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General Reactivity of 2-Lithiobenzothiazole to Various Electrophiles and the Use as a Formyl Anion Equivalent in the Synthesis of α-Hydroxy Carbonyl Compounds

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The reaction of 2-lithiobenzothiazole with a variety of electrophiles such as aldehydes, ketones, carboxylic esters, lactones, nitriles, and amides afforded the expected addition and substitution products. Trimethylsilyl chloride readily reacted with the benzothiazolyl anion to give 2-trimethylsilylbenzothiazole, while common alkyl halides including primary iodide and benzyl halides, as well as epoxides, did not react with the anion. This characteristic nucleophilicity of the anion was also demonstrated by its reaction with phenacyl halides and 5-chloro-2-pentanone leading to the formation of benzothiazolyl-substituted small-ring ethers. In order to demonstrate the value of 2-lithiobenzothiazole as a masked formyl anion, 2-(α-hydroxyalkyl)benzothiazoles were transformed into α-hydroxy carbonyl compounds in three reaction steps without masking the α-hydroxy groups. Quaternization of various 2-(α-hydroxyalkyl)benzothiazoles with methyl iodide in DMF afforded the corresponding 2-(α-hydroxyalkyl)-3-methylbenzothiazolium iodides in high yields and the subsequent alkylation or reduction of the $C=N^+$ link was readily accomplished with organolithium and Grignard reagents or sodium borohydride leading to the corresponding 2-(α-hydroxyalkyl)-3-methylbenzothiazolines with or without another 2-substituents. Hydrolysis of former compounds performed in aqueous acetonitrile, buffered to pH 7 and containing $AgNO_3$, gave the desired α-hydroxy ketones.

Umpolung[1] of the normal reactivity by modifying structural units has become one of the prevailing methods of choice in synthetic organic chemistry. Particularly, carbanions stabilized by adjacent sulfur atoms have been well-documented,[2] since Corey and Seebach[3] first utilized 2-lithio-1,3-dithiane as a formyl anion equivalent. Carbanions of cyclic imines stabilized by an adjacent heteroatom can also be regarded as an important formyl anion equivalent candidate due to the convertibility of the imine function with an adjacent heteroatom into a carbonyl group. However, notable differences in chemical stability between the cyclic imine adjacent oxygen atom and one adjacent sulfur atom have appeared. That is, the metalated oxazoline was reported to be unstable even at −78 °C,[4] while the corresponding benzothiazolyl anion seems to be stable as a masked formyl anion.[5] Despite much work in the benzothiazole field, however, only one example[6] of the use of 2-lithiobenzothiazole as a formyl anion equivalent has been described and there has been no study regarding its general reactivity to various electrophiles in spite of its importance and necessity. It is a purpose of the present paper to describe the fundamental and detailed studies of the general reactivity of 2-lithiobenzothiazole (**2**) toward different electrophiles (Scheme 1) and show the interesting differences in chemical reactivity between 2-lithio-1,3-dithiane or related reagents and **2**. We will also examine the utility of the lithium reagent **2** as a formyl anion equivalent with respect to the synthesis of α-hydroxy carbonyl compounds.

Preparation and Properties of 2-Lithiobenzothiazole (2). The conversion of benzothiazole (**1**) into the anion **2** was most conveniently achieved by adding 1.1 equiv of *n*-BuLi to a solution of **1** in THF at −78 °C which gave rise to a clear orange-colored solution. The progress of the lithiation was followed by deuteration of the reaction mixture with D_2O. When the solution was quickly quenched with D_2O after the addition of *n*-BuLi, the ^1H NMR spectrum of the product **3** (E=D), which had been isolated in 95% yield, showed 98% deuterium incorporation. This indicates that

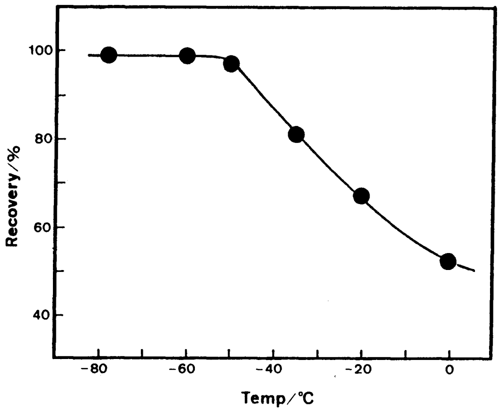
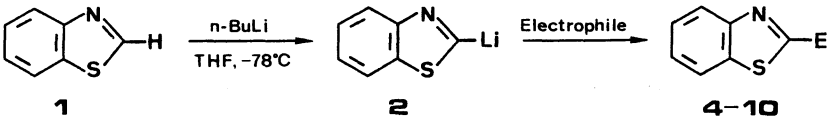


Fig. 1. Stability of 2-lithiobenzothiazole (**2**) in THF. Recovery percentages of benzothiazole (**1**) after quenching the anion solution with water at various temperatures.



Scheme 1.

nearly quantitative metalation of **1** in THF at −78 °C occurs instantaneously. It is important and necessary for the reaction of **2** with a variety of electrophiles together with its operation to examine the stability of the anion **2** in THF at various temperatures. Thus, the yield of recovered **1** was monitored by quenching the THF solution containing the anion **2** with water after warming from −78 °C to several different temperatures (Fig. 1). As clearly indicated in Fig. 1, the anion **2** in THF is very stable below −50 °C, while it decomposes

Table 1. Reaction of 2-Lithiobenzothiazole (**2**) with Aldehydes and Ketones[a]

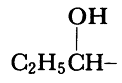
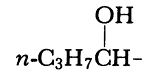
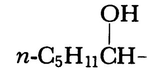
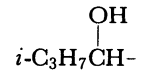
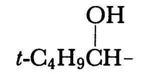
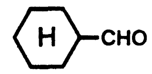
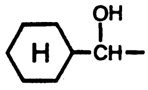
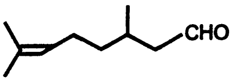
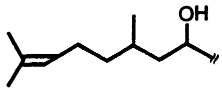
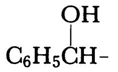
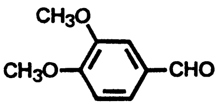
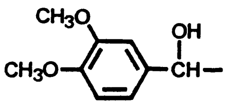
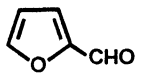
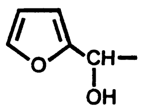
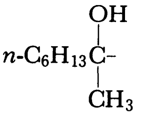
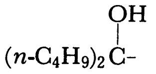
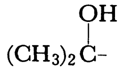
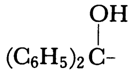
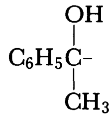
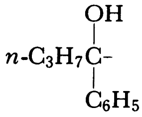
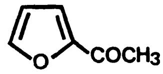
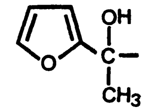
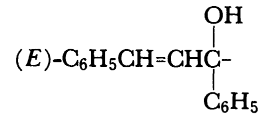
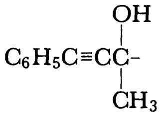
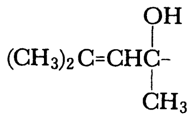
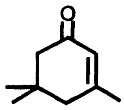
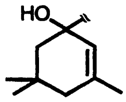
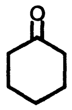
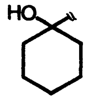
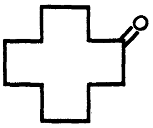
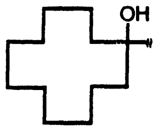
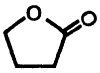
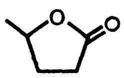
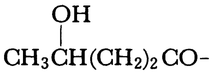
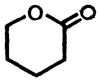
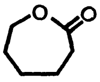
Entry	Electrophile	Product	E	Yield/%[b]
1	C_2H_5CHO	**4a**	 $C_2H_5\overset{OH}{\overset{\vert}{C}}H-$	70
2	n-C_3H_7CHO	**4b**	 $n\text{-}C_3H_7\overset{OH}{\overset{\vert}{C}}H-$	78
3	n-$C_5H_{11}CHO$	**4c**	 $n\text{-}C_5H_{11}\overset{OH}{\overset{\vert}{C}}H-$	89
4	i-C_3H_7CHO	**4d**	 $i\text{-}C_3H_7\overset{OH}{\overset{\vert}{C}}H-$	c)
5	t-C_4H_9CHO	**4e**	 $t\text{-}C_4H_9\overset{OH}{\overset{\vert}{C}}H-$	85
6		**4f**		72
7		**4g**[d]		77[e]
8	C_6H_5CHO	**4h**	 $C_6H_5\overset{OH}{\overset{\vert}{C}}H-$	77
9		**4i**		85[e]
10		**4j**		73
11	n-$C_6H_{13}COCH_3$	**5a**	 $n\text{-}C_6H_{13}\overset{OH}{\underset{CH_3}{C}}-$	c)
12	$(n\text{-}C_4H_9)_2CO$	**5b**	 $(n\text{-}C_4H_9)_2\overset{OH}{\overset{\vert}{C}}-$	88[e]
13	$(CH_3)_2CO$	**5c**	 $(CH_3)_2\overset{OH}{\overset{\vert}{C}}-$	77
14	$(C_6H_5)_2CO$	**5d**	 $(C_6H_5)_2\overset{OH}{\overset{\vert}{C}}-$	88
15	$C_6H_5COCH_3$	**5e**	 $C_6H_5\overset{OH}{\underset{CH_3}{C}}-$	88
16	n-$C_3H_7COC_6H_5$	**5f**	 $n\text{-}C_3H_7\overset{OH}{\underset{C_6H_5}{C}}-$	c)

Table 1. (Continued)

Entry	Electrophile	Product	E	Yield/%[b]
17		**5g**		85
18	(E)-$C_6H_5CH{=}CHCOC_6H_5$	**5h**	 $(E)\text{-}C_6H_5CH{=}CH\overset{OH}{\underset{C_6H_5}{C}}\text{-}$	83[f]
19	$C_6H_5C{\equiv}CCOCH_3$	**5i**	 $C_6H_5C{\equiv}C\overset{OH}{\underset{CH_3}{C}}\text{-}$	78[f]
20	$(CH_3)_2C{=}CHCOCH_3$	**5j**	 $(CH_3)_2C{=}CH\overset{OH}{\underset{CH_3}{C}}\text{-}$	71[f]
21		**5k**		50[e,f]
22		**5l**		78
23		**5m**		86

a) In all cases, 2-lithiobenzothiazole (**2**) was reacted with 1.1 equiv of the carbonyl compounds in THF at −78 °C for 1 h. b) Yields of pure products after recrystallization unless otherwise noted. c) The crude oily product was quantitatively obtained. d) A mixture of diastereomers. e) Yield of pure product after short-column chromatography on silica gel. f) Conjugate-addition product was not obtained.

Table 2. Reaction of 2-Lithiobenzothiazole (**2**) with Esters and Lactones[a]

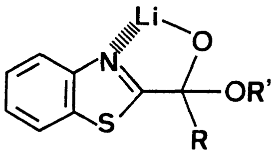
Entry	Electrophile	Product	E	Yield/%[b]
1	$C_6H_5COOC_2H_5$	**6a**	C_6H_5CO-	76
2	$C_2H_5COOC_2H_5$	**6b**	C_2H_5CO-	68
3	n-$C_5H_{11}COOC_2H_5$	**6c**	n-$C_5H_{11}CO$-	63
4	i-$C_3H_7COOC_2H_5$	**6d**	i-C_3H_7CO-	64[c]
5	t-$C_4H_9COOCH_3$	**6e**	t-C_4H_9CO-	69[c]
6		**7a**	$HO(CH_2)_3CO$-	79
7		**7b**	 $CH_3\overset{OH}{C}H(CH_2)_2CO$-	80
8		**7c**	$HO(CH_2)_4CO$-	99
9		**7d**	$HO(CH_2)_5CO$-	96

a) In all cases, 2-lithiobenzothiazle (**2**) was reacted with 1.1 equiv of esters or lactones in THF at −78 °C to room temperature. b) Yields of pure products after recrystallization unless otherwise noted. c) Yield of pure product after short-column chromatography on silica gel.

considerably above −50 °C and the degree of this decomposition increased in proportion to the temperature of the solution. Accordingly, in the following experiments, electrophiles were added immediately to the anion solution after the addition of *n*-BuLi and the temperature of the reaction mixture was kept below −50 °C until the reaction was almost completed.

Hydroxyalkylation of 2 with Aldehydes and Ketones. Aldehydes and ketones reacted readily with the anion **2** to give the corresponding 2-(α-hydroxyalkyl)benzothiazoles in high yields. Table 1 lists a number of reaction products **4a**—**j** and **5a**—**m** together with their yields. The reactions were almost completed within 1 h at −78 °C and the reaction time did not vary with the steric and electronic character of the carbonyl compounds. Under the present conditions, a readily enolized ketone, such as cyclohexanone, produced the product **5l** in high yield by carbonyl addition (Entry 22). This demonstrates the very effective nucleophilicity of the lithium reagent **2**. When α,β-unsaturated ketones were employed as carbonyl substrates (Entries 18—21), the α-hydroxy products **5h**—**k** were selectively obtained in good yields showing a high preference of the anion **2** for nonconjugate 1,2-addition to α,β-unsaturated carbonyl compounds.

Acylations of 2 with Esters and Lactones. The reactions of the anion **2** with esters effectively lead to the formation of 2-acylbenzothiazole derivatives **6a**—**e**. Lactones constituted with a variety of ring sizes can also be employed as an acylating reagent of the anion **2** producing the corresponding 2-(hydroxyacyl)benzothiazoles (**7a**—**d**) in excellent yields. These results are summarized in Table 2. In contrast to acylations of 2-lithio-1,3-dithianes in which a large excess of acylating reagents is required in order to avoid the proton abstraction of the primary product by the unreacted lithium reagent or the formation of diadduct, 1.1 equiv of esters or lactones were effectively used in the present reactions with no limitations on the acylations of **2**. Therefore, in the present acylations, the acylating reagents could be added to the anion solution at −78 °C. The reason for the efficient acylations in the present cases should ascribe to the high stability of the initial adducts **11** derived from the chelating effect peculiar to the benzothiazole ring shown in Scheme 2. In fact, in some cases, the adducts **11** separated from the reaction mixture and even an acidic hydrolysis of them was needed for effectively obtaining the acylated product.



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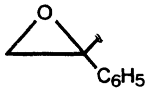
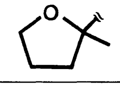
Scheme 2.

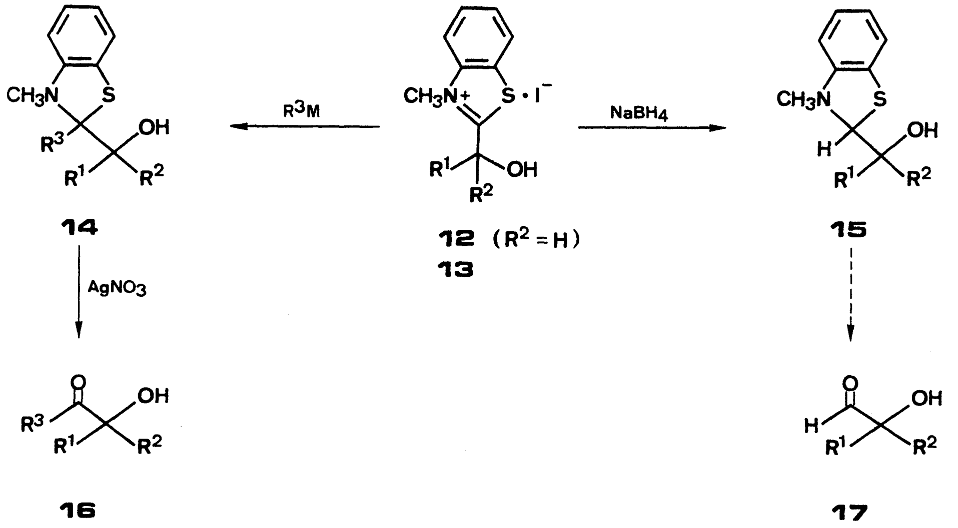
Reaction of 2 with Other Electrophiles. As well as esters and lactones, *N,N*-disubstituted amides and nitriles could also be used as acylating reagents as shown in Table 3. It is noteworthy that the reaction of the anion **2** with enolizable *N,N*-disubstituted amide, *N,N*-dimethylacetamide, proceeded effectively without enolization of the acylating reagent to afford 2-acetylbenzothiazole (**6f**) in excellent yield (Entry 2). This is in contrast to the similar acylation of 2-lithio-1,3-dithianes in which *N,N*-disubstituted amide as an acylating reagent is limited to a nonenolizable compound such as *N,N*-dimethylformamide. Alkylation of a formyl anion equivalent by using alkyl halides is one of useful and frequently encountered reactions. Many carbanions stabilized by adjacent heteroatoms have been known to be well-alkylated with common alkyl halides. However, we have found that alkylation of the anion **2** at −78—−50 °C could not proceed even with primary alkyl iodides or benzyl halides and in these reaction benzothiazole (**1**) was almost always rec-

Table 3. Reaction of 2-Lithiobenzothiazole (**2**) with Various Electrophiles[a]

Entry	Electrophile	Product	E	Yield/%[b]
1	C_6H_5CN	**6a**	C_6H_5CO-	82[c]
2	$(CH_3)_2NCOCH_3$	**6f**	CH_3CO-	77[c]
3	$(CH_3)_3SiCl$	**8**	$(CH_3)_3Si-$	96[d]
4	$C_6H_5COCH_2Br$	**9**		67
5	$C_6H_5COCH_2Cl$	**9**		92
6	$CH_3CO(CH_2)_3Cl$	**10**		90

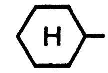
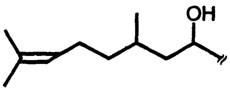
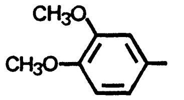
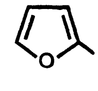
a) In all cases, 2-lithiobenzothiazole (**2**) was reacted with 1.1 equiv of electrophiles in THF at −78 °C to room temperature. b) Yields of pure products after short-column chromatography on silica gel unless otherwise noted. c) Yield of pure product after recrystallization. d) Yield of crude, nearly pure product.

overed after quenching with water. On the other hand, trimethylsilylation of **2** proceeded rapidly at −78 °C with trimethylsilyl chloride (Entry 3). Accordingly, common alkyl halides can not be used successfully in alkylations of the anion **2**. In order to assess the nucleophilic nature of **2**, the reactions with phenacyl bromide, phenacyl chloride, or 5-chloro-2-pentanone were carried out (Entries 4—6). Interestingly, the cyclic ether derivatives **9** and **10** were selectively obtained in excellent yields. These results show that the products are formed by the nucleophilic attack of **2** at the carbonyl carbon followed by intramolecular cyclization. This emphatically suggests that nucleophilicity of **2** towards the halogenated carbon is very low. The reaction of epoxides with **2** was also examined but this did not lead to the formation of the expected 2-(β-hydroxyalkyl)benzothiazole derivatives. In this case, **1** was recovered after quenching with



Scheme 3.

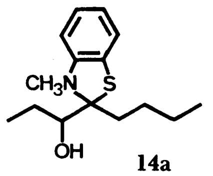
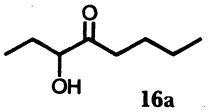
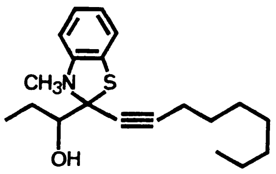
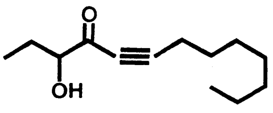
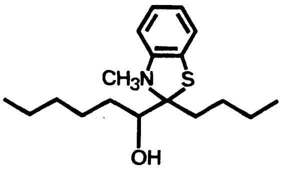
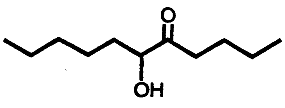
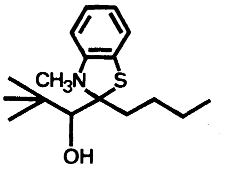
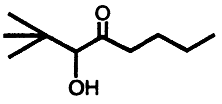
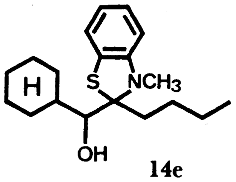
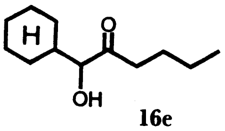
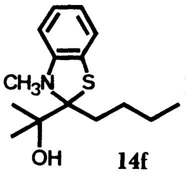
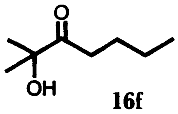
Table 4. Preparation of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Iodides (**12** and **13**)[a]

Entry	2-(α-Hydroxyalkyl)-benzothiazole	Product	R^1	R^2	Reaction time/h	Isolated yield/%
1	**4a**	**12a**	C_2H_5-	H	9.5	90
2	**4c**	**12b**	n-C_5H_{11}-	H	90	92
3	**4d**	**12c**	i-C_3H_7-	H	19.5	99[b,c]
4	**4e**	**12d**	t-C_4H_9-	H	19.5	97
5	**4f**	**12e**		H	48	95
6	**4g**	**12f**		H	90	83
7	**4h**	**12g**	C_6H_5-	H	48	99
8	**4i**	**12h**		H	72	75
9	**5a**	**13a**	n-C_6H_{13}-	CH_3-	99	51[b,c]
10	**5c**	**13b**	CH_3-	CH_3-	24	79
11	**5d**	**13c**	C_6H_5-	C_6H_5-	99	62
12	**5e**	**13d**	C_6H_5-	CH_3-	98	85
13	**5f**	**13e**	n-C_3H_7-	C_6H_5-	96	72[b,c]
14	**5g**	**13f**		CH_3-	98	97
15	**5l**	**13g**	-$(CH_2)_5$-		96	84
16	**5m**	**13h**	-$(CH_2)_{11}$-		98	78

a) All the reactions were carried out with 6 equiv of iodomethane in DMF under refluxing.
b) Reaction was carried out with the corresponding crude oily 2-(α-hydroxyalkyl)benzothiazole.
c) Yield from benzothiazole (**1**).

water. Therefore, the reaction of 2-(lithiomethyl)benzothiazole with carbonyl compounds is much more available rather than this reaction for obtaining 2-(β-hydroxyalkyl)benzothiazole derivatives.[7)] It should be noted that the reaction of the anion **2** with alkyl halides or small-ring ethers at higher temperature (>−50 °C) was generally unavailable and unsatisfactory because the nucleophilicity of **2** towards the alkyl halides or the small-ring ethers did not depend on temperature and the reaction was not exempted from the decomposition of the anion itself as previously shown.

Table 5. Alkylation[a)] of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Salts (**12** and **13**) to 2-Substituted 2-(α-Hydroxyalkyl)-3-methylbenzothiazolines (**14**) and Hydrolysis[b)] to α-Hydroxy Ketones (**16**)

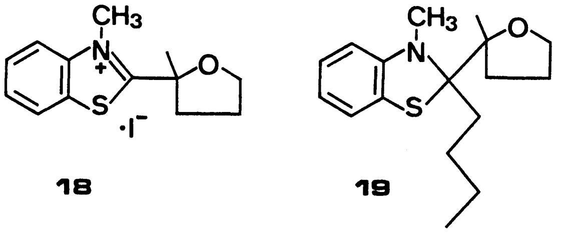
Salt	R^3M	Alkylation product	Yield/%[c)]	Hydrolysis product	Yield/%[d)]
12a	n-C_4H_9Li	 **14a**	Quant.	 **16a**	49
12a	n-C_4H_9MgBr	**14a**	Quant.		
12a	n-$C_7H_{15}C{\equiv}CLi$	 **14b**	98[c)]	 **16b**	64[e)]
12b	n-C_4H_9Li	 **14c**	93	 **16c**	47
12d	n-C_4H_9Li	 **14d**	Quant.	 **16d**	41
12e	n-C_4H_9Li	 **14e**	Quant.	 **16e**	45
13b	n-C_4H_9Li	 **14f**	49	 **16f**	44

a) All the reactions were carried out with 2.2 equiv of organometalic reagents in THF at −78 °C (30 min) to room temperature (1 h). b) All the reactions were carried out with 3 equiv of $AgNO_3$ in aqueous acetonitrile buffered to pH 7 at room temperature to 45°C. c) Yields of isolated nearly pure products unless otherwise noted. d) Isolated yields from the corresponding benzothiazolium salts unless otherwise noted. e) Yield from **14b** after purification by short-colum chromatography on silica gel.

An Application to the Synthesis of α-Hydroxy Carbonyl Compounds. We have further investigated the synthetic utility of the lithium reagent **2** as a formyl anion equivalent in the synthesis of α-hydroxy carbonyl compounds. As outlined in Scheme 3, the methodology comprises the quaternization of 2-(α-hydroxyalkyl)benzothiazoles (**4** and **5**) and the subsequent alkylation or reduction of the resulting salts **12** and **13** with organolithium and Grignard reagents or $NaBH_4$ leading to the corresponding 2,2-disubstituted benzothiazolines (**14**) or 2-substituted benzothiazolines (**15**), followed by their hydrolysis under mildly neutral conditions.

Methylation of **4** and **5** is very important not only for the present methodology but for our different methodology reported previously.[8] Therefore, we have examined this reaction with a variety of selected 2-(α-hydroxyalkyl)benzothiazoles (Table 4). It was found that these quaternizations could be conveniently and efficiently performed by the treatment with 6 equiv of methyl iodide in DMF at reflux temperature affording the desired iodides **12** and **13** in high yields, although the reaction of **5** derived from ketones (Entries 9—16) was generally more sluggish than that of **4** derived from aldehydes (Entries 1—8) and required a longer reaction time.

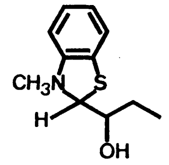
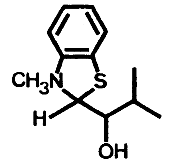
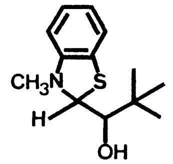
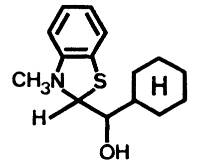
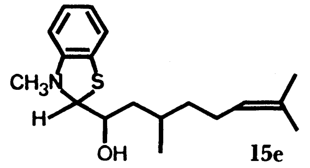
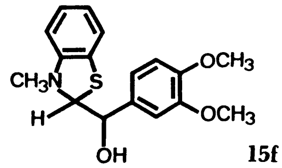
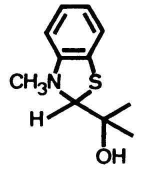
In order to obtain the 2-substituted 2-(α-hydroxyalkyl)benzothiazolines (**14**), we have studied the direct alkylation at the C-2 position of the thiazolium ring of **12** and **13** and discovered that 2 equiv of alkyl or alkynyllithium and Grignard reagents reacted cleanly with the several test α-hydroxy salts **12a**, **b**, **d**, **e**, and **13b** to give, after aqueous workup, the expected products **14a**—**f** in excellent yields (Table 5). Moreover, when the 2-(2-furyl)benzothiazolium iodide (**18**), which resulted from the aforementioned methylation of **10** (90% yield), was used in the reaction with *n*-BuMgBr (1.1 equiv), the benzothiazoline **19** was obtained in nearly quantitative yield (Scheme 4). However, we observed that the reaction of 2-(α-hydroxybenzyl)-3-methylbenzothiazolium iodide (**12g**) with *n*-BuLi or *n*-BuMgBr in THF gave considerable amounts of benzaldehyde together with the expected alkylation prod-



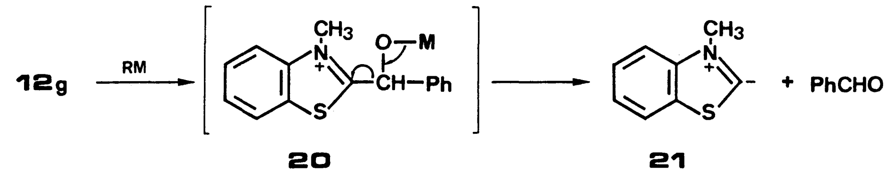
18 **19**

Scheme 4.

Table 6. $NaBH_4$ Reduction of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Salts (**12** and **13**) to 2-(α-Hydroxyalkyl)-3-methylbenzothiazolines (**15**)[a]

Salt	Product		Yield/%[b]
12a		**15a**	88
12c		**15b**	Quant.
12d		**15c**	Quant.
12e		**15d**	Quant.
12f		**15e**	Quant.
12h		**15f**	71
13b		**15g**	82

a) All the reactions were carried out with 5 equiv of $NaBH_4$ in ethanol at 0 °C (30 min) to room temperature (1 h). b) Yields of isolated, nearly pure products.



Scheme 5.

uct. This reaction most likely involves the elimination of the ylide **21** from the alkoxy intermediate **20** (Scheme 5).[9] Hydrolysis of crude 2-(α-hydroxyalkyl)benzothiazolines (**14**) obtained here to the α-hydroxy ketones **16** was examined at the same time (Table 5). This could be effectively accomplished under mildly neutral conditions using $AgNO_3$ in an aqueous acetonitrile-phosphate buffer (0.05 M,[†] pH 7) solvent system,[10] affording the corresponding α-hydroxy ketones **16a—f** in good yields without any evidence of dehydration.

On the other hand, for obtaining the 2-substituted benzothiazolines (**15**), the reduction of the salts **12** and **13** with $NaBH_4$ was found to be very easy. Thus, the several test substances **12a, c, d, e, f, h,** and **13b** were cleanly reduced with no limitations by using 5 equiv of $NaBH_4$ in ethanol at 0 °C to room temperature to give **15a—g** in excellent yields (Table 6). In the present study, we did not examine the direct hydrolysis of **15** to α-hydroxy aldehydes **17**, since the latter compounds were well known to be generally unstable. However, it should be expected that these thiazolines **15** could be useful as a protected form of α-hydroxy aldehydes **17** because of easy convertibility of 2-substituted 3-methylbenzothiazoline function into a formyl group.[10]

Experimental

Melting points were recorded on a Yanagimoto micro melting-point apparatus and are uncorrected. ^1H NMR spectra were measured with a JEOL PMX-60 spectrometer at 60 MHz using tetramethylsilane as an internal reference. IR spectra were recorded on a JASCO A-202 spectrophotometer. GLC analyses were carried out on a Shimadzu Gas Chromatograph GC-6AM equipped with a hydrogen flame ionization detector using glass columns (1.5 m) packed with 2% Silicone OV-7 on Uniport HP (60—80 mesh). Silica gel (Wakogel C-300) was used for short-column chromatography. TLC was carried out on Merck precoated silica gel plates (Merck silica gel 60 F_{254}).

Materials. Tetrahydrofuran (THF) was freshly distilled over $LiAlH_4$ before use. Commercially available benzothiazole was purified by distillation. Butyllithium was obtained commercially as a 1.6 M solution in hexane. 0.05 M Phosphate buffer was prepared by dilution of the 0.1 M solution (pH 7, 0.4 M Na_2HPO_4+0.4 M KH_2PO_4) which was commercially available. The other reagents and solvents were obtained as high-grade commercial products and purified by the usual methods.

General Procedure for the Preparation of 2-Lithiobenzothiazole (2) Solution in THF. A stirred solution (0.5 M) of benzothiazole (**1**) in dry THF under nitrogen was cooled to −78 °C (Dry Ice/methanol bath) and 10% excess of butyllithium in hexane (1.6 M) was added dropwise (ca. 5 ml min^{-1}). Just before the addition had been completed, the anion solution gave rise to a clear and orange-colored solution. At the completion of the butyllithium addition, benzothiazole (**1**) was metalated quantitatively (>98% by ^1H NMR) as determined by deuteration of the solution with D_2O. The reaction vessel was continuously purged with nitrogen until the workup after the reaction with electrophiles.

The stability of the anion solution was determined by quenching the solutions (5 mmol scales) with a large excess of water after warming (ca. 5 °C min^{-1}) to several different temperatures. The aqueous mixtures were extracted with dichloromethane and the organic layers were dried with $MgSO_4$. Recovered yields of benzothiazole (**1**) were determined by GLC using pentylbenzene as an internal standard (Fig. 1).

General Procedure for the Reaction of the Anion 2 with Aldehydes and Ketones. A solution (0.55 M) of carbonyl compound (1.1 equiv to **1**) in dry THF was slowly added to the stirred solution of the anion **2** at −78 °C and the stirring was continued at the same temperature for 1 h. After removing the cold bath, the mixture was stirred for an additional 10 min and then quenched with a large excess of water. The aqueous mixture was extracted with benzene and the organic layer was washed thoroughly with water and then dried with $MgSO_4$. The mixture was evaporated under reduced pressure and the residue was completely dried in vacuo to give crude 2-(α-hydroxyalkyl)benzothiazoles (**4** and **5**). Purification of the products were performed by recrystallization for compounds **4a—c, 4e, 4h, 4j, 5c—e, 5g—j, 5l,** and **5m** or short-column chromatography for compounds **4d, 4g, 4i, 5a, 5b,** and **5k**. The results are summarized in Table 1. The ^1H NMR and physical data of the products are as follows (compounds **4f** and **5f** were characterized after conversion into the corresponding 3-methylbenzothiazolium iodides **12e** and **13e**).

4a: Colorless needles (acetone); mp 102—102.5 °C; ^1H NMR ($CDCl_3$) δ=1.00 (t, 3H, CH_3, J=7 Hz), 1.93 (m, 2H, CH_2), 4.50 (brs, 1H, OH), 4.90 (t, 1H, CH, J=6 Hz), 7.17 (m, 2H, Arom), and 7.68 (m, 2H, Arom). Found: C, 62.02; H, 5.80; N, 7.21%. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25%.

4b: Colorless needles (acetone/hexane); mp 89—90 °C; ^1H NMR ($CDCl_3$) δ=0.92 (t, 3H, CH_3, J=7 Hz), 1.17—2.13 (m, 4H, $2CH_2$), 3.93 (d, 1H, OH, J=5 Hz), 4.95 (q, 1H, CH), 7.17 (m, 2H, Arom), and 7.67 (m, 2H, Arom). Found: C, 63.81; H, 6.30; N, 6.56%. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76%.

4c: Colorless needles (acetone/hexane); mp 62.5—63 °C; ^1H NMR ($CDCl_3$) δ=0.67—2.17 (brm, 11H, n-C_5H_{11}), 3.27 (d, 1H, OH, J=5 Hz), 4.97 (q, 1H, CH), 7.27 (m, 2H, Arom), and 7.77 (m, 2H, Arom). Found: C, 66.37; H, 7.27; N, 5.86%. Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95%.

4d: Colorless oil; ^1H NMR ($CDCl_3$) δ=0.97 (d, 6H, $2CH_3$, J=7 Hz), 2.15 (m, 1H, CH), 4.77 (d, 1H, C$\underline{H}$OH, J=5 Hz), 5.05 (brs, 1H, OH), 7.25 (m, 2H, Arom), and 7.80 (m, 2H, Arom). Found: C, 63.69; H, 6.21; N, 6.75%. Calcd for $C_{11}H_{13}NOS$: C, 63.73; H, 6.32; N, 6.76%.

4e: Colorless needles (acetone); mp 110—111 °C; ^1H NMR ($CDCl_3$) δ=1.00 (s, 9H, $3CH_3$), 4.35 (brs, 1H, OH), 4.60 (brs, 1H, CH), 7.26 (m, 2H, Arom), and 7.75 (m, 2H, Arom). Found: C, 65.05; H, 6.87; N, 6.34%. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33%.

4g: Colorless oil; ^1H NMR ($CDCl_3$) δ=0.67—2.17 (brm, 16H), 3.73 (d, 1H, OH, J=5 Hz), 4.67, (brm, 1H, C$\underline{H}$OH), 5.00 (brm, 1H, HC=C), 7.23 (m, 2H, Arom), and 7.73 (m, 2H, Arom). Found: C, 70.52; H, 7.98; N, 4.65%. Calcd for $C_{17}H_{23}NOS$: C, 70.55; H, 8.01; N, 4.84%.

[†] 1M=1 mol dm^{-3}.

4h: Colorless needles (acetone/hexane); mp 124.5—125 °C; ^{1}H NMR (CDCl$_3$) δ=4.56 (brs, 1H, OH), 5.96 (s, 1H, CH), 7.19 (m, 7H, C_6H_5 and Arom), and 7.64 (m, 2H, Arom). Found: C, 69.73; H, 4.71; N, 5.69%. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.60; N, 5.80%.

4i: Colorless needles; mp 78—79 °C; ^{1}H NMR (CDCl$_3$) δ=3.73 (s, 6H, 2CH$_3$O), 4.67 (brs, 1H, OH), 5.93 (brs, 1H, CH), 6.70 (s, 1H, Arom), 6.87 (m, 2H, Arom), 7.20 (m, 2H, Arom), and 7.67 (m, 2H, Arom). Found: C, 63.55; H, 4.96; N, 4.51%. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65%.

4j: Colorless needles (acetone/hexane); mp 155—155.5 °C; ^{1}H NMR (CDCl$_3$) δ=4.07 (br, 1H, OH), 6.02 (br, 1H, CH), 6.50 (q, 1H, Furan-H), 7.35 (m, 2H, Arom), 7.62 (d, 1H, Furan-H, *J*=2 Hz), 7.68 (m, 2H, Arom), and 8.13 (d, 1H, Furan-H, *J*=4 Hz). Found: C, 62.55; H, 3.76; N, 5.96%. Calcd for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.06%.

5a: Colorless oil; ^{1}H NMR (CDCl$_3$) δ=0.60—2.17 (m, 16H, *n*-C$_6$H$_{13}$ and CH$_3$), 3.90 (brs, 1H, OH), 7.20 (m, 2H, Arom), and 7.76 (m, 2H, Arom). Found: C, 68.59; H, 8.31; N, 5.39%. Calcd for $C_{15}H_{21}NOS$: C, 68.40; H, 8.04; N, 5.32%.

5b: Colorless oil; ^{1}H NMR (CDCl$_3$) δ=0.60—2.17 (m, 18H, 2*n*-C$_4$H$_9$), 3.50 (s, 1H, OH), 7.21 (m, 2H, Arom), and 7.75 (m, 2H, Arom). Found: C, 68.51; H, 8.26; N, 4.52%. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05%.

5c: Colorless needles (hexane/acetone); mp 93—93.5 °C; ^{1}H NMR (CDCl$_3$) δ=1.70 (s, 6H, 2CH$_3$), 3.60 (s, 1H, OH), 7.20 (m, 2H, Arom), and 7.72 (m, 2H, Arom). Found: C, 62.28; H, 5.73; N, 7.32%. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25%.

5d: Colorless needles (acetone/hexane); mp 149.5—150 °C; ^{1}H NMR (CDCl$_3$) δ=4.47 (s, 1H, OH), 7.17 (m, 12H, 2C$_6$H$_5$ and Arom), and 7.70 (m, 2H, Arom). Found: C, 75.63; H, 4.72; N, 4.46%. Calcd for $C_{20}H_{15}NOS$: C, 75.68; H, 4.76; N, 4.41%.

5e: Colorless needles (benzene/hexane); mp 80.5—81 °C; ^{1}H NMR (CDCl$_3$) δ=2.04 (s, 3H, CH$_3$), 4.07 (s, 1H, OH), and 6.93—7.90 (m, 9H, C$_6$H$_5$ and Arom). Found: C, 70.37; H, 5.21; N, 5.45%. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49%.

5g: Colorless needles (acetone/hexane); mp 115.5—116 °C; ^{1}H NMR (CDCl$_3$) δ=2.03 (s, 3H, CH$_3$), 4.23 (s, 1H, OH), 6.23 (m, 2H, Furan-H), 7.23 (m, 3H, Furan-H and Arom), and 7.77 (m, 2H, Arom). Found: C, 63.69; H, 4.48; N, 5.85%. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71%.

5h: Colorless needles (acetone/hexane); mp 169.5—170 °C; ^{1}H NMR (CDCl$_3$) δ=3.93 (s, 1H, OH), 6.78 (m, 2H, CH=CH), 7.20 (m, 12H, 2C$_6$H$_5$ and Arom), and 7.77 (m, 2H, Arom). Found: C, 76.76; H, 4.95; N, 3.99%. Calcd for $C_{22}H_{17}NOS$: C, 76.94; H, 4.99; N, 4.08%.

5i: Colorless needles (acetone/pentane); mp 134.5—135 °C; ^{1}H NMR (CDCl$_3$) δ=2.07 (s, 3H, CH$_3$), 4.20 (brs, 1H, OH), 7.17 (m, 7H, C$_6$H$_5$ and Arom), and 7.79 (m, 2H, Arom). Found: C, 73.01; H, 4.77; N, 4.71%. Calcd for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01%.

5j: Colorless needles (acetone); mp 144—144.5 °C; ^{1}H NMR (CDCl$_3$) δ=1.57—1.87 (m, 9H, 3CH$_3$), 3.38 (s, 1H, OH), 5.62 (m, 1H, HC=C), 7.20 (m, 2H, Arom), and 7.73 (m, 2H, Arom). Found: C, 66.87; H, 6.57; N, 5.82%. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00%.

5k: Colorless needles; mp 105—106 °C; ^{1}H NMR (CDCl$_3$) δ=0.97 (s, 3H, CH$_3$), 1.13 (s, 3H, CH$_3$), 1.73 (s, 3H, CH$_3$), 1.88 (brd, 2H, CH$_2$, *J*=4 Hz), 2.00 (s, 1H, $\mathrm{C\underline{H}H}$), 2.01 (s, 1H, $\mathrm{CH\underline{H}}$), 3.47 (brs, 1H, OH), 5.52 (m, 1H, $\mathrm{\underline{H}}$-C=C-), 7.17 (m, 2H, Arom), and 7.72 (m, 2H, Arom). Found: C, 70.03; H, 7.12; N, 4.93%. Calcd for $C_{16}H_{19}NOS$: C, 70.29; H, 7.00; N, 5.12%.

5l: Colorless needles (acetone/hexane); mp 106.5—107 °C; ^{1}H NMR (CDCl$_3$) δ=1.10—2.43 (m, 10H, 5CH$_2$), 3.27 (s, 1H, OH), 7.19 (m, 2H, Arom), and 7.73 (m, 2H, Arom). Found: C, 66.83; H, 6.56; N, 5.84%. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00%.

5m: Colorless needles (acetone/hexane); mp 148—148.5 °C; ^{1}H NMR (CDCl$_3$) δ=1.40 (br, 18H, 9CH$_2$), 2.00 (br, 4H, 2CH$_2$), 2.97 (s, 1H, OH), 7.23 (m, 2H, Arom), and 7.77 (m, 2H, Arom). Found: C, 71.73; H, 8.65; N, 4.23%. Calcd for $C_{19}H_{27}NOS$: C, 71.88; H, 8.57; N, 4.41%.

General Procedure for the Reaction of the Anion 2 with Esters and Lactones. A solution (0.55 M) of ester or lactone (1.1 equiv to **1**) in dry THF was slowly added to the stirred solution of the anion **2** in THF at −78 °C and the mixture was stirred for 1 h. After removal of the cold bath, the mixture was continuously stirred for 30 min and then quenched with a large excess of water (in experiments with lactones, 0.1 M hydrochloric acid was used in place of water for the quenching). The aqueous mixture was extracted with benzene and the extract was washed thoroughly with water. The organic layer was dried with MgSO$_4$ and concentrated under reduced pressure to give crude 2-acylbenzothiazoles (**6** and **7**). Purification of the products was performed by recrystallization for compounds **6a—c** and **7a—d** or short-column chromatography for compounds **6d** and **6e**. The results are summarized in Table 2. The ^{1}H NMR and physical data of the products are as follows.

6a: Pale yellow needles (ethanol); mp 103.5—104.5 °C (lit,[5] mp 102.5 °C); ^{1}H NMR (CDCl$_3$) δ=7.30 (m, 5H, C$_6$H$_5$), 7.63 (m, 2H, Arom), and 8.10 (m, 2H, Arom).

6b: Colorless needles (ethanol); mp 76—77 °C; ^{1}H NMR (CDCl$_3$) δ=1.27 (t, 3H, CH$_3$, *J*=7 Hz), 3.25 (q, 2H, CH$_2$), 7.33 (m, 2H, Arom), and 7.85 (m, 2H, Arom). Found: C, 62.73; H, 4.65; N, 7.39%. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32%.

6c: Colorless needles (ethanol); mp 61—62 °C; ^{1}H NMR (CDCl$_3$) δ=1.00 (t, 3H, CH$_3$, *J*=7 Hz), 1.12—1.73 (m, 6H, 3CH$_2$), 3.20 (t, 2H, CH$_2$CO, *J*=6 Hz), 7.30 (m, 2H, Arom), and 7.82 (m, 2H, Arom). Found: C, 66.93; H, 6.45; N, 5.90%. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00%.

6d: Colorless oil; ^{1}H NMR (CDCl$_3$) δ=1.30 (d, 6H, 2CH$_3$, *J*=7 Hz), 3.92 (m, 1H, CH), 7.30 (m, 2H, Arom), and 7.83 (m, 2H, Arom). Found: C, 64.37; H, 5.38; N, 6.70%. Calcd for $C_{11}H_{11}NOS$: C, 64.36; H, 5.40; N, 6.82%.

6e: Colorless needles; mp 54.5—55.5 °C; ^{1}H NMR (CDCl$_3$) δ=1.53 (s, 9H, 3CH$_3$), 7.33 (m, 2H, Arom), and 7.87 (m, 2H, Arom). Found: C, 65.75; H, 5.94; N, 6.29%. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.97; N, 6.39%.

7a: Colorless needles (hexane/acetone); mp 93—93.5 °C; ^{1}H NMR (CDCl$_3$) δ=2.02 (m, 2H, CH$_2$), 3.30 (t, 2H, CH$_2$CO, *J*=7 Hz), 3.67 (t, 2H, $\mathrm{C\underline{H}_2OH}$, *J*=6 Hz), 3.67 (br, 1H, OH), 7.33 (m, 2H, Arom), and 7.85 (m, 2H, Arom). Found: C, 59.82; H, 5.06; 6.15%. Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33%.

7b: Colorless needles (acetone/hexane); mp 81—82 °C; ^{1}H NMR (CDCl$_3$) δ=1.23 (d, 3H, CH$_3$, *J*=6 Hz), 1.97 (q, 2H, CH$_2$), 3.32 (t, 2H, CH$_2$CO, *J*=7 Hz), 3.83 (m, 1H, CH), 4.35 (d, 1H, OH, *J*=8 Hz), 7.27 (m, 2H, Arom), and 7.83 (m, 2H, Arom). Found: C, 61.26; H, 5.50; N, 5.84%. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95%.

7c: Colorless needles (acetone/hexane); mp 89.5—90.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.33—2.50 (m, 4H, $2CH_2$), 3.22 (t, 2H, CH_2CO, J=7 Hz), 3.62 (t, 2H, $C\underline{H}_2OH$, J=6 Hz), 3.62 (br, 1H, OH), 7.27 (m, 2H, Arom), and 7.87 (m, 2H, Arom). Found: C, 61.24; H, 5.51; N, 5.89%. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95%.

7d: Colorless needles (acetone/hexane); mp 81.5—82.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.17—2.17 (m, 6H, $3CH_2$), 3.20 (t, 2H, CH_2CO, J=7 Hz), 3.50 (br, 1H, OH), 3.57 (t, 2H, $C\underline{H}_2OH$, J=6 Hz), 7.33 (m, 2H, Arom), and 7.85 (m, 2H, Arom). Found: C, 62.64; H, 6.18; N, 5.54%. Calcd for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62%.

Reaction of the Anion 2 with Benzonitrile. A solution of benzonitrile (2.84 g, 27.5 mmol) in dry THF (5 ml) was added to the stirred solution of the anion **2** (prepared from 25 mmol of **1**) at −78 °C and the mixture was continuously stirred for 1 h. After removing the cold bath, the mixture was stirred for an additional 10 min and then hydrolyzed with concd hydrochloric acid (5 ml). The acidic solution was continuously stirred until the temperature reached room temperature. The mixture was poured into same amount of water and the aqueous mixture was extracted with benzene. The benzene extract was washed thoroughly with water and the organic layer was dried with $MgSO_4$. The crystals obtained by evaporation of the organic layer under reduced pressure were triturated in pentane and filtered to give the crude 2-benzoylbenzothiazole (**6a**). Recrystallization from ethanol afforded pure **6a** as pale yellow needles (5.33 g, 82%); mp 103.5—104.5 °C (lit,[5]) mp 102.5 °C).

Reaction of the Anion 2 with *N,N*-Dimethylacetamide. A solution of *N,N*-dimethylacetamide (2.40 g, 27.5 mmol) in dry THF (50 ml) was added to the stirred solution of the anion **2** (prepared from 25 mmol of **1**) at −78 °C and the mixture was continuously stirred for 1 h. The mixture was allowed to warm to room temperature and continuously stirred for an additional 30 min. The mixture was quenched with a large excess of water and extracted with benzene. The organic layer was washed thoroughly with water and dried with $MgSO_4$ and then evaporated under reduced pressure to give the crude crystalline 2-acetylbenzothiazole (**6f**). Recrystallization from acetone afforded pure **6f** as colorless needles (3.22 g, 73%); mp 108.5—109.5 °C; ^{1}H NMR ($CDCl_3$) δ=2.72 (s, 3H, CH_3), 7.30 (m, 2H, Arom), and 7.83 (m, 2H, Arom). Found: C, 60.83; H, 3.80; N, 7.78%. Calcd for C_9H_7NOS: C, 60.99; H, 3.98; N, 7.90%.

Reaction of the Anion 2 with Trimethylsilyl Chloride. Trimethylsilyl chloride (3.26 g, 30 mmol) was added to the stirred solution of the anion **2** (prepared from 25 mmol of **1**) at −78 °C and the mixture was continuously stirred for 1 h. The mixture was allowed to warm to room temperature and continuously stirred for 1 h. The mixture was concentrated under reduced pressure and the residue was extracted with hexane. The hexane extract was washed thoroughly with water and the organic layer was dried with $MgSO_4$. After evaporation of the solvent under reduced pressure gave the nearly pure (monitored by GLC) 2-trimethylsilylbenzothiazole (**8**) as a pale yellow oil (4.98 g, 96%). Purification by distillation afforded pure **8** as a colorless oil; bp 121—122 °C/ 5 mmHg[††] (lit,[11]) bp 139 °C/15 mmHg).

Reaction of the Anion 2 with Phenacyl Halides. A solution of phenacyl bromide or chloride (27.5 mmol) in dry THF (5 ml) was added to the stirred solution of the anion **2** (prepared from 25 mmol of **1**) at −78 °C and the mixture was then stirred for 1 h. The mixture was allowed to warm to room temperature and continuously stirred for 1 h. The mixture was concentrated under reduced pressure and the residue was diluted with benzene and then washed thoroughly with water. The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure to give the crude oily 2-(2-phenyl-2-oxiranyl)benzothiazole (**9**). Purification by short-column chromatography afforded pure **9** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ=3.15 (d, 1H, $C\underline{H}H$, J=6 Hz), 3.43 (d, 1H, $CH\underline{H}$, J=6 Hz), 7.17 (m, 7H, C_6H_5 and Arom), and 7.50 (m, 2H, Arom). Found: C, 70.83; H, 4.69; N, 5.48%. Calcd for $C_{15}H_{12}NOS$: C, 70.84; H, 4.76; N, 5.51%.

Reaction of the Anion 2 with 5-Chloro-2-pentanone. A solution of 5-chloro-2-pentanone (3.32 g, 27.5 mmol) in dry THF (5 ml) was added to the stirred solution of the anion **2** (prepared from 25 mmol of **1**) at −78 °C and the mixture was stirred for an additional 50 min at the same temperature. The mixture was allowed to warm to room temperature and continuously stirred for 2 h. The mixture was concentrated under reduced pressure and the residue was extracted with benzene. The benzene extract was washed thoroughly with water and the organic layer was dried with $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude oily 2-(2-methyltetrahydro-2-furanyl)benzothiazole (**10**). Purification by distillation afforded pure **10** as a colorless oil (4.94 g, 90%); bp 138.2 °C/2.5 mmHg; ^{1}H NMR ($CDCl_3$) δ=1.32 (s, 3H, CH_3), 1.84 (m, 4H, $2CH_2$), 3.83 (t, 2H, CH_2O), 7.16 (m, 2H, Arom), and 7.72 (m, 2H, Arom). Found: C, 65.72; H, 5.97; N, 6.39%. Calcd for $C_{12}H_{13}NOS$: C, 65.76; H, 6.18; N, 6.41%.

General Procedure for the Preparation of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Iodides (12 and 13). The solution of 2-(α-hydroxyalkyl)benzothiazole (**4** or **5**) (48 mmol) in dimethylformamide (18 ml) and methyl iodide (18 ml) was refluxed with stirring for the appropriate times (see Table 4). After cooling to room temperature, the mixture was diluted with diethyl ether (50 ml) and cooled in an ice bath to completely precipitate the salt. The separated needles were collected by filtration, washed thoroughly with diethyl ether, and then dried in vacuo to afford the crude 2-(α-hydroxyalkyl)-3-methylbenzothiazolium salt (**12** or **13**). Recrystallization was performed from methanol to afford pure **12** and **13**. The results are summarized in Table 4. ^{1}H NMR and physical data of the products are as follows.

12a: Colorless needles (methanol); mp 206—209 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.03 (t, 3H, CH_3, J=7 Hz), 1.85 (m, 2H, CH_2), 4.27 (s, 3H, CH_3N), 5.42 (q, 1H, CH), 7.31 (br, 1H, OH), 7.67 (m, 2H, Arom), and 8.23 (m, 2H, Arom). Found: C, 39.47; H, 4.21; N, 4.06%. Calcd for $C_{11}H_{14}NOSI$: C, 39.42; H, 4.21; N, 4.18%.

12b: Colorless needles (methanol/acetone); mp 126.5—127 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=0.67—2.00 (br, 11H, n-C_5H_{11}), 4.22 (s, 3H, CH_3N), 5.42 (br, 1H, CH), 7.34 (br, 1H, OH), 7.72 (m, 2H, Arom), and 8.23 (m, 2H, Arom). Found: C, 44.33; H, 5.31; N, 3.62%. Calcd for $C_{14}H_{20}NOSI$: C, 44.57; H, 5.34; N, 3.71%.

12c: Colorless needles (methanol/acetone); mp 188.5—189 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.12 (d, 3H, CH_3, J=7 Hz), 1.42 (d, 3H, CH_3, J=7 Hz), 2.53 (m, 1H, CH), 4.58 (s, 3H, CH_3N), 5.67 (br, 1H, $C\underline{H}OH$), 7.27 (br, 1H, OH), 8.02 (m, 2H, Arom), and 8.57 (m, 2H, Arom). Found: C, 41.33; H,

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[††] 1 mmHg≈133.322 Pa.

4.62; N, 3.84%. Calcd for $C_{12}H_{16}NOSI$: C, 41.27; H, 4.62; N, 4.01%.

12d: Colorless needles (methanol); mp 212—212.5 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.33 (s, 9H, 3CH_3), 4.67 (s, 3H, CH_3N), 5.63 (d, 1H, CH, J=4 Hz), 7.17 (d, 1H, OH, J=4 Hz), 8.03 (m, 2H, Arom), and 8.53 (m, 2H, Arom). Found: C, 43.02; H, 4.96; N, 3.65%. Calcd for $C_{13}H_{18}NOSI$: C, 42.98; H, 4.99; N, 3.86%.

12e: Colorless needles (methanol/acetone); mp 196.5—197 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.17—2.50 (br, 11H, cyclohexyl), 4.53 (s, 3H, CH_3N), 5.60 (br, 1H, CH), 7.28 (br, 1H, OH), 8.00 (m, 2H, Arom), and 8.17 (m, 2H, Arom). Found: C, 46.04; H, 5.47; N, 3.53%. Calcd for $C_{15}H_{20}NOSI$: C, 46.28; H, 5.18; N, 3.60%.

12f: Colorless needles (methanol/acetone); mp 161.5—162 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.17—2.67 (m, 16H), 4.63 (s, 3H, CH_3N), 5.33 (m, 1H, HC=C), 5.67 (br, 1H, C$\underline{H}$OH), 7.33 (br, 1H, OH), 8.00 (m, 2H, Arom), and 8.52 (m, 2H, Arom). Found: C, 49.63; H, 6.19; N, 3.11%. Calcd for $C_{18}H_{26}NOSI$: C, 50.12; H, 6.07; N, 3.25%.

12g: Colorless needles (acetone/methanol); mp 122—123 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=4.10 (s, 3H, CH_3N), 6.65 (s, 1H, CH), 7.38 (m, 6H, OH and C_6H_5), 7.70 (m, 2H, Arom), and 8.30 (m, 2H, Arom). Found: C, 47.08; H, 3.62; N, 3.61%. Calcd for $C_{15}H_{14}NOSI$: C, 47.01; H, 3.68; N, 3.66%.

12h: Colorless needles (methanol/acetone); mp 184.5—185.5 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=4.03 (s, 6H, 2CH_3O), 4.40 (s, 3H, CH_3N), 6.80 (s, 1H, CH), 7.27 (s, 2H, OH and Arom), 7.40 (m, 2H, Arom), 8.03 (m, 2H, Arom), and 8.53 (m, 2H, Arom). Found: C, 45.82; H, 3.99; N, 3.07%. Calcd for $C_{17}H_{18}NO_3SI$: C, 46.06; H, 4.09; N, 3.16%.

13a: Colorless needles (methanol/ether); mp 161.5—162 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=0.60—1.67 (brm, 13H, n-C_6H_{13}), 1.82 (s, 3H, CH_3), 3.28 (br, 1H, OH), 4.35 (s, 3H, CH_3N), 7.73 (m, 2H, Arom), and 8.28 (m, 2H, Arom). Found: C, 47.40; H, 5.99; N, 3.58%. Calcd for $C_{16}H_{24}NOSI$: C, 47.41; H, 5.97; N, 3.46%.

13b: Colorless needles (methanol/acetone); mp 178.5—179 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=2.08 (s, 6H, 2CH_3), 4.60 (s, 3H, CH_3N), 7.33 (s, 1H, OH), 7.97 (m, 2H, Arom), and 8.50 (m, 2H, Arom). Found: C, 39.56; H, 4.17; N, 4.00%. Calcd for $C_{11}H_{14}NOSI$: C, 39.42; H, 4.21; N, 4.18%.

13c: Colorless needles (methanol/acetone); mp 203—204 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=3.53 (br, 1H, OH), 4.05 (s, 3H, CH_3N), 7.32 (s, 10H, 2C_6H_5), 7.73 (m, 2H, Arom), and 8.17 (m, 2H, Arom). Found: C, 54.89; H, 3.96; N, 3.17%. Calcd for $C_{21}H_{18}NOSI$: C, 54.91; H, 3.95; N, 3.05%.

13d: Colorless needles (methanol/acetone); mp 169.5—170 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=2.02 (s, 3H, CH_3), 3.27 (br, 1H, OH), 3.93 (s, 3H, CH_3N), 7.40 (s, 5H, C_6H_5), 7.75 (m, 2H, Arom), and 8.30 (m, 2H, Arom). Found: C, 48.31; H, 3.99; N, 3.60%. Calcd for $C_{16}H_{16}NOSI$: C, 48.37; H, 4.06; N, 3.53%.

13e: Colorless needles (methanol/ether); mp 170.5—171 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=0.67—1.67 (brm, 7H, n-C_3H_7), 3.67 (br, 1H, OH), 3.90 (s, 3H, CH_3N), 7.33 (s, 5H, C_6H_5), 7.73 (m, 2H, Arom), and 8.22 (m, 2H, Arom). Found: C, 50.86; H, 4.70; N, 3.38%. Calcd for $C_{18}H_{20}NOSI$: C, 50.83; H, 4.74; N, 3.29%.

13f: Colorless needles (methanol/acetone); mp 139—140 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=2.10 (s, 3H, CH_3), 3.57 (brs, 1H, OH), 3.92 (s, 3H, CH_3N), 6.47 (q, 1H, Furan-H), 6.77 (d, 1H, Furan-H, J=3 Hz), 7.50—8.00 (m, 3H, Furan-H and Arom), and 8.23 (m, 2H, Arom). Found: C, 43.44; H, 3.65; N, 3.67%. Calcd for $C_{14}H_{14}NO_2SI$: C, 43.42; H, 3.64; N, 3.62%.

13g: Colorless needles (methanol/acetone); mp 179.5—180 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=2.07 (s, 10H, 5CH_2), 3.27 (br, 1H, OH), 4.43 (s, 3H, CH_3N), 7.77 (m, 2H, Arom), and 8.28 (m, 2H, Arom). Found: C, 44.82; H, 4.81; N, 3.69%. Calcd for $C_{14}H_{18}NOSI$: C, 44.81; H, 4.83; N, 3.73%.

13h: Colorless needles (methanol); mp 221—221.5 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.33 (brs, 18H, 9CH_2), 2.03 (br, 4H, 2CH_2), 3.57 (br, 1H, OH), 4.67 (s, 3H, CH_3N), 7.80 (m, 2H, Arom), and 8.27 (m, 2H, Arom). Found: C, 51.96; H, 6.51; N, 2.83%. Calcd for $C_{20}H_{30}NOSI$: C, 52.29; H, 6.58; N, 3.05%.

18: Colorless needles (methanol/acetone); mp 195—195.5 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=1.50 (s, 3H, CH_3), 2.00 (m, 4H, 2CH_2), 3.99 (m, 2H, CH_2O), 4.25 (s, 3H, CH_3N), 7.69 (m, 2H, Arom), and 8.20 (m, 2H, Arom). Found: C, 43.33; H, 4.45; N, 3.94%. Calcd for $C_{13}H_{16}NOSI$: C, 43.22; H, 4.46; N, 3.88%.

General Procedure for the Alkylation of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Iodides (12 and 13). A solution (1.6 M) of butyllithium (4.4 mmol) in hexane or a solution (0.8 M) of Grignard reagents (4.4 mmol; prepared from the corresponding bromide or chloride in THF) was added dropwise to a stirred and cooled suspension of 2-(α-hydroxyalkyl)benzothiazolium salt (**12** or **13**) (2 mmol) at −78 °C in the same solvent (10 ml). The mixture was stirred for 30 min at −78 °C and then allowed to warm to room temperature. After being stirred for 1 h, the mixture was quenched with large excess of water. After separation of the organic layer, the aqueous layer was extracted with dichloromethane. The combined organic layer was dried with $MgSO_4$ and filtered through silica gel (Wakogel C-300). Concentration of the solvent under reduced pressure afforded the nearly pure (monitored by TLC) 2-substituted 2-(α-hydroxyalkyl)-3-methylbenzothiazoline (**14**) as a viscous oil. A THF solution of 1-nonynyllithium (prepared by lithiation of 1,1-dibromo-1-nonene with butyllithium) was similarly used, giving the corresponding 2-(α-hydroxyalkyl)benzothiazolines (**14b**) which was isolated by short-column chromatography. These results are summarized in Table 5.

These compounds were used in the next hydrolysis step without further purification and identified at the same time by means of this hydrolysis transformation to the corresponding α-hydroxy ketones.

General Procedure for the Reduction of 2-(α-Hydroxyalkyl)-3-methylbenzothiazolium Iodides (12 and 13) with $NaBH_4$. The benzothiazolium salt **12** or **13** (2.0 mmol), dissolved in ethanol (8 ml), was treated with sodium borohydride (0.38 g, 10 mmol) at 0 °C. After stirring for 30 min at 0 °C and then 1 h at room temperature, the reaction mixture was diluted with water (30 ml) and the aqueous mixture was extracted with dichloromethane. The dichloromethane extract was dried with $MgSO_4$ and filtered through silica gel (Wakogel C-300). Concentration of the filtrate under reduced pressure afforded the nearly pure (monitored by TLC) 2-(α-hydroxyalkyl)-3-methylbenzothiazolines (**15**). The results are summarized in Table 6. ^{1}H NMR data of the products are as follows: **15a**: Viscous oil; ^{1}H NMR ($CDCl_3$) δ=1.05 (t, 3H, CH_3), 1.57 (m, 2H, CH_2), 2.62 (br, 1H, OH), 3.00 (s, 3H, CH_3N), 3.57 (m, 1H, C$\underline{H}$OH), 4.81 (d, 1H, NCHS), and 6.91 (m, 4H, Arom). **15b**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=0.87 (d, 3H, CH$_3$), 0.98 (d, 3H, CH$_3$), 1.93 (m, 1H, CH), 2.70 (s, 1H, OH), 2.87 (s, 3H, CH$_3$N), 3.30 (dd, 1H, C$\underline{H}$OH), 4.60 (d, 1H, NCHS), and 6.67 (m, 4H, Arom). **15c**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=0.97 (s, 9H, 3CH$_3$), 2.80 (s, 3H, CH$_3$N), 3.28 (dd, 1H, C$\underline{H}$OH), 3.33 (s, 1H, OH), 4.54 (d, 1H, NCHS), and 6.73 (m, 4H, Arom). **15d**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=0.71—2.38 (br, 11H, cyclohexyl), 2.86 (s, 3H, CH$_3$N), 3.00 (br, 1H, OH), 3.33 (dd, 1H, C$\underline{H}$OH), 4.71 (d, 1H, NCHS), and 6.79 (m, 4H, Arom). **15e**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=0.71—2.29 (m, 16H), 2.90 (s, 3H, CH$_3$N), 3.00 (br, 1H, OH), 3.81 (m, 1H, C$\underline{H}$OH), 4.67 (d, 1H, NCHS), 5.00 (m, 1H, CH=C), and 6.72 (m, 4H, Arom). **15f**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=2.57 and 2.83 (s, 3H, CH$_3$N), 3.29 (br, 1H, OH), 3.76 (s, 6H, 2CH$_3$O), 4.43 and 4.69 (d, 1H, C$\underline{H}$OH), 4.86 and 5.04 (d, 1H, NCHS), and 6.10—7.00 (m, 7H, Arom). **15g**: Viscous oil; ^{1}H NMR (CDCl$_3$) δ=0.95 (s, 6H, 2CH$_3$), 2.90 (s, 3H, CH$_3$N), 3.33 (dd, 1H, OH), 4.67 (d, 1H, NCHS), and 6.79 (m, 4H, Arom).

General Procedure for the Hydrolysis of 2-Substituted 2-(α-Hydroxyalkyl)-3-methylbenzothiazolines (14) to α-Hydroxy Ketones (16) with AgNO$_3$. Silver nitrate (0.51 g, 3.0 mmol), dissolved in water (5 ml), was added to the stirred solution of 2-substituted 2-(α-hydroxyalkyl)benzothiazoline (**14**) (prepared from 2.0 mmol of **12** or **13**) in acetonitrile (30 ml) and 0.05 M-pH 7-phosphate buffer (6.0 ml). After 15 min at room temperature, additional silver nitrate (0.51 g, 3.0 mmol), dissolved in water (5 ml), was added to the solution (in some cases, a yellow precipitate began to form during this second addition). After another 20 min at room temperature, triethylamine (0.20 g, 2.0 mmol) was added in order to neutralized the released acid (HNO$_3$) and stirring was continued for further 1 h at 45 °C. Saturated aqueous NaCl solution was added to the reaction mixture and the mixture was filtered through Celite. The filtrate was extracted with diethyl ether and ether extract was filtered through silica gel (Wakogel C-300). Evaporation of the solvent under reduced pressure gave the almost pure α-hydroxy ketones (**16**) that was free of 2-(methylamino)benzenethiol. The results are summarized in Table 5. Spectral data of the products are as follows: **16a**: Viscous oil; IR (neat) 3450 (OH) and 1700 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=1.00 (t, 6H, 2CH$_3$), 1.13—2.10 (m, 6H, 3CH$_2$), 2.40 (t, 2H, CH$_2$C=O), 3.50 (d, 1H, OH), and 4.12 (q, 1H, C$\underline{H}$OH). **16b**: Viscous oil; IR (neat) 3450 (OH), 1695 (C=O), and 1590 cm^{-1} (C$\equiv$C); ^{1}H NMR (CDCl$_3$) δ=1.00 (t, 6H, 2CH$_3$), 1.12—2.12 (m, 12H, 6CH$_2$), 2.48 (t, 2H, CH$_2$C$\equiv$C), 4.33 (t, 1H, C$\underline{H}$OH), and 5.33 (s, 1H, OH). **16c**: Viscous oil; IR (neat) 3450 (OH) and 1700 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=0.90 (m, 6H, 2CH$_3$), 1.14—2.00 (m, 12H, 6CH$_2$), 2.50 (t, 2H, CH$_2$C=O), 3.62 (d, 1H, OH), and 4.14 (q, 1H, C$\underline{H}$OH). **16d**: Viscous oil; IR (neat) 3450 (OH) and 1670 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=1.06 (s, 9H, 3CH$_3$), 1.06 (t, 3H, CH$_3$), 1.10—1.86 (m, 4H, 2CH$_2$), 2.52 (t, 2H, CH$_2$C=O), 3.40 (d, 1H, OH), and 3.81 (d, 1H, C$\underline{H}$OH). **16e**: Viscous oil; IR (neat) 3480 (OH) and 1710 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=0.71—2.10 (m, 18H, cyclohexyl and *n*-C$_3$H$_7$), 2.48 (t, 2H, CH$_2$C=O), 3.52 (d, 1H, OH), and 4.00 (dd, 1H, C$\underline{H}$OH). **16f**: Viscous oil; IR (neat) 3450 (OH) and 1700 cm^{-1} (C=O); ^{1}H NMR (CDCl$_3$) δ=0.79 (t, 3H, CH$_3$), 1.14 (s, 6H, 2CH$_3$), 1.20—1.90 (m, 4H, 2CH$_2$), 2.48 (t, 2H, CH$_2$C=O), and 3.48 (d, 1H, OH).

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