A New Method for the Preparation of 1-Ethynyl Ethers

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During our study[2] of the stannylcupration of acetylenic ethers we required [2-^{13}C]-**1** for mechanistic studies. Existing methods[3] for the synthesis of acetylenic ethers involve dehydrohalogenation of 2-halo,[4] 1,2-dihalo vinyl ethers,[5] or haloacetals[6] using KOH, $NaNH_2$, or *n*-BuLi. These procedures are incompatible with labile functional groups and, if applied to the preparation of ^{13}C-labeled compounds, would require regiospecific preparation of 1- or 2-^{13}C-labeled halo vinyl ethers, which is cumbersome.

We report a new, general and efficient method for the preparation of acetylenic ethers which we have applied to the preparation of ^{13}C-labeled and functionalized acetylenic ethers.

Results and Discussion

The commercial availability of ^{13}C-labeled acetyl chloride, encouraged us to consider the possible transformation of an acetate (**2**) to an acetylenic ether (**1**). For this process, the transformation of an ester to the corresponding enol phosphate **3** followed by *trans*-elimination analogous to Negishi's conversion of methyl ketones to terminal acetylenes[7] was an obvious strategy (Scheme 1, path b).

While the conversion of ketones and acetates to the corresponding enol phosphates are well-known processes,[8] the presence of a vinyl alkoxy group in the latter complicates the subsequent elimination. Initial reactions involving treatment of octyl acetate (**2**) with 1 equiv of LDA followed by addition of diethyl chlorophosphate in the presence of HMPA (1.1 equiv), gave the corresponding enol phosphate **3**. "One-pot" reactions in which 2 equiv of LDA was added to **3** at −78 °C gave 70–80% of 1-octanol (**4**) and 10–20% of the desired octyl ethynyl ether (**1**) (Table 1, entry 3). Both products can be envisioned as arising from 1,2–*trans*-elimination of **3** (Scheme 1, paths a and b). It has been reported[9] that elimination of alkoxides from *trans*-β-lithio vinyl ethers is facile even at −100 °C.

When **2** was treated, at −78 °C, with 3 equiv of LDA, followed by addition of diethyl chlorophosphate in HMPA (8 equiv), the principal product, **5** (58%, Table 1, entry 4), arose from 1,2-phosphate migration (Scheme 1, path c). The latter reaction has been extensively studied by Weimer in cyclic ketones,[10] lactones, and α-substituted esters.[11] Reported yields for conversion of α-substituted esters to the corresponding α-(diethoxyphosphinyl) esters are in the range of 0–26%. The use of KTMP or *t*-BuLi

Scheme 1. Synthesis of Octyl Ethynyl Ether 1

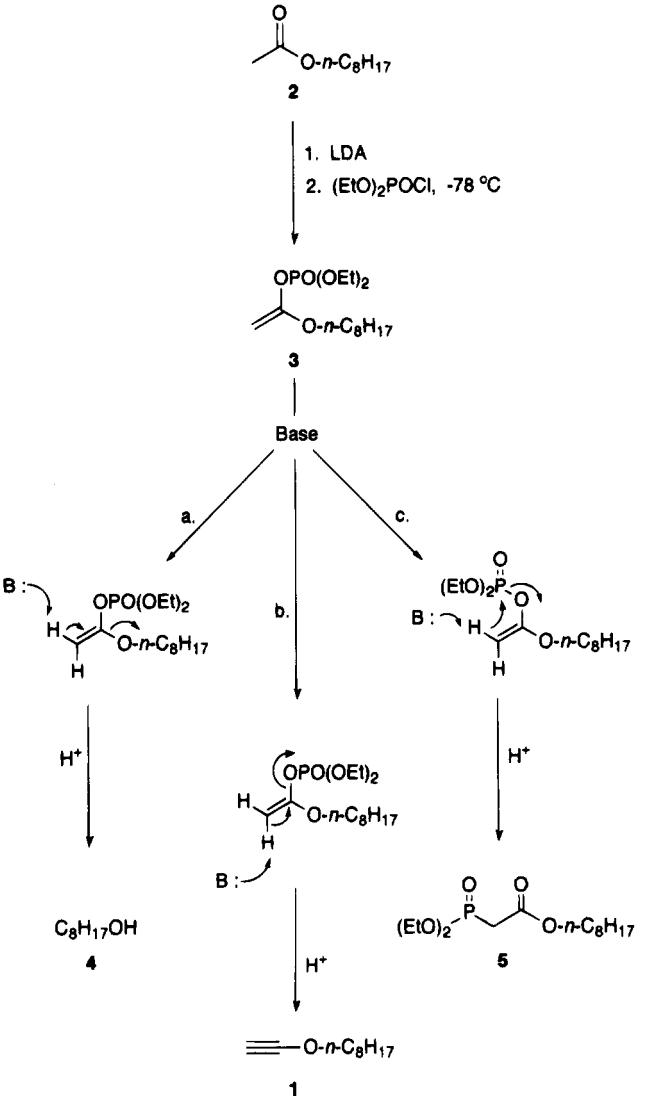

Table 1. Effect of Base on Efficiency of Conversion of Enol Phosphate 3 to 1-Alkynyl Ethers[f]

		products (%)[a]		
entry	base	1	4	5
1	NaH	–	100	–
2	MeLi	–	100	–
3	LDA[b]	15	80	5
4	LDA/HMPA[c]	24	*d*	58
5	*t*-BuLi/HMPA[c]	16	10	74
6	KTMP/HMPA[c]	28	7	55
7	*t*-BuLi/TMEDA	27	13	*e*
8	*t*-BuLi/HMPA	35	5	60
9	*t*-BuLi	40	45	5

[a] Calculated by GC analysis. [b] 1 equiv of HMPA was used in this reaction. [c] 8 equiv of HMPA was used. [d] Octyl acetate was produced in this reaction (24%). [e] 60% of octyl acetate was produced. [f] All reactions were performed in THF at −78 °C using 2 equiv of base per 1 equiv of enol phosphate **3**. Reactions in entries 3–5 were carried out using a "one-pot" procedure. In entries 1, 2, 6–9 enol phosphate **3** was first isolated and then treated with base.

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Table 2. Effect of Solvent and Temperature on Conversion of Enol Phosphate 3 into Octyl Ethynyl Ether 1 with *t*-BuLi

entry	temp (°C)[a]	solvent	% yield[b]
1	−78	THF	40
2	−100	THF	46
3	−100	pentane[c]	55
4	−100	pentane[c,d]	65

[a] Internal temperature. [b] Yield of chromatographically isolated compound. [c] 10% of THF was used in this case. [d] This sample was LiCl free.

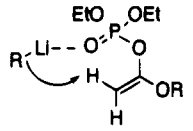


Figure 1. Coordination of a lithium base RLi with the phosphate group.

in the presence of HMPA appears to offer significant advantages for promotion of this process (Table 1, entries 5 and 6).

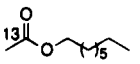
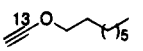
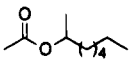
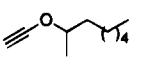
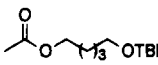
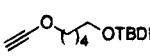
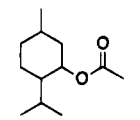
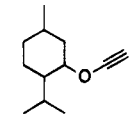
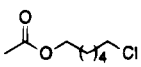
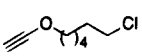
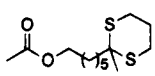
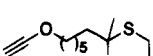
Even with sterically hindered bases such as LDA preferential abstraction of the hydrogen *trans* to the alkoxy group was observed (Table 1, entries 3 and 4). Superior yields of **1** were obtained if enol phosphate **3** was first isolated and then treated with base. Sterically undemanding bases such as NaH and MeLi afforded only alkoxide elimination (Table 1, entries 1 and 2). Only in the case of *t*-BuLi were reasonable yields of **1** obtained from **3** (Table 1, entries 8 and 9). Lowering the temperature of the elimination from −78 to −100 °C in the *t*-BuLi-promoted process further increased the yield (Table 2, entries 1 and 2).

We considered it likely that alkoxide elimination and 1,2-phosphate migration might be promoted by coordination of the lithium base[12] and phosphate oxygen favoring abstraction of the hydrogen *trans* to the alkoxy group (Figure 1).

The presence of LiCl, formed in the first step, could also promote abstraction of the hydrogen *trans* to the alkoxy group by formation of a chelate.[13] Yields of **1** were marginally improved when LiCl was removed from enol phosphate **3** prior to treatment with *t*-BuLi. This can be executed without chromatography by dissolution of the crude quenched reaction mixture (from the preparation of **3**) in pentane and filtration of the LiCl precipitate before subjecting it to elimination. When this procedure was executed prior to treatment of **3** with *t*-BuLi (2.2 equiv) at −100 °C, followed by warming of the reaction mixture to −30 °C before quenching, yields of **1** increased from 55 to 65% (Table 2, entries 3 and 4).

This new method has been applied to the synthesis of ^{13}C-labeled acetylenic ethers **1** and derivatives containing labile groups previously unaccessible (Table 3, entry 5). Several attempts to obtain acetylenic ether **14**, by treatment of the corresponding enol phosphate of acetate **9** with *t*-BuLi (2.2 equiv) at −100 °C, followed by warming to −30 °C and treatment with *i*-PrOH, resulted in an inseparable mixture (ca. 8:2) of **14** and 7,7-dimethyloctyl ethynyl ether, from nucleophilic displacement of the primary chloride by *t*-BuLi. Presumably, the later reaction was favoured by the increase in the reaction temperature from −100 to −30 °C. Treatment of the enol phosphate of **9** with 1.8 equiv of *t*-BuLi at −100 °C followed by treatment with *i*-PrOH at −85 °C (internal temperature) resulted in a clean formation of **14** (Table 3, entry 5).

Table 3. Transformation of Acetates into Ethynyl Ethers

Entry	Acetate	Acetylenic Ether	% Yield[a]
1	 **2**	 **1**	65
2	 **6**	 **11**	68
3	 **7**	 **12**	63
4	 **8**	 **13**	64
5	 **9**	 **14**	55
6	 **10**	 **15**	57

[a] Yield of chromatographically isolated compound.

This new method provides easy access to functionalized and ^{13}C-labeled 1-ethynyl ethers in acceptable yields.

Experimental Section

General Methods. All glassware and syringes were dried in an oven overnight at 140 °C and flushed with argon immediately prior to use. Transfers of reagents were performed with syringes equipped with stainless-steel needles. All reactions were carried out under a positive pressure of argon. THF was refluxed and freshly distilled from potassium/benzophenone ketyl under argon atmosphere. Argon was passed through a Drierite column (40 cm × 3 cm). HMPA was fractionally distilled under vacuum (68−70 °C/1.1 mmHg) from calcium hydride, collected and stored over activated 4 Å molecular sieves. Diisopropylamine was freshly distilled from sodium under argon. Alkyllithiums were titrated according to Watson and Eastham.[14] Diethylchlorophosphate was purchased from Sigma and stored over activated 4 A molecular sieves. ^{1}H-NMR spectra were recorded on a Bruker AMX-400 spectrometer. Mass spectra were obtained on a Hewlett-Packard 5985B spectrometer using electron impact at 70 eV. Infrared spectra were obtained on a Perkin Elmer series 1600 FT spectrometer. Acetates not com-

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mercially available were prepared from the corresponding alcohols according to Steglich.[15]

Typical Procedure. Preparation of [2-^{13}C]Ethynyl Octyl Ether ([2-^{13}C]-1). A solution of [2-^{13}C]octyl acetate[2] (1.73 g, 10 mmol) in THF (2 mL) was added to a cold (−78 °C) THF solution (6.5 mL) of LDA [prepared from 1.5 mL (10.6 mmol) of diisopropylamine and 4.25 mL (10.4 mmol) of *n*-BuLi 2.45 M at −40 °C] and the mixture stirred for 45 min. at this temperature. A solution of diethyl chlorophosphate (1.7 mL, 12.0 mmol) in HMPA (2.5 mL) was then added and the mixture stirred at the same temperature for 3 h. The reaction mixture was treated with 5 mL of a THF:water mixture (1:1), warmed to room temperature, and extracted with ether (2 × 30 mL). The organic extracts were washed with water (2 X 15 mL) and dried over anhyd $MgSO_4$. After concentration *in vacuo* the remaining oil was dissolved in pentane (~40 mL) and the LiCl removed by filtration through fritted glass.[16]

The pentane solution thus obtained (~40 mL) was cooled to −100 °C (internal temperature) using a liquid nitrogen-ether bath (addition of *ca.* 5 mL of THF was needed to maintain product in solution) and *tert*-BuLi (12.4 mL, 21 mmol, 1.7 M in pentane) was added dropwise.[17] The internal temperature was allowed to rise to −30 °C at which point to the mixture was added 2-propanol (2−3 mL) and then water (3 mL). The mixture was extracted with ether (2 × 20 mL), and the extracts were washed with water (2 × 15 mL) and dried over anhyd $MgSO_4$. Evaporation of solvent gave a crude product which was dissolved in pentane and filtered through a pad of silica gel (6 × 4 cm) (pretreated with Et_3N) and eluted with pentane. Evaporation of solvent affored 1.0 g of [2-^{13}C]-1 (65% yield). For spectroscopic characteristics of this compound and preparation of [2-^{13}C]octyl acetate see ref 2.

For compound **14**, after treatment of the corresponding enol phosphate with *tert*-BuLi,[17] the reaction mixture was allowed to warm from −100 to −85 °C and quenched at the latter temperature. The crude product was extracted into pentane which was concentrated by distillation at atmospheric pressure through a Vigreaux column. Purification by filtration through silica gel followed by concentration of the pentane solution as above yielded a residue which was further purified by distillation under vacuum.

1-[(Diethoxyphosphinyl)oxy]vinyl Octyl ether (3): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, 3H, J = 7 Hz), 1.20−1.32 (br s, 10H), 1.35 (t, 6H, J = 7 Hz), 1.70 (m, 2H), 3.52 (d, 1H, J = 3.5 Hz), 3.77 (t, 2H, J = 6.5 Hz), 3.85 (dd, 1H, J = 3.5 Hz, $^4J_{P-H}$ = 2.0 Hz), 4.19 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0, 16.0, 22.6, 25.8, 28.6, 29.1, 29.2, 31.7, 64.5, 67.6, 69.3, 157.0; IR (film) 1669 1242, 1166, 1036; MS (CI) *m/e* (rel intensity) 309 (M + 1, 17), 197 (100), 155 (83).

Octyl α-(diethoxyphosphinyl)acetate (5): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, 3H, J = 7 Hz), 1.15−1.27 (m, 10 H), 1.30 (t, 6H, J = 7 Hz), 1.60 (m, 2H), 2.95 (d, 2H, $^2J_{P-H}$ = 22 Hz), 4.10 (t, 2H, J = 7 Hz), 4.15 (dq, 4H, J = 7.0 Hz, $^3J_{P-H}$ = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9, 16.3, 22.5, 25.8, 28.5, 29.1, 31.7, 33.7, 35.1, 62.6, 65.7, 165.8; IR (film) 2930, 2857, 1737, 1272, 1027 cm^{-1}; MS (CI) *m/e* (rel intensity) 309 (M + 1, 100).

5-[(*tert*-Butyldimethylsilyl)oxy]pentyl acetate (7):[18] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.87 (s, 9H), 1.40 (m, 2H), 1.54 (m, 2H), 1.63 (m, 2H), 3.60 (t, 2H, J = 6.5 Hz), 4.50 (t, 2H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ −5.3, 18.3, 20.9, 22.3, 25.9, 28.5, 32.4, 62.9, 64.5, 171.0; IR (film) 2930, 1743, 1240, 1098, 836, 776 cm^{-1}; MS (CI) *m/e* (rel intensity) 261 (M + 1, 100), 201 (21), 117 (6). Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H: 10.84. Found: C, 60.06; H: 10.66.

5-Chlorohexyl acetate (9): ^{1}H NMR ($CDCl_3$, 100 MHz) δ 0.31−0.95 (m, 8H), 2.02 (s, 3H), 3.54 (t, 2H, J = 7Hz), 4.05 (t, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.9, 25.3, 26.5, 28.5, 32.5, 44.8, 64.3, 171.0; IR (film) 2940, 1740, 1243, 1049, 730 cm^{-1}; MS (CI) *m/e* (rel intensity) 179 (M + 1, 100), 119 (15). Anal. Calcd for $C_8H_{15}O_2Cl$: C, 53.78; H: 8.46. Found: C, 53.77; H: 8.49.

2-[6′-(Acetyloxy)hexyl]-2-methyl-1,3-dithiane (10):[19] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30−1.42 (m, 4H), 1.43−1.53 (m, 2H), 1.61 (s, 3H), 1.63 (m, 2H), 1.85−1.91 (m, 2H), 1.92−2.00 (m, 2H), 2.05 (s, 3H), 2.80−2.90 (m, 4H), 4.05 (t, 2H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.3, 25.4, 25.8, 26.5, 27.8, 28.5, 29.4, 41.7, 49.2, 64.4, 171.0; IR (film) 2935, 2858, 1738, 1237, 1037 cm^{-1}; MS (EI) *m/e* (rel intensity) 276 (M$^+$, 20), 133 (100), 74 (47). Anal. Calcd for $C_{13}H_{24}S_2O_2$: C, 56.48; H: 8.75. Found: C, 56.66; H: 8.96.

***n*-Octyl ethynyl ether (1):** ^{1}H NMR ($CDCl_3$, 100 MHz) δ 0.88 (t, 3H), 1.30 (br s, 10H), 1.51 (s, 1H), 1.76 (m, 2H), 4.07 (t, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0, 22.6, 25.3, 26.0 , 28.6, 29.1, 31.7, 79.0, 91.3; IR (film) 3328, 2152, 1467, 1094 cm^{-1}; MS (EI), *m/e* (rel intensity) 112 (M$^+$ − C_2H_2O, 3), 97 (4), 83 (15), 71 (94), 57 (100). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H: 11.76. Found: C, 77.62; H: 11.82.

2-Octyl ethynyl ether (11): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, 3H, J = 7.0 Hz), 1.20−1.30 (m, 6H), 1.36 (d, 3H, J = 7.0 Hz), 1.45−1.58 (m, 2H), 1.54 (s, 1H), 1.70−1.80 (m, 2H), 4.10−4.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0, 19.1, 22.5, 25.1, 27.3, 29.0, 31.7, 35.3, 85.7, 89.8; IR (film) 3331, 2145, 1105 cm^{-1}; MS (EI) *m/e* (rel intensity) 112 (M$^+$ − C_2H_2O, 29), 83 (56), 70 (100), 55 (67). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H: 11.76. Found: C, 78.12; H: 12.00.

5-(*tert*-Butyldimethylsiloxy)pentyl ethynyl ether (12): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.04 (s, 6H), 0.86 (s, 9H), 1.42 (m, 2H), 1.50 (s, 1H), 1.54 (m, 2H), 1.76 (m, 2H), 3.60 (t, 2H, J = 7 Hz), 4.05 (t, 2H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 100.6) δ 5.3, 18.3, 21.7, 25.9, 26.1, 28.4, 32.2, 62.8, 78.9, 91.2; IR (film) 3330, 2153, 1256, 1099 cm^{-1}; MS (EI), *m/e* (rel intensity) 201 (M$^+$ − C_2H_2O, 1), 143 (37), 129 (17), 115 (11), 99 (56), 75 (100). Anal. Calcd for $C_{13}H_{26}SiO_2$: C, 64.41; H, 10.81. Found: C: 64.28; H: 10.89.

Menthyl ethynyl ether (13): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (d, 2H, J = 7.0 Hz), 0.92 (d, 2H, J = 7.0 Hz), 0.96 (d, 2H, J = 7.0 Hz), 1.15−1.30 (m, 3H), 1.40−1.50 (m, 2H), 1.52 (s, 1H), 1.63−1.72 (m, 2H), 2.10−2.18 (m, 1H), 2.27 (dddd, 1H, J = 12, 4, 4, 2 Hz), 3.86 (ddd, 1H, J = 11, 11, 4.5 Hz); ^{13}C NMR ($CDCl_3$, 100.6) δ 16.3, 20.5, 21.9, 23.5, 26.0, 27.1, 31.6, 34.0, 39.4, 46.8, 88.3, 89.8; IR (film) 3331, 2145, 1102, cm^{-1}; MS (EI) *m/e* (rel intensity) 138 (M$^+$ − C_2H_2O, 42), 123 (27), 95 (100), 81 (81). Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H: 11.18. Found: C: 80.39, H: 11.73.

6-Chlorohexyl ethynyl ether (14): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35−1.50 (m, 4H), 1.53 (s, 1H), 1.70−1.83 (m, 4H), 3.53 (t, 2H, J = 7.0 Hz), 4.07 (t, 2H, J = 7Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.7, 26.2, 26.4, 28.5, 32.4, 44.8, 78.7, 91.1; IR (film) 3321, 2152, 1468, 1120 cm^{-1}; MS (EI) *m/e* (rel intensity) 118 (M$^+$ − C_2H_2O, 21), 82 (42), 69 (25), 55 (31), 43 (100); Anal Calcd. for $C_8H_{13}OCl$: C, 59.81; H: 8.16. Found: C, 59.97; H: 8.33.

2-[6′-(Ethynyloxy)hexyl]-2-methyl-1,3-dithiane (15): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32−1.56 (m, 6H), 1.52 (s, 1H), 1.61 (s, 3H), 1.76 (m, 2H), 1.87−1.98 (m, 4H), 2.83−2.86 (m, 4H), 4.07 (t, 2H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 24.3, 25.2, 25.4, 26.1, 26.5, 27.8, 28.5, 29.2, 41.6, 49.2, 78.9, 91.2; IR (film) 3312, 2149, 1093 cm^{-1}; MS (EI) *m/e* (rel intensity) 216 (M$^+$ − C_2H_2O, 6), 133 (100), 106 (19), 74 (60). Anal. Calcd for $C_{13}H_{22}S_2O$: C, 60.42; H: 8.58. Found: C, 60.74; H: 8.76.

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(15) Höfle, G.; Steglich, W.; Vorbrüggen, H *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

(16) It is recommended to perform both steps sequentially. Decomposition of the enol phosphate was observed when this crude was stored overnight.

(17) For the preparation of **14**, the *tert*-BuLi was added from a dropping funnel containing an outer jacket filled with dry ice/acetone.

(18) The corresponding monosilylated diol was prepared according to McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51* , 3388.

(19) The corresponding alcohol was prepared by reaction of 6-bromohexyl *tert*-butyldimethylsilyl ether, with 2-lithio-2-methyl-1,3-dithiane (ref 20), followed by reaction with NH_4F.

(20) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.