(13) Elemental analyses and molecular weight determinations were by Galbraith Laboratories, Knoxville, Tenn.; IR spectra were determined using a Beckman Acculab 4 and Perkin-Elmer 625 spectrophotometer; H NMR spectra were determined with a Varian T-60 (in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as internal standard). All melting points are uncorrected. TLC comparisons of products and reaction mixtures were carried out on silica gel plates (Quantum Industries) with benzene–hexane–methanol (4:6:1) or benzene as solvent.
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α-Hetero-Substituted Phosphonate Carbanions. 7.[1] Synthesis of Deoxybenzoins and Benzo[*b*]furans

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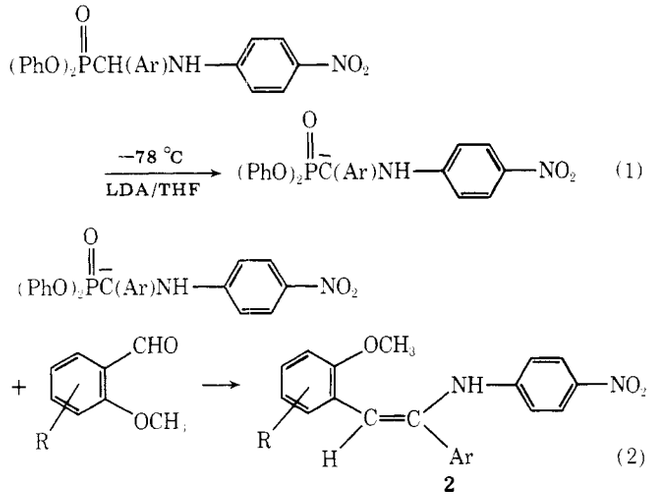
In a series of papers, we have described the utility of α-hetero-substituted phosphonate carbanions for the preparation of a wide variety of different classes of compounds.[3a–e] We now report the synthesis of new deoxybenzoins, which are readily converted to the corresponding benzofurans through the use of diphenyl 1-(4-nitroanilino)-1-arylmethanephosphonate as the carbanion precursor.

Scheme I



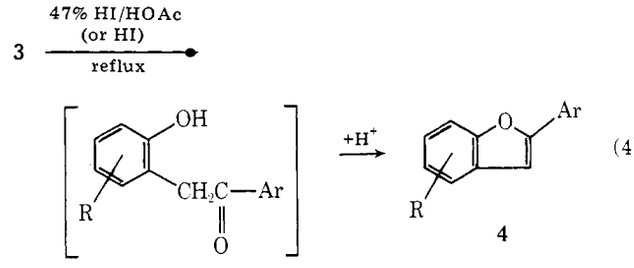
3a, Ar, 4-chlorophenyl; R = H
b, Ar, 3,4-dichlorophenyl; R = H
c, Ar, 4-chlorophenyl; R = 3,5-dibromo
d, Ar, 4-chlorophenyl; R = 3-methoxy

The reaction sequence used to obtain the desired deoxybenzoins proceeded according to the equations in Scheme I.

Reactions of various α-hetero-substituted phosphonate carbanions, generated with lithium diisopropylamine (LDA) in tetrahydrofuran at −78 °C, with substituted o-anisaldehydes afford the corresponding enamines. These enamines proved to be difficult to purify and isolate from the reaction mixture. In two cases, efforts were extended to isolate the enamines. These enamines are easily identified by the N–H stretching frequency at ~3380 cm^{-1} in the infrared and the N–H signal at δ ~6.5 ($CDCl_3$) or ~9.0 (Me_2SOd_6) in the NMR. These assignments were confirmed by D_2O exchange, thus both NMR as well as IR data support the enamine rather than the isomeric imine structure for these compounds. The NMR data for the crude (nonisolated) enamines were consistent with the data for the isolated enamines.

These enamines underwent smooth acid hydrolysis to afford the corresponding benzyl phenyl ketones (deoxybenzoins) which would be difficult to prepare via known literature methods.[4a–c] These deoxybenzoins were yellow oils and purification by column chromatography using silica gel was the most expedient method. These ketones are readily identified by NMR and IR methods. The carbonyl stretching frequency at ~1700 cm^{-1} in the infrared proved especially valuable for this purpose.

These ketones, when treated with 47% HI in HOAc (or 47% HI alone), underwent an ether cleavage and then cyclized presumably via the corresponding phenol to the desired benzofuran.[5a–e] This is illustrated in reaction 4.



4a, Ar, 4-chlorophenyl; R = H
b, Ar, 3,4-dichlorophenyl; R = H
c, Ar, 4-chlorophenyl; R = 5,7-dibromo
d, Ar, 4-chlorophenyl; R = 7-methoxy
e, Ar, 4-chlorophenyl; R = 7-hydroxy
f, Ar, 2-phenylethenyl; R = H
g, Ar, 4-chlorophenyl; R = 4,5-$(CH)_4$

In the case of 2-phenylethenyl (2-methoxyphenyl) ketone, only fusion with pyridine hydrochloride at 210–220 °C for 2 h afforded the corresponding benzofuran (**4f**). The reported yields for the benzofurans are overall yields (reaction 1–4). They vary considerably and do not reflect optimized conditions. The benzofurans thus obtained are colorless crystalline compounds. They are easily characterized by their elemental analyses and spectral data.

Compound **4e** was oxidized by Fremy's radical to the expected quinone. Thus, now readily available deoxybenzoins provide via the corresponding benzo[*b*]furans an easy entry into the hitherto little known class of benzo[*b*]furan-4,7-diones.[6]

This preparation of deoxybenzoins and benzofurans illustrates a number of features: (1) a variety of substituents can easily be introduced into the benzyl phenyl ketone (deoxybenzoin) system just by varying the substitution of the starting phosphonate and the o-anisaldehyde; (2) formation of benzofurans via this reaction route offers a more facile entry into the substituted benzofuran ring system than hitherto known methods,[7a–e] and (3) the formation of benzofurans proceeds by use of readily available starting materials.

Experimental Section

General. Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded using a Beckman IR-18A infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Perkin-Elmer RMU-7 Instrument. Mi-

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croanalysis were performed by Integral Microanalytical Laboratories, Inc. of Raleigh, N.C.

Preparation of Phosphonates. The phosphonates were obtained as previously described.[1] Diphenyl 1-(4-nitrophenylamino)-1-(4-chlorophenyl)methanephosphonate was prepared: $C_{25}H_{20}ClN_2O_5P$, mp 172.5–174 °C (95% ethanol); NMR ($CDCl_3$) δ 5.0 and 5.4 (dd, 1 H, J = 25, 8 Hz, exchangeable with D_2O, collapse to doublet, J = 25 Hz), 6.4–8.1 (m, 19 H); mass spectra (M^+) 494. Anal. Calcd. for $C_{25}H_{20}ClN_2O_5P$: C, 60.68; H, 4.07; N, 5.66. Found: C, 60.34; H, 3.83; N, 5.48.

Preparation of Enamines. To a mixture of freshly distilled tetrahydrofuran and diisopropylamine at −78 °C was added 1 equiv of n-butyllithium. The mixture was stirred for 20 min then 1 equiv of the appropriately substituted phosphonate dissolved in THF was slowly added. A deep blue or purple color was generated indicating formation of the phosphonate carbanion. After completion of the phosphonate addition (~15–20 min), 1 equiv of the appropriately substituted o-anisaldehyde dissolved in THF was added and stirring was continued until room temperature was reached. After removal of the THF in vacuo, water was added to the remaining red oil which was extracted with three portions of carbon tetrachloride. The organic layers were combined and dried over anhydrous $MgSO_4$ and after removal of CCl_4 the layers gave the crude enamine.

1-(3,4-Dichlorophenyl)-1-(4-nitroanilino)-2-(2-methoxyphenyl)ethene: yield 57%; mp 161–3 °C (absolute ethanol); IR (KBr) 3380 cm^{-1}; NMR (Me_2SO-d_6) δ 3.8 (s, 3 H), 6.4–8.1 (m, 12 H), 9.03 (s, 1 H, exchangeable with D_2O); mass spectrum (M^+) 414 (32), (M + 2) 416 (20.63), (M + 4) 418 (3.83). Anal. Calcd for $C_{21}H_{16}Cl_2N_2O_3$: C, 60.74; H, 3.88; N, 6.75; Cl, 17.07. Found: C, 60.69; H, 3.59; N, 6.53; Cl, 17.02.

1-(4-Chlorophenyl)-1-(4-nitroanilino)-2-(2-methoxyphenyl)ethene: yield 40%; mp 168–9 °C (95% ethanol); IR (KBr) 3360 cm^{-1}; NMR ($CDCl_3$) δ 3.83 (s, 3 H), 3.90 (s, 3 H), 6.4–6.57 (d, 2 H, J = 10 Hz), 6.47 (s, 1 H, exchangeable with D_2O), 6.9–7.6 (m, 8 H), 7.9–8.03 (d, 2 H, J = 10 Hz); mass spectrum (M^+) 410 (10.1), (M + 2) 412 (4.2). Anal. Calcd for $C_{22}H_{19}ClN_2O_4$: C, 64.32; H, 4.66; Cl, 8.63; N, 6.82. Found: C, 64.21, H, 4.63; Cl, 8.80; N, 6.47.

Preparation of Benzyl Phenyl Ketones (Deoxybenzoins). The enamine was taken up in 300–400 mL of MeOH and 100 mL of 37% HCl was added and refluxed for 2–3 h whereupon a color change from reddish to yellow (or yellow-orange) was noted. The solution was cooled, diluted with a fivefold excess of water, and extracted with three portions (200 mL each) of chloroform. The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and removal of the remaining $CHCl_3$, the crude product was purified on a short column (usually 25 mm × 100 mm) of silica gel with $CHCl_3$ elution. The ketones thus purified were yellowish oils.

2-Methoxyphenylmethyl 4-Chlorophenyl Ketone (3a): IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 3 H), 4.2 (s, 2 H), 6.6–8.2 (m, 8 H); mass spectrum (M^+) 260 (13.49), (M + 2) 262 (4.03). Anal. Calcd for $C_{15}H_{13}ClO_2$: Cl, 13.60. Found: Cl, 13.61.

2-Methoxyphenylmethyl 3,4-Dichlorophenyl Ketone (3b): IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 3 H), 4.2 (s, 2 H), 6.6–8.1 (m, 7 H); mass spectrum (M^+) 294, (M + 2) 296. Anal. Calcd for $C_{15}H_{12}Cl_2O_2$: Cl, 24.02. Found: Cl, 24.13.

3,5-Dibromo-2-methoxyphenylmethyl 4-Chlorophenyl Ketone (3c): IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (s, 3 H), 4.2 (s, 2 H), 6.9–8.1 (m, 6 H); mass spectrum (M^+) 418, (M + 2) 420, (M + 4) 422. Anal. Calcd for $C_{15}H_{11}Br_2ClO_2$: C, 43.05; H, 2.64. Found: C, 42.15; 42.49.[8]

2,3-Dimethoxyphenylmethyl 4-Chlorophenyl Ketone (3d): IR (neat) 1700 cm^{-1}; NMR ($CDCl_3$) δ 3.8 (2s, 6 H), 4.2 (s, 2 H), 6.6–8.2 (m, 7 H); mass spectrum (M^+) 290 (77), (M + 1) 291 (12), (M + 2) 292 (24.2). Anal. Calcd for $C_{16}H_{15}ClO_3$: Cl, 12.19. Found: Cl, 12.27.

Preparation of Benzo[*b*]furans. For every 2 g of the benzyl phenyl ketones was added 100 mL of 47% HI (unless otherwise indicated) and refluxing was continued for 12 h. After cooling and dilution with water, the product was extracted with two portions of chloroform. The combined organic extracts were dried over anhydrous $MgSO_4$. After removal of the chloroform the products were crystallized to yield the desired 2-substituted benzo[b]furans.

2-(4-Chlorophenyl)benzo[*b*]furan (4a): yield 51%; mp 144–144.5 °C (absolute ethanol) (lit.[5d] mp 149 °C); NMR ($CDCl_3$) δ 7.0 (s, 1 H), 7.1–7.9 (m, 8 H); mass spectrum (M^+) 228, (M + 2) 230. Anal. Calcd for $C_{14}H_9ClO$: C, 73.53; H, 3.97; Cl, 15.50. Found: C, 73.69; H, 4.02; Cl, 15.56.

2-(3,4-Dichlorophenyl)benzo[*b*]furan (4b): yield 66%; mp 107 °C (absolute ethanol); NMR ($CDCl_3$) δ 7.0 (s, 1 H), 7.1–7.8 (m, 6 H), 8.0 (d, 1 H, J = 2 Hz); mass spectrum (M^+) 262 (100), (M + 2) 264 (62.3), (M + 4) 266 (10.7). Anal. Calcd for $C_{14}H_8Cl_2O$: C, 63.91; H, 3.06; Cl, 26.95. Found: C, 63.70; H, 3.03; Cl, 26.73.

5,7-Dibromo-2-(4-chlorophenyl)benzo[*b*]furan (4c): yield 31%; mp 157 °C (95% ethanol); NMR (Me_2SO-d_6) δ 7.2 (s, 1 H), 7.4–8.0 (m, 6 H); mass spectrum (M^+) 384, (M + 2) 386, (M + 4) 388. Anal. Calcd for $C_{14}H_7Br_2ClO$: C, 43.51; H, 1.83. Found: C, 43.24; H, 1.59.

2-(4-Chlorophenyl)-7-methoxybenzo[*b*]furan (4d): yield 25%; mp 66 °C; NMR ($CDCl_3$) δ 4.0 (s, 3 H), 6.6–8.0 (m, 8 H); mass spectrum (M^+) 258 (100), (M + 2) 260 (45). Anal. Calcd for $C_{15}H_{11}ClO_2$: C, 69.64; H, 4.29; Cl, 13.70. Found: C, 69.77; H, 4.21; Cl, 13.91.

2-(4-Chlorophenyl)-7-Hydroxybenzo[*b*]furan (4e). This benzofuran was more conveniently prepared by using anhydrous $AlBr_3$ in dry benzene[10] and refluxing for 4 h: yield 50%; mp (155–156 °C); IR ($CDCl_3$) 3200 cm^{-1} (broad OH); NMR (Me_2CO-d_6) δ 6.6–7.05 (m, 4 H), 7.4 (d, 2 H, J = 10 Hz), 7.7 (d, 2 H, J = 10 Hz), 8.4 (broad s, 1 H, exchangeable with D_2O); mass spectrum (M^+) 244 (100), (M + 1) 245 (47), (M + 2) 246 (100). Anal. Calcd for $C_{14}H_9ClO_2$: C, 68.77; H, 3.71. Found: C, 69.08; H, 3.81.

2-(2-Phenylethenyl)benzo[*b*]furan (4f): yield 6%; mp 122–3 °C (absolute ethanol) (lit.[9] 121–122 °C); NMR ($CDCl_3$) δ 6.7 (s, 1 H), 7.0–7.7 (m, 11 H); mass spectrum (M^+) 220. Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.50. Found: C, 87.19; H, 5.12.

2-(4-Chlorophenyl)naphtho[2,1-*b*]furan (4g): yield 31%; mp 152.5–153.5 °C (95% ethanol); NMR ($CDCl_3$) δ 7.2–8.2 (m, aromatic H only); mass spectrum (M^+) 278 (100), (M + 2) 280 (36). Anal. Calcd for $C_{18}H_{11}ClO$: C, 77.56; H, 3.98; Cl, 12.72. Found: C, 77.06; H, 3.63; Cl, 12.72.

4,7-Dihydro-2-(4-chlorophenyl)benzo[*b*]furan-4,7-dione. To a stirred solution of 0.83 mg (.34 mmol) of 2-(4-chlorophenyl)-7-hydroxybenzofuran in 60 mL of dry acetone was added 0.3653 g (1.4 mmol) of potassium nitrosulfonate in 60 mL of 0.0558 M KH_2PO_4. The reaction was stirred 1 h and diluted with water and the product was extracted with chloroform. After drying the organic layer with Na_2SO_4, concentration and column chromatography using silica gel (10 mm × 50 mm) with benzene afforded orange-purple crystals. Recrystallization from chloroform/pentane (90:10) afforded bright orange crystals: yield 30%; mp 223–224 °C; NMR ($CDCl_3$) δ 6.7 (s, 2 H), 7.0 (s, 1 H), 7.5 (d, 2 H, J = 8 Hz), 7.9 (d, 2 H, J = 8 Hz); mass spectrum (M^+) 258 (100), (M + 1) 259 (21.5), (M + 2) 260 (46). Anal. Calcd for $C_{14}H_3ClO_3$: C, 65.01; H, 2.73. Found: C, 64.49; H, 2.62.

Acknowledgment. This investigation was partially supported by Grant CA-16666, awarded by the National Cancer Institute, DHEW. A gift of n-butyllithium by Lithium Corp. of America is acknowledged with appreciation.

Registry No.—2a, 66495-70-3; **2b,** 66495-71-4; **2c,** 66495-72-5; **2d,** 66495-73-6; **2e,** 66495-74-7; **2f,** 66495-75-8; **2g,** 66495-76-9; **3a,** 66495-77-0; **3b,** 66551-65-3; **3c,** 66495-78-1; **3d,** 66495-79-2; **3e,** 66495-80-5; **3f,** 66495-81-6; **3g,** 66495-82-7; **4a,** 39195-66-9; **4b,** 65246-48-2; **4c,** 66495-83-8; **4d,** 66495-84-9; **4e,** 66495-85-0; **4f,** 40723-99-7; **4g,** 66495-86-1; 4,7-dihydro-2-(4-chlorophenyl)benzo[b]furan-4,7-dione, 66495-87-2; o-anisaldehyde, 135-02-4; 3,5-dibromo-o-anisaldehyde, 61657-65-6; 3-methoxy-o-anisaldehyde, 86-51-1; 3-hydroxy-o-anisaldehyde, 66495-88-3; 2-methoxy-1-naphthaldehyde, 5392-12-1; diphenyl 1-(4-nitrophenylamino)-1-(4-chlorophenyl)methanephosphonate, 66495-89-4; diphenyl 1-(4-nitrophenylamino)-1-(3,4-dichlorophenyl)methanephosphonate, 66495-90-7; diphenyl 1-(4-nitrophenylamino)-1-(2-phenylethenyl)-methanesphosphonate, 64944-01-0.

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Preparation of Ketene Thioacetals from Dithioic Acid Dianions

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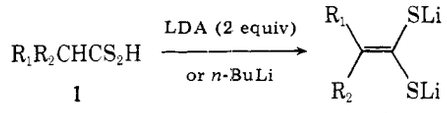
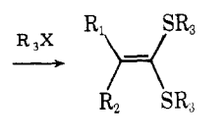
Ketene thioacetals have received considerable attention in recent years as important synthetic intermediates.[2] Although a host of ingenious methods exists for their synthesis,[3] we sought a method which would make them available from intermediates which are easily accessible. To this end, we have investigated the generation and alkylation of dithioic acid dianions.[4]

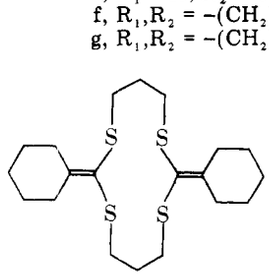


1 2

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1, R_2 = -(CH_2)_5-$



3a, $R_1 = R_2 = H$; $R_3 = C_2H_5$
b, $R_1 = R_2 = H$; $R_3 = -(CH_2)_3-$
c, $R_1 = H$; $R_2 = R_3 = CH_3$
d, $R_1 = H$; $R_2 = CH_3$; $R_3 = C_2H_5$
e, $R_1 = H$; $R_2 = CH_3$; $R_3 = -(CH_2)_3-$
f, $R_1, R_2 = -(CH_2)_5-$; $R_3 = C_2H_5$
g, $R_1, R_2 = -(CH_2)_5-$; $R_3 = -(CH_2)_3$



4

The dithioic acids are conveniently prepared by quenching the appropriate Grignard reagent with carbon disulfide.[5] By this procedure the dithioic acids can be obtained in yields of 40–70%, except in the case of **1a** which is prepared in 20% yield. In spite of the diminished yield in the latter case, the ready availability of the starting reagents overcomes this difficulty.

Dianion formation is readily accomplished by the addition of the acid to 2 equiv of lithium diisopropylamide (LDA) in THF containing 3 equiv of hexamethylphosphoramide (HMPA) in THF (0 → 25 °C). The HMPA serves to solubilize the precipitated dianion, which is too viscous to permit stirring. Alternatively, *n*-butyllithium effects dianion formation at −78 °C. Although precipitation occurs in this instance as well, stirring is possible and the addition of HMPA is not necessary. The generation of the dianion of the branched acid **1c** is not readily achieved with *n*-BuLi at −78 °C unless 4 equiv of tetramethylethylenediamine (TMEDA) is present.

Table I

Entry	Dithioic acid	Method	Alkyl halide	Ketene thioacetal[a] (yield, %)
1	**1a**	A[b]	C_2H_5I	**3a** (97)[d]
2	**1a**	B[c]	C_2H_5I	**3a** (81)[d]
3	**1a**	A	$BrCH_2CH_2CH_2Cl$	**3b** (45)[d]
4	**1b**	A	C_2H_5I	**3d** (86)[e]
5	**1b**	B	C_2H_5I	**3d** (91)[e]
6	**1b**	A	CH_3I	**3c** (75)[e]
7	**1b**	B	CH_3I	**3c** (71)[e]
8	**1b**	A	$BrCH_2CH_2CH_2Cl$	**3e** (54)[e]
9	**1b**	B	$BrCH_2CH_2CH_2Cl$	**3d** (31)[e]
10	**1c**	A	C_2H_5I	**3f** (87)[e]
11	**1c**	C[f]	C_2H_5I	**3f** (71)[d]
12	**1c**	D[g]	$BrCH_2CH_2CH_2Cl$	**3g** (51)[h]

[a] All new compounds are in full accord with their NMR spectrum, combustion analysis, and/or mass spectrum. [b] LDA (2 equiv), HMPA (3 equiv), THF, 0 → 25 °C, 1 h; 2 equiv of RX, −78 °C → room temperature. [c] *n*-BuLi (2 equiv), THF, −78 °C, 1 h; 2 equiv of RX, −78 °C → room temperature. [d] VPC. [e] Distilled. [f] *n*-BuLi (2 equiv), TMEDA (4 equiv), THF, −78 °C, 4 h; 2 equiv of RX, −78 °C → room temperature. [g] Reagents of method A added simultaneously and slowly at room temperature to THF. [h] Sublimed and recrystallized.

The yields for cycloalkylation employing 1-bromo-3-chloropropane are less than in the cases using methyl or ethyl iodide. No substantial improvement in yield was obtained when 1,3-diiodopropane was used. The major difficulty to be overcome in the cycloalkylation was that of polymerization. Alkylation of **1c** by the LDA method gave dimer **4** in 28.5% yield. This difficulty was overcome by employing dilution techniques (entry 12, Table I).

Confirmation of dianion formation was obtained by quenching the alleged dianion **2b** (method B) with 3 equiv of methanol-d_1 followed by acidification and exchange of the carboxyl proton. The NMR spectrum revealed a deuterium coupled doublet [δ 1.35 (3 H, $J_{H,H}$ = 7 Hz, CH_3CHD–)] and a deuterium coupled quartet [δ 3.00 (1 H, $J_{H,H}$ = 7 Hz, CH_3CHD–)]. That the α deuterium was not introduced as a consequence of methoxide exchange was confirmed by noting the lack of deuterium incorporation when the lithium salt of **1b** was exposed to 1 equiv of $LiOCH_3$ and 2 equiv of CH_3OD in THF under the reaction conditions.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Diisopropylamine and hexamethylphosphoramide were distilled from calcium hydride and stored over molecular sieves. Tetramethylethylenediamine (TMEDA) was distilled from potassium hydroxide and stored over molecular sieves. Alkyl halides were distilled prior to use. Gas chromatograms were obtained using a Varian Aerograph Model 90-P instrument with a 6 ft × 0.25 in, 5% SE 30 on Anakrom 60–70 mesh SD column (TC corrected; **3d** internal standard). NMR spectra were obtained on Perkin-Elmer R32, Bruker HX-270, or Varian CFT-20 instruments using Me_4Si as an internal standard. Elemental analyses were performed by Atlantic Microlabs (Atlanta). Standardization of *n*-butylithium in hexane was effected by the diphenylacetic acid technique.[6]

2-Ethylidene-1,3-dithiane (3e) (Entry 8). To a solution of LDA (prepared at 0 °C from 18.0 mL (128 mmol) of diisopropylamine and 46 mL (2.4 M, 110 mmol) of *n*-BuLi/hexane in 240 mL of THF at 0 °C) maintained under an atmosphere of N_2 was added at 0 °C 27.0 mL (150 mmol) of HMPA, followed by a solution of 5.3 mL (50 mmol) of propanedithioic acid (**1b**) in 5 mL of THF over a period of 10 min.

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