DMAD adduct were formed: NMR δ 0.30 (s, 18 H), 3.7 (s, 6 H), 6.8–7.05 (m, 2 H), and 7.1–7.4 ppm (m, 2 H); MS-CI calcd for $C_{20}H_{29}O_5Si_2$ (P + H), 405.1553; found, 405.1561.

All attempts to use an aqueous wash (including ammonia solutions) prior to treatment with DMAD gave reduced yields of **13b** (15–28%).

13c: A cooled solution of **3** was transferred to a dropping funnel and added over a period of 10 min to a solution of 3 equiv of allyl bromide in THF at 0 °C. The mixture was allowed to warm to room temperature with stirring for 1.5 h, then washed and dried as before, and filtered into a solution of DMAD in ether. Evaporation and chromatography (9/1 Skelly-solv/CH_2Cl_2 to neat CH_2Cl_2, silica gel) gave 360 mg (39%) of pure **13c**: NMR δ 3.0–3.35 (m, 2 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 5.0–5.35 (m, 2 H), 5.61–6.19 (m, 1 H), 5.9 (s, 1 H), and 6.9–7.4 ppm (m, 4H); MS-CI calcd for $C_{17}H_{17}O_5$ (P + H), 301.1076; found, 301.1049.

Lithiation of 6. From 0.16 g (0.14 mL, 1.0 mmol) of **1**, **3** was made as before and treated with 1.05 mmol of CH_3I. After 0.3 h (22 °C), the solution was cooled in an ice bath and 1.0 mmol of CH_3Li added. A slight excess of D_2O was added after 0.3 h, and the solution containing **15** was washed several times with cold brine and then dried over K_2CO_3. Examination of the ^2H NMR of this solution, using as reference lines the natural abunance deuterium peaks of diethyl ether at 1.09 and 3.59 ppm, showed a strong singlet at 7.89 ppm attributed to **15** and a smaller absorption (ca. 10%) at 8.08 ppm attributed to 1-deuterioisobenzofuran (from unmethylated intermediate). In addition, a broad peak at 2.64 ppm was observed. While this was thought to be due to residual deuterated water, this was confirmed by conversion of the product to the *N*-phenylmaleimide cycloadduct. The ^1H NMR spectrum of this crude product indicated ca. 50% conversion to cycloadducts. The ^2H NMR (CCl_4, C_6H_{12} internal standard) exhibited a strong absorption at 5.55 ppm (for **16** exo and endo). No peaks appeared in the aromatic region or at 1.8–2.1 ppm, allowing the conclusion that lithiation of **6** had not occurred on the benzo ring or at the methyl group. The extent of lithiation to give **14** was estimated from both ^1H and ^2H NMR spectra to be ≃65%.

Dimethyl 1,4-Dihydro-1-ethyl-4-methyl-1,4-epoxynaphthalene-2,3-dicarboxylate (18). A solution of **3** was prepared as above from 6.1 mmol of **1** in 10 mL of THF with 9.3 mL of CH_3Li in ether (2.1 equiv) at 0 °C. To this dark solution was added 1.05 equiv of CH_3I; within minutes the color had faded to a pale yellow. An additional 1.1 equiv of CH_3Li was then added; gas evolution was complete within 0.5 h (3 °C), accompanied by darkening of the solution. Excess (2.0 equiv) of ethyl iodide was then added, and the mixture stirred with warming to room temperature for 1 h. After again cooling in an ice bath, 1 equiv of trimethylsilyl chloride was added, and the resulting solution then added to 6.1 mmol of DMAD in ether. After 0.3 h, the (dark) mixture was washed with brine, dried over K_2CO_3, filtered, and

rotary evaporated to give 1.53 g of crude product. Chromatography (silica gel, Skelly-solv to CH_2Cl_2) gave 850 mg (45%) essentially pure **18**: NMR δ 1.0 (t, J = 7 Hz, 3 H), 1.85 (s, 3 H), 2.1–2.5 (m, 2 H, diastereotopic methylene protons), 3.6 (s, 6 H), and 6.7–7.2 ppm (m, 4 H); MS calcd for $C_{17}H_{18}O_5$, 302.1154; found, 302.1167.

Formation and Reactions of 1,3-Dilithioisobenzofuran (19). A solution of 3.1 mmol of **1** and 0.15 mmol of diisopropylamine in 5.0 mL of THF was treated at 0 °C with 12.7 mmol of methyllithium in ether (9.0 mL). The flask was allowed to warm to ambient temperature; after 2 h gas evolution ceased and the contents were very dark brown. The mixture was cooled to −78 °C, and excess (1.0 mL) of D_2O was added. After the usual cold brine wash and drying, the solution was filtered into 3.1 mmol of 2-butenolide in ether, and the mixture kept at room temperature overnight. Rotary evaporation followed by silica gel chromatography (Skelly-solv to CH_2Cl_2) gave 73 mg (13%) of *exo*-**21** and 128 mg (22%) of *endo*-**22**, both as oils.

21: NMR δ 2.7–3.1 (m, 2 H), 4.3–4.7 (m, 2 H), 5.35 and 5.65 (both s, bridgehead protons, ≤ 0.15 H each), and 7.3 ppm (br, s, 4 H); MS-CI calcd for $C_{12}H_9D_2O_3$ (P + H), 205.0831; found, 205.0822.

22: NMR δ 3.3–3.8 (m, 3 H), 3.9–4.3 (m, 1 H), 5.4 and 5.6 (both d, bridgehead, J = 6 Hz, ≤0.15 H each), and 7.25 (br s, 4 H); MS-CI found, 205.0818.

Preparation of **19** using *n*-butyllithium (12.7 mmol) in hexane (8.5 mL) at 0 °C gave a dark brown solution with a copious colorless precipitate. After brief warming to room temperature the mixture was cooled to −78 °C, treated with D_2O, and worked up in the usual manner. Addition to DMAD gave, after chromatography, 250 mg (31%) of cycloadduct **23**: NMR δ 3.8 (s, 6 H), 5.8 (s, 0.16 H, bridgehead protons), and 6.9–7.5 ppm (m, 4 H), MS calcd for $C_{14}H_{10}D_2O_5$, 262.0810; found, 262.0809.

Dimethyl 1,4-Dihydro-1,4-dimethyl-1,4-epoxynaphthalene-2,3-dicarboxylate (25). A solution of **19** was prepared as described above with 11.0 mmol of CH_3Li in ether (7.9 mL), with stirring for 3 h at ambient temperature. After cooling to 0 °C, excess CH_3I (15.5 mmol) in 5.0 mL of THF was added, causing a rapid change in color from dark brown to pale yellow. After stirring for 0.3 h at 23 °C, the mixture was washed and dried in the usual way and added to DMAD solution. Chromatography gave 381 mg (43%) of **25** and 202 mg (23%) of **9**. **25**: NMR δ 1.9 (s, 6 H), 3.65 (s, 6 H), and 6.8–7.4 ppm (m, 4 H); MS calcd for $C_{16}H_{16}O_5$, 288.0998; found, 288.1005.

Acknowledgment. Financial support by the University of California Cancer Research Coordinating Committee is gratefully acknowledged. The NSF partially funded the instrument used to obtain ^2H NMR spectra. We thank Dr Hugh Webb for obtaining the MS data and Prof. J. T. Gerig and Allan Kerschaw for their help with NMR spectra. Dr. H. Gschwend (Ciba-Geigy Corp.) and Profs. F. Bordwell (Northwestern) and A. Streitwieser (UC Berkeley) provided helpful correspondence.

Registry No. 1 (R = Me), 67536-29-2; 1 (R = Et), 75802-19-6; **2**, 270-75-7; **3**, 88000-84-4; **3** (ditrimethylsilylated DMAD adduct), 88001-02-9; **4**, 88000-85-5; **5**, 88000-86-6; **6**, 61200-10-0; **7**, 61200-12-2; **8**, 61247-33-4; **9**, 88000-87-7; **10**, 88000-88-8; **11**, 88080-26-6; **12**, 88000-89-9; **13a**, 88000-90-2; **13b**, 88000-97-9; **13c**, 88001-00-7; **14**, 88000-91-3; **15**, 88000-92-4; *exo*-**16**, 88000-93-5; *endo*-**16**, 88000-94-6; **18**, 88000-95-7; **19**, 88000-96-8; **21**, 88000-98-0; **22**, 88080-27-7; **23**, 88000-99-1; **25**, 88001-01-8; DMAD, 762-42-5; *N*-phenylmaleimide, 941-69-5; norbornene, 498-66-8.

Alkylmetal Asymmetric Reduction. 13.[1] A Sterically Crowded Chiral Organoaluminum Compound as a Reducing Agent of Ketones

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Optically active carbinols were obtained by reducing the corresponding ketones with [[(1*S*,2*R*)-6,6-dimethylbicyclo[3.1.1]heptan-2-yl]methyl]aluminum dichloride. The reactions, which have been carried out at room temperature, are fast and afforded the carbinols in good chemical and optical yields. The extent of the enantioselectivity, along with the stereochemistry of the process, was found to depend on the structure of the ketone employed. The overall results indicated that the present reducing method may be a convenient route to obtain secondary alcohols of high enantiomeric purity under mild conditions.

The production of optically active intermediates from achiral starting materials via asymmetric induction has been of increasing interest in recent years. One of the most widely studied aspects of this field has been the synthesis of optically active carbinols from enantioselective reduction of prochiral ketones. This transformation may be achieved by the use of metal hydrides in which chiral organic moietes are ligated to the metal,[2-5] and high asymmetric reductions have been reported in individual cases.[2,4] Recently, *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (Midland's reagent)[6,7] and 9-BBN adducts of nopol benzyl ether[8,9] have been successfully used in the asymmetric reduction of a broad spectrum of ketones, even with α,β-acetylenic ketones.[7,8] These reagents give excellent enantioselectivity, even if the reductions are slow in comparison to those of other methods[2-5] and if the bulky substituted ketones are not reduced to the corresponding carbinols.[6]

Some years ago we have investigated the reduction of prochiral ketones by optically active aluminum trialkyls,[10] that in some cases possess a good ability to show enantiomeric discrimination. As a continuation of this investigation, we developed a novel method for effecting reduction of prochiral ketones with high enantioselectivity

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