Selective Coupling of [(Alkylthio)allyl]titanium Reagent with Carbonyl Compounds. Facile Entry to Alkenyl Oxiranes and 2-(Arylthio)-1,3-butadienes

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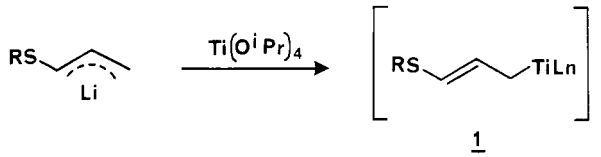
The unusual versatility of sulfur has led to many important developments in organic synthesis. Especially noteworthy is a large body of data relating to the reaction of sulfur-stabilized allylic carbanions.[1] Thus, the need for stereoselective methods for the synthesis of olefinic β-hydroxy sulfides, potential synthetic intermediates for stereochemically pure alkenyl oxiranes and 2-(arylthio)-1,3-alkadienes, is attested to by numerous recent publications in this area.[2] The available methods generally have sought to optimize stereoselectivity but as a consequence have suffered a loss of generality, viz., only one substitution type of olefinic β-hydroxy sulfide is obtainable after a rather tedious sequence, albeit in a state of high yield and purity.[2a,b] This communication deals with the reaction between a wide variety of [(alkylthio)allyl]titanium reagents of type **1** and carbonyl compounds as a promising versatile synthetic method.[3]



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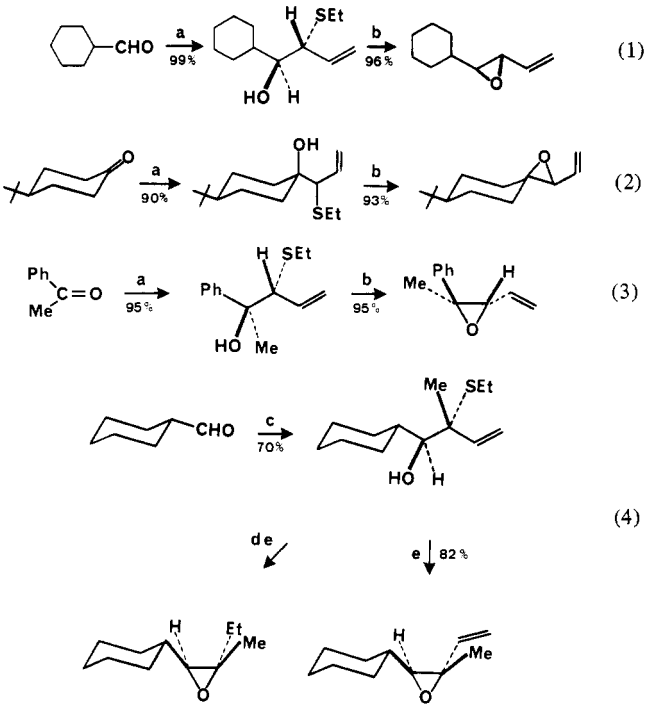
The major results of our findings are illustrated in Table I. Several trends emerge from these data. First, the substitution pattern of the starting sulfide can have a pronounced effect on α/γ ratio in the final condensation products.[1,2c] With nonsubstituted sulfides ($R^1 = R^2 = R^3 = R^4 = H$) or α- and β-mono- and disubstituted sulfides (R^1 and/or R^2 = Me), the α/γ ratios are about 97–99% with most aldehydes studied. On the other hand, a dramatic alteration in product distribution occurs when the condensation with aldehydes was carried out by using γ-substituted sulfides (R^3 and/or R^4 = Me); excellent γ selectivity was observed (entries 15, 16, and 19). It is highly interesting that α- and γ-disubstituted sulfide ($R^1 = R^3$ = Me) gave the α adduct almost exclusively (entry 18). The second important trend that may be seen from the data in Table I is the exceedingly high erythro selectivity of the reaction. Even the aromatic ketone gave the erythro alcohol selectively (entry 7). Furthermore, *the erythro stereoselectivity was not affected by the α branches of the starting sulfides*. It should be noted that [(alkylthio)allyl]lithium or other similar organometallic species are totally unsatisfactory reagents for such rigorously regio- and stereoselective transformations.[4]

Scheme I



[a] CH_2=$CHCH_2SEt$-*t*-BuLi-Ti(O-*i*-Pr)$_4$, THF, −78 °C. [b] Me_3OBF_4, CH_2Cl_2, 0 °C; aqueous NaOH, 25 °C. [c] CH_2=CHCHMeSEt-*t*-BuLi-Ti(O-*i*-Pr)$_4$, THF, −78 °C. [d] H_2NNH_2-H_2O_2-$CuSO_4$, aqueous EtOH, 0–25 °C. [e] Me_3OBF_4, CH_2Cl_2, 0–25 °C; *n*-BuLi, −78 °C.[16]

Even more important is the experimental simplicity of our new process.[5]

Further study is required before the stereochemical and mechanistic details of these reactions can be fully understood. However, the broad scope and utility of the method are apparent. Thus, the well-known procedure to desulfurize via sulfonium salt formation followed by base-catalyzed cyclization[7] converts this reaction into a new stereoselective entry to alkenyl oxirane synthesis (eq 1 and 2, Scheme I).[8] In addition, it is noteworthy that the same cyclization process can even be applied effectively for the preparation of trisubstituted oxiranes (eq 3 and 4), for which there exists no stereoselective methodology.

We next chose to examine the related system in which the alkyl substituent was replaced by the silyl group. This latter function,

(1) For a general review, see: Negishi, E. "Organometallics in Organic Synthesis"; Wiley: New York, 1980; Vol. 1.

(2) For stereoselective approaches: (a) Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1980**, *21*, 4883. (b) Pohmakotr, M.; Geiss, K.-H.; Seebach, D. *Chem. Ber.* **1979**, *112*, 1420. For regioselective approaches: (c) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Org. Chem.* **1980**, *45*, 195 and references therein. (d) Geiss, K.-H.; Seebach, D.; Seuring, B. *Chem. Ber.* **1977**, *110*, 1833. (e) Seebach, D.; Geiss, K.-H.; Pohmakotr, M. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 437. (f) Kondo, K.; Matsui, K.; Negishi, A. *Chem. Lett.* **1974**, 1371. (g) Atlani, P. M.; Biellmann, J. F.; Dube, S.; Vicens, J. J. *Tetrahedron Lett.* **1974**, 2665.

(3) For some recent synthetic methods using organotitanium reagents: (a) Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Org. Chem.* **1982**, *47*, 2225. (b) Widler, L.; Seebach, D. *Helv. Chim. Acta* **1982**, *65*, 1085. (c) Reetz, M. T.; Steinbach, R.; Wenderoth, B.; Westermann, J. *Chem. Ind. (London)* **1981**, 541 and references cited therein.

(4) For example, the [α-methyl(phenylthio)allyl]titanium (see entry 11 of Table I) gave 33% yield of the α adduct (erythro/threo = 61:39) and 62% yield of the γ adduct. Analogously, the [β-methyl(phenylthio)allyl]lithium (see entry 13 of Table I) produced 26% yield of the α-adduct (erythro/threo = 52:48) and 73% yield of the γ adduct.

(5) To a solution of allylphenyl sulfide (0.36 g, 2.4 mmol) in dry THF (8 mL) was added butyllithium (2.4 mmol)[6] dropwise at −78 °C, and the orange mixture was stirred at 0 °C for 30 min. Titanium tetraisopropoxide (0.71 mL, 2.4 mmol) was added to the resultant solution at −78 °C, and the resulting solution was stirred for 10 min. Cyclohexanecarbaldehyde (0.24 mL, 2.0 mmol) was added over a period of 5 min at −78 °C, and the mixture was stirred at −78 °C for 10 min and then at 0 °C for 1 h. After the usual workup, the product was purified by column chromatography to give the erythro-sulfide **4** quantitatively (0.52 g). For prevention of thioallylic rearrangements of the produced phenyl sulfides (see: Kozikowski, A. P.; Huie, E. *J. Am. Chem. Soc.* **1982**, *104*, 2059), small amount of hydroquinone or 2,6-di-*tert*-butyl-4-methylphenol was added during the workup and chromatographic operations.

(6) *sec*- or *tert*-butyllithium was required for generation of the [(alkylthio)allyl]lithium species. The generation of [(phenylthio)allyl]lithium was accomplished with *n*-butyllithium without any difficulties (see ref 2). In contrast, *tert*-butyllithium was recommended for the preparation of [α-alkyl(phenylthio)allyl]lithium.

(7) Shanklin, J. R.; Johnson, C. R.; Ollinger, J.; Coates, R. M. *J. Am. Chem. Soc.* **1973**, *95*, 3429. See also: Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Chem. Soc., Chem. Commun.* **1978**, 785.

(8) Recent efforts for the preparation of disubstituted oxiranes: (a) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1982**, 237. (b) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1981**, *103*, 1283. (c) Ochiai, M.; Fujita, E. *Tetrahedron Lett.* **1980**, *21*, 4369. (d) Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 1279. (e) Van Ende, D.; Krief, A. *Tetrahedron Lett.* **1976**, 457. (f) Paladini, J.-C.; Chuche, J. *Bull. Soc. Chim. Fr.* **1974**, 187. (g) La Rochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126. (h) Lyle, G. G.; Keefer, L. K. *Ibid.* **1966**, *31*, 3921.

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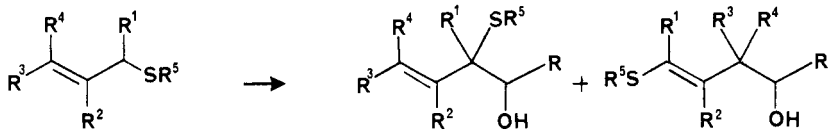
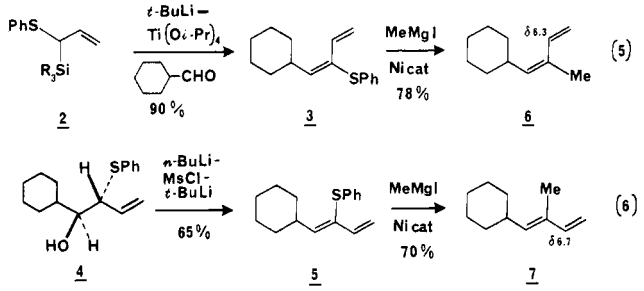
Table I. Regio- and Stereoselectivity in the Reaction of Allyltitanium Reagents and Carbonyl Compounds[a]



entry	sulfide[b] R¹	R²	R³	R⁴	R⁵	carbonyl compd[c]	product,[d] % yield: α adduct (erythro/threo)[e]	γ adduct
1	H	H	H	H	Ph	$C_6H_{11}CHO$	99 (>30:1)	<1
2	H	H	H	H	Et	$C_6H_{11}CHO$	99 (>30:1)	<1
3	H	H	H	H	Et	n-$C_5H_{11}CHO$	87 (>30:1)	5
4	H	H	H	H	Et	n-$C_3H_7CH{=}CHCHO$	93 (9:1)	3
5	H	H	H	H	Et	PhCHO	94 (6:1)	2
6	H	H	H	H	Et	4-*tert*-butylcyclohexanone	90[f]	7
7	H	H	H	H	Et	$C_6H_5COCH_3$	95 (>30:1)[g]	5
8	H	H	H	H	^{t}Bu	$C_6H_{11}CHO$	93 (>30:1)	2
9	H	H	H	H	^{t}Bu	n-$C_5H_{11}CHO$	90 (>30:1)	<1
10	H	H	H	H	^{t}Bu	PhCHO	99 (9:1)	<1
11	CH_3	H	H	H	Ph	$C_6H_{11}CHO$	99 (>30:1)[16]	<1
12	CH_3	H	H	H	Et	$C_6H_{11}CHO$	70 (>30:1)[h,16]	<1
13	H	CH_3	H	H	Ph	$C_6H_{11}CHO$	96 (>30:1)	4
14	H	CH_3	H	H	Et	$C_6H_{11}CHO$	98 (>30:1)	2
15	H	H	CH_3	H	Ph	$C_6H_{11}CHO$	2	98
16	H	H	CH_3	H	Et	$C_6H_{11}CHO$	<1	93
17	CH_3	CH_3	H	H	Ph	$C_6H_{11}CHO$	83 (>30:1)[i]	<1
18	CH_3	H	CH_3	H	Ph	$C_6H_{11}CHO$	71 (>30:1)[i]	4
19	H	H	CH_3	CH_3	Ph	$C_6H_{11}CHO$	<1	99

[a] All reactions were performed on a 2–3-mmol scale with the same experimental procedure as described in the text. [b] The starting sulfides were prepared from the corresponding allylic bromides and phenyl- or alkylthiols under basic conditions. The α-alkylated sulfides were synthesized by the alkylation of [(alkyl- or phenylthio)allyl]lithium with methyl iodide in THF. [c] Freshly distilled prior to use. [d] Isolated pure product. All products have been characterized by spectral data. New compounds also have satisfactory elemental and/or mass spectral analyses. [e] Unless otherwise specified, stereochemical assignments were based on conversion to the corresponding oxiranes (see ref 7). Erythro/threo ratio was determined by GC and NMR analyses of the α adduct and/or the corresponding oxirane. [f] The major product (>97%) was found to be the structure as illustrated in eq 2. The stereochemical assignment was based on the method of Trost.[8g] [g] The product was transformed to the saturated trans oxirane by (1) H_2NNH_2–H_2O_2–$CuSO_4$ in aqueous ethanol at 0–25 °C, (2) $Me_3O{\cdot}BF_4$ in CH_2Cl_2 at 0 °C and then aqueous NaOH at 0–25 °C, and the product was spectrally and chromatographically identified by comparison with an authentic specimen that was independently prepared from MCPBA oxidation of the *E*- and *Z*-2-phenyl-2-pentene. [h] The product was transformed to the saturated trans oxirane (see eq 4). [i] Structure determination was not unambiguous but was based on (1) extrapolation from the other examples and (2) the characteristic features of NMR spectrum were almost identical with those of entry 11 and very different from those of the threo isomer.

when positioned as in formula **2**, has the potential of Peterson elimination[9] following *α-selective* addition to carbonyl compounds so as to produce 2-(phenylthio)-1,3-alkadiene, an intriguing structure as a Diels–Alder component. Thus, metalation of **2**[10] (1.0 equiv of *t*-BuLi at 0 °C for 1 h), metal exchange using $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 equiv at −78 °C for 10 min), and condensation of the resulting titanium derivative with cyclohexanecarbaldehyde (0.8–0.9 equiv at −78 °C for 10 min) followed by elimination of Me_3SiO^- (at 0 °C for 1 h, 25 °C for 1 h) afforded the *E*-sulfide **3**,[11,12] resulting from the α-erythro-selective carbonyl addition followed by syn elimination.[13] Further generally useful results were obtained from the direct dehydration from the sulfide **4** (entry 1 of Table I): Sequential treatment of the sulfide **4** in THF first with *n*-BuLi (1.0 equiv at 0 °C for 5 min), then MsCl (1.0 equiv at 0 °C for 1 h), and finally *t*-BuLi (2.0 equiv at −78 °C for 5 min, 0 °C for 2 h) produced the *Z*-sulfide **5**[13] stereospecifically via the remarkable syn elimination of MsOH.[14] Exposure of these sulfides **3** and **5** to methylation conditions (MeMgI with Ni catalyst)[15] led to dienes **6** and **7**, respectively, with rigorous stereospecificities.



(9) For a general review, see: Chan, T.-H. *Acc. Chem. Res.* **1977**, *10*, 442. See also: Jarvie, A. W. P. *Organomet. Chem. Rev., Sect. A* **1970**, *6*, 153. For stereoselective olefination using Peterson reaction, see: Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568.

(10) Hiroi, K.; Chen, L.-M. *J. Chem. Soc., Chem. Commun.* **1981**, 377.

(11) The sulfides **3** and **5** were converted to the corresponding sulfoxides through $NaIO_4$ oxidation. The large downfield shift (ΔH_1 shift = 6.38 ppm) of the resonances of HC=CS(O)Ph of the structure **3** in the presence of $Eu(fod)_3$ (0.4 equiv) is expected from its *E* configuration. On the other hand, the *Z*-isomer **5** revealed a small downfield shift (1.29 ppm) under the same conditions.

(12) *E*/*Z* = 10:1; the *E* isomer was slowly isomerized to the *Z* isomer at 25 °C.

(13) Although the other possible explanation is the α-threo-selective carbonyl addition followed by anti elimination, the α-erythro-selective reaction mechanism seems to be more likely since the similar syn elimination of Me_3SiO^- using $Ti(O\text{-}i\text{-}Pr)_4$ was observed previously (*Chem. Lett.* **1982**, 1093) and since $Me_3SiCH_2CH{=}CH_2$ on treatment with *t*-BuLi-$Ti(O\text{-}i\text{-}Pr)_4$ followed by cyclohexanecarbaldehyde gave the *Z* diene selectively (Ikeda, Y., unpublished results).

(14) The reaction is highly stereospecific. Thus, the corresponding threo isomer, obtained from the [(phenylthio)allyl]lithium followed by separation by column chromatography, gave the *E* isomer exclusively under the same reaction conditions. The details of these results will be published as a full paper.

(15) The vinyl sulfide and MeMgI in the presence of $NiCl_2(PPh_3)_2$ in benzene were heated at reflux for 2 h. See: (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637.

(16) Sulfonium salt thus obtained was treated with *n*-butyllithium (1 equiv) at −78 °C. It should be noted that the usual reaction conditions[7] gave none of the desired product in this case. The same reaction proceeds but in very low yield with use of the corresponding phenylthio derivatives.

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Supplementary Material Available: Spectroscopic data (NMR and IR) of new compounds described in this paper (3 pages). Ordering information is given on any current masthead page.

First Experimental Demonstration of NMR Dynamic Frequency Shifts: Dispersion vs. Absorption (DISPA) Line Shape Analysis of Sodium-23 in Aqueous Sodium Laurate/Lauric Acid Solution

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One of the most fundamental operating axioms of experimental NMR is that nuclei with the same chemical environment must have the same Larmor frequency (i.e., same chemical shift). However, quadrupolar nuclei of spin >1 (e.g., ^{7}Li, ^{11}B, ^{17}O, ^{23}Na, ^{25}Mg, ^{27}Al, ^{35}Cl, ^{39}K, ^{43}Ca, ^{81}Br, etc.) exhibit two or more types of transitions. For rapid molecular rotational diffusion ($\omega_0\tau_c \ll 1$, where ω_0 is the Larmor frequency and τ_c is the rotational correlation time) all the transitions have the same chemical shift and (exponential) T_1 and T_2 relaxation. For slower motion ($\omega_0\tau_c \gtrsim 1$, as in micelles, membrane vesicles, polymers, or biological macromolecules) the widths and frequencies of the various transitions can be different.[1-4]

For a spin $^3/_2$ nucleus, analysis of the *theoretical* spectrum in Figure 1 clearly shows the two component transitions of different position and width, for $\omega_0\tau_c = 1.2$. For spin $^3/_2$, the relative areas of the two peaks will be 3:2 for any choice of τ_c. Unfortunately, *experimental* demonstration of such a case is not straightforward. First, although the presence of two line widths can be shown,[5-7] the asymmetry in the composite peak is in practice difficult to distinguish from a small phase misadjustment and thus will likely be overlooked. Second, the usual 180°–τ–90° inversion–recovery pulse sequence will not distinguish between the two transitions, because a 90° sampling pulse serves to mix the two longitudinal recovery rates.[4]

The extraordinary sensitivity of the dispersion vs. absorption (DISPA) plot to slight deviations from Lorentzian line shape[8] affords a simple and reliable way to visualize the chemical shift difference between the two peaks. Phase misadjustment acts simply to rotate the DISPA plot[8] and is thus readily distinguished from other non-Lorentzian line shape effects.

Figure 2a shows a ^{23}Na NMR spectrum of ordinary 1.0 M NaCl in D_2O. Although no apodization was applied to the free induction decay from which the absorption and dispersion spectra were computed, the circularity of the accompanying DISPA plot indicates a near-perfect Lorentzian shape for the peak. Thus, any deviations from the DISPA reference circle for other samples will reflect properties of the line shape, rather than any experimental artifacts or signal or data processing.

Figure 2b shows the ^{23}Na NMR spectrum (center) and cor-

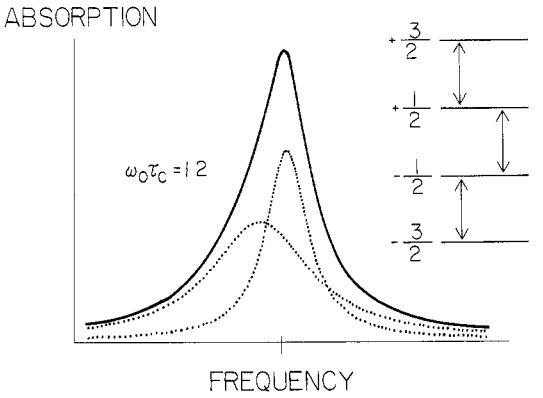

Figure 1. Energy-level diagram (right) and single-quantum NMR spectrum (left) for a spin $^3/_2$ nucleus with rotational correlation time $\tau_c = 1.2/\omega_0 \simeq 15$ ns for ^{23}Na at 7.0 T. The narrow component line arises from the $^{-1}/_2$ to $^{+1}/_2$ transition, and the broad component from the $^{+1}/_2$ to $^{+3}/_2$ and $^{-3}/_2$ to $^{-1}/_2$ transitions. Note the distinct chemical shift difference between the broad and narrow transitions.

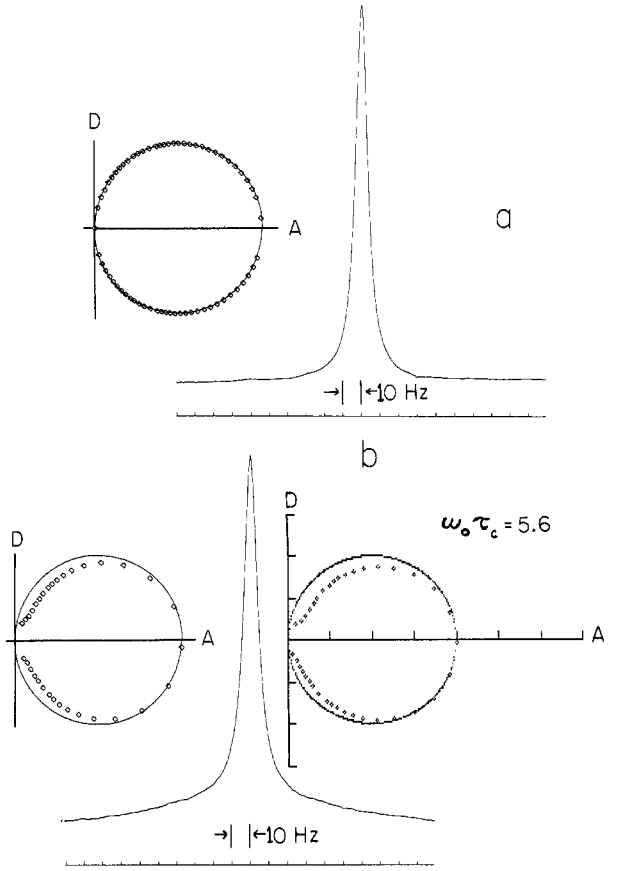

Figure 2. (a) Experimental ^{23}Na NMR spectrum and its corresponding DISPA plot for 1.0 M NaCl in D_2O, obtained from Fourier transformation of an unapodized 4096-point time-domain data set at a spectrometer frequency of 79.388 MHz, with a 90° excitation pulse (44 μs), for one cycle of an 8-pulse phase-alternating sequence. The close fit of the experimental data to the DISPA reference circle indicates a near-perfect Lorentzian line shape. (b) Experimental ^{23}Na NMR spectrum and its corresponding DISPA plot (left) for 120 mM NaCl, 20 mM sodium laurate, and 5 mM lauric acid in aqueous (15% D_2O) solution. The sample was milky white, with a sodium laurate concentration of about twice the critical micelle concentration for 0.1 M NaCl solutions of sodium laurate.[13] Detection was as in Figure 2a, except for 20° excitation pulse width. The experimental DISPA plot (left) closely matches that computed for $\omega_0\tau_c = 5.6$ (right), as discussed in the text.

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