reduction of the crude bis-hemiacetal, affords the key diol-ditosylate **2**[9] with adequate efficiency, thereby paving the way for the crown ether forming macrocyclization reaction leading to THYME cage **1**. Gratifyingly, addition of a dry DMF solution of diol-ditosylate **2** to a suspension of oil-free sodium hydride in dry DMF over 12 h (final concentration 0.002 M) followed by removal of solvent at reduced pressure, aqueous workup (dichloromethane), and flash chromatography[10] on Woelm N III alumina gives the tricyclic THYME cage **1** (white microcrystalline solid, mp 118-123 °C, 33-35% yield) as the major product.

The physical and spectral properties of cage **1** are consistent with the high symmetry (D_{2h}) and tricyclic nature of the molecule. Cage **1** is soluble in water, dichloromethane, and chloroform. It is slightly soluble in toluene and insoluble in hexane. The mass spectrum of cage **1** shows an abundant molecular ion (16% of the base peak); the ^{1}H NMR spectrum shows two peaks [($CDCl_3$) δ 3.50-3.83 (br s, 2 H, OCH_2CH_2O), 4.13, 4.31 (ABq, 1 H, J = 11.8 Hz, allylic CH_2)], and the proton-decoupled ^{13}C NMR spectrum shows four unique carbon resonances [($CDCl_3$) δ 67.95, 69.80, 71.11, 136.58). Recrystallization of the chromatographed solid from toluene affords prisms of a 1:1 toluene solvate suitable for X-ray analysis. This solvate loses toluene slowly at room temperature and pressure and rapidly at reduced pressure. After removal of toluene in vacuo, the remaining solid exhibits a melting point identical with that of the chromatographed material. The assigned structure is unequivocally proven by single-crystal X-ray analysis of the toluene solvate[12] (Figure 1). As indicated by the extreme ease with which toluene is lost from this solvate, toluene molecules in the crystal are not associated with molecules of the cage. As expected, the free ligand adopts a conformation in the crystal effectively filling the cavity space. The atoms of the cage are located about a center of symmetry. The two planes defined by the THYME units are parallel but are not perpendicular to the plane defined by the four olefinic carbons. While all of the OCH_2CH_2O units are gauche, four of the eight allylic methylenes are pointing inside the cavity. This sort of behavior is common in crystalline free crown ethers[3] and is not indicative of a poor host.

In conclusion, the efficacy of an approach to the synthesis of novel cylindrical polyether hosts is proven with the directed total synthesis of THYME cage **1**. We hope that compound **1** and related hosts will prove interesting and useful as ion binders, hosts for organic species, and catalysts. Studies on the complexation properties of host **1** are in progress as are studies directed toward extension of the synthetic strategy to preparation of larger cylindrical cages and other topologically fascinating structures.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research, to the Research Corporation and the National Science Foundation (RIAS) for financial assistance, and the University of Colorado Computing Center for blocks of computer time. We thank Professor Donald J. Cram for many helpful discussions during the early phases of this work.

Supplementary Material Available: Tables of atomic positional and thermal parameters and observed and calculated structure factors (6 pages). Ordering information is given on any current masthead page.

(12) Crystals of cage **1** grown from toluene are triclinic, space group $P\bar{1}$—C_i^1 (no. 2) with a = 8.451 (4) Å, b = 10.722 (7) Å, c = 10.054 (6) Å, α = 93.05 (5)°, β = 102.59 (4)°, γ = 95.33° and U = 882.7 (8) Å^3. On the basis of density considerations (D_0 = 1.29, D_c = 1.26 g/cc) there is one molecule of cage and one molecule of toluene per unit cell. Three dimensional X-ray data were collected on a computer controlled Nicolet P$\bar{1}$ four-circle diffractometer by using graphite monochromated Mo K$\bar{\alpha}$ radiation and θ-2θ scans. Of the 1730 reflections measured up to 2θ = 40° 1091 were determined to be observed [$F_o^2 > 3.0\sigma(F_o^2)$]. The structure was solved by direct methods and was refined using full-matrix least-squares procedures. Hydrogen atoms, except the methyl hydrogens of the disordered toluene, were located and included in fixed idealized positions. The disordered toluene solvent was treated as a rigid group in refinement. All other nonhydrogen atoms were treated anisotropically. At convergence, the final residuals were R = 0.056 and wR = 0.070. Full details of the structural analysis will be reported.

Facile Carbon-Carbon Bond Rotation in Azaallyllithium Reagents

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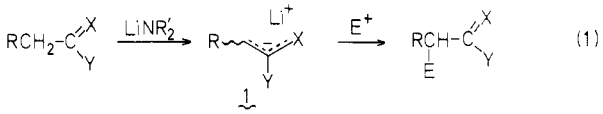
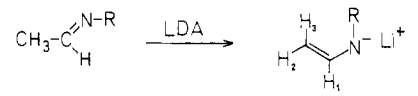
Stabilized carbanions (**1**), generally prepared by lithium dialkylamide deprotonation of carbonyl compounds and their derivatives, are an important and versatile class of reactive intermediates. Recent work has emphasized the stereoselectivity which



(1)

can be obtained in reactions employing these intermediates.[1] In particular, we and others have related the overall stereoselectivity observed in a two-step asymmetric synthesis involving the reaction sequence of eq 1 in part to the stereochemistry about the C_1-C_2 bond in **1**.[2] This of course assumes that the C_1-C_2 bond is "rigid" on the synthetic time scale. Previous studies[3] as well as the present study support this belief; however, the present study demonstrates the first unambiguous example of rapid C_1-C_2 bond rotation in an azaallyllithium reagent. These results clearly show that the utility of intermediates like **1** in stereoselective reactions may be determined not only by the stereoselectivity of their formation but also by the surprisingly low barrier to C_1-C_2 bond rotation.

Aldimines **2a** and **2b** were prepared by the reaction of acetaldehyde with the appropriate primary amine. Deprotonation of **2a** and **2b** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) produced the azaallyllithium reagents **3a** and **3b**, respectively. In both cases, the rotation about the C_1-C_2 bond was



2 3

a: R = c-C_6H_{11}

b: R = $C(CH_3)_3$

readily observed by variable temperature ^{1}H NMR spectroscopy. At low temperature (0 °C), the formyl proton, H_1, appeared as a doublet of doublets (**3a**: δ 6.90, J_{cis} = 7.7 Hz, J_{trans} = 14.5 Hz; **3b**: δ 6.93, J_{cis} = 7.4 Hz, J_{trans} = 14.6 Hz). The ^{1}H NMR spectrum reported for **3a** at 25 °C in THF-d_8 is virtually identical with that which we observed.[3c] These vicinal coupling constants were similar to those reported for the lithium enolate of acetaldehyde[4] and the azaallyllithium reagents prepared from acetaldehyde dimethylhydrazone[3a] and *N*-isopropylacetaldimine.[5] However, warming solutions of **3a** and **3b** led to an unexpected, reversible change in the multiplicity of the H_1 signals. At 70 °C,

(1) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, 4233-4236. Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137-3139. Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 206-208. Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

(2) Davenport, K. G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D. E. *J. Am. Chem. Soc.* **1979**, *101*, 5654-5659. Hoobler, M. A.; Bergbreiter, D. E.; Newcomb, M. *Ibid.* **1978**, *100*, 8182-8185. Meyers, A. I.; Synder, E. S.; Ackerman, J. J. *Ibid.* **1978**, *100*, 8186-8189.

(3) (a) Newcomb, M.; Bergbreiter, D. E. *J. Chem. Soc., Chem. Commun.* **1977**, 486-488. (b) Knorr, R.; Low, P. *J. Am. Chem. Soc.* **1980**, *102*, 3041-3043. (c) Knorr, R.; Weiss, A.; Low, P.; Rapple, E. *Chem. Ber.* **1980**, *113*, 2462-2489. (d) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877. (e) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 2502-2512.

(4) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560-562.

(5) Fraser, R. R.; Chuaqui-Offermanns, N.; Houk, K. N.; Rondan, N. G. *J. Organomet. Chem.* **1981**, *206*, 131-136.

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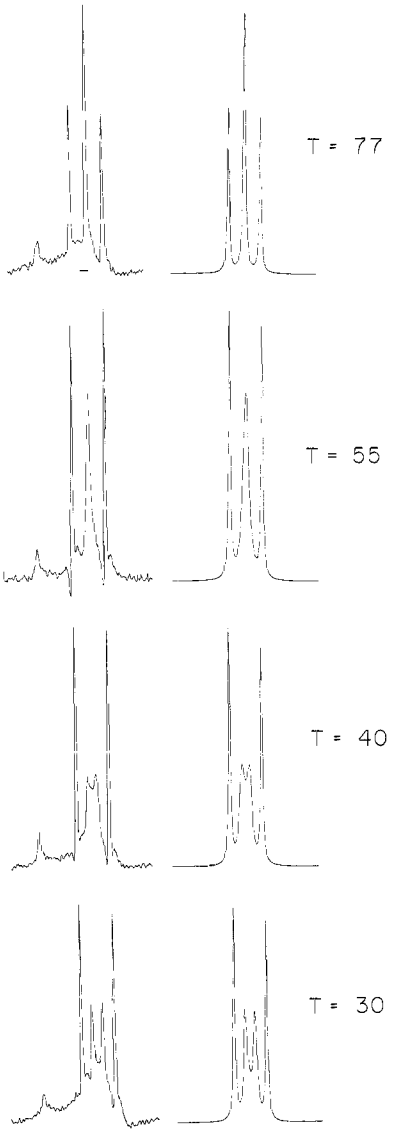
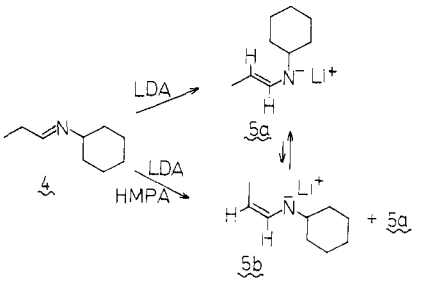


Figure 1. Experimental (200 MHz) and simulated ^{1}H NMR spectra for the formyl proton region of azaallyllithium reagent **3b** at various temperatures.

the H_1 signals appeared as triplets (**3a**: J_{av} = 11.1 Hz; **3b**: J_{av} = 10.9 Hz). These spectral changes correspond to those expected from a dynamic system with facile C_1–C_2 bond rotation on the NMR time scale at 70 °C. Simulated spectra calculated using the program DNMR3[6] provided an estimate for the free energy of activation for this process of 17.7 ± 0.3 kcal/mol at 40 °C for **3a** and 16.9 ± 0.3 kcal/mol at 40 °C for **3b**. The error limits represent the maximum estimated error based on our ability to match calculated and experimental spectra. Figure 1 shows the formyl proton region of the observed and calculated spectra for azaallyllithium reagent **3b**.

Alternative explanations for the above spectral behavior besides C_1–C_2 rotation include a rapid protonation–deprotonation process or perhaps a reversible aldol-like reaction with unreacted starting material.[7] Both such processes were ruled out by control experiments in which a sufficient amount of *n*-butyllithium was added to solutions of **3a** and **3b** to consume all of the diisopropylamine generated during the deprotonation of **2a** or **2b**. Under such conditions, unreacted aldimine and any proton source capable of rapidly isomerizing **3a** or **3b** would not be expected to be present. We observed that *n*-butyllithium addition had no effect on the dynamic NMR behavior described above.

Scheme I



Below 0 °C other unrelated dynamic phenomena were seen in the ^{1}H NMR spectra of **3a** and **3b**. These phenomena evidently are the same as those described by Knorr et al. for **3a**[3c] and Fraser and Houk for **3** [R = $CH(CH_3)_2$] and related species.[5] These authors ascribe these phenomena to quadrupole relaxation[3c] and slow C–N bond rotation about the bond to the nitrogen substituent.[5]

Incorporation of an alkyl substituent at C-2 of the azaallyllithium reagent would be expected to slow the rate of C_1–C_2 bond rotation. Experimentally, this is the case. When *N*-cyclohexylpropionaldimine (**4**) was deprotonated with excess LDA in THF the E_{C-C} azaallyllithium reagent **5a** (δ 6.40, d, J = 13.5 Hz) was the only product detected by ^{1}H NMR spectroscopy (Scheme I).[8] Deprotonation of **4** with an LDA solution containing 2 equiv of hexamethylphosphoramide (HMPA) per lithium ion gave predominantly the Z_{C-C} azaallyllithium **5b** (δ 6.25, d, J = 7.5 Hz) (**5a**:**5b** = 44:56). The stereoselective effect of LDA and LDA–HMPA deprotonations of **4** is consistent with the effects seen in similar deprotonations of carbonyl compounds and derivatives.[9] Upon standing at 27 °C the **5a**/**5b** mixture slowly isomerized to an equilibrated mixture (**5a**:**5b** = 82:18) with a free energy of activation of 22.6 kcal/mol. This isomerization is catalyzed by the HMPA present in this reaction mixture since **5a** prepared by LDA deprotonation did not isomerize at 27 °C in 10 h but did isomerize to give the equilibrium mixture after HMPA addition. Azaallyllithium reagents derived from ketimines apparently isomerize at similar rates; from Meyers' recent report,[10] we can estimate a crude free energy of activation of <25 kcal/mol at 60 °C for this isomerization process.

The low rotational barrier which we observed about the C_1–C_2 bonds of **3a**, **3b**, **5a**, and **5b** are of both theoretical and practical significance. As expected, the free energy of activation for C_1–C_2 bond rotation in these azaallyllithium reagents lies between that of allyllithium ($\Delta G^{\ddagger}$ = 10.7 kcal/mol at −51 °C)[11] and that of 1-oxaallyllithium ($\Delta G^{\ddagger}$ > 21 kcal/mol at 90 °C based on observation of a sharp doublet of doublets for the formyl proton of this stabilized carbanion at this temperature). From a practical standpoint, our results suggest that bond rotation in azaallyllithium reagents may be an experimentally facile process which can lead to equilibration of synthetically useful intermediates. While the mechanism for this "rotational" process does not involve a protonation–deprotonation or aldol–retro aldol process (vide supra), other mechanisms including those discussed previously for allyllithium[11] are certainly plausible. Indeed, the observation of HMPA catalysis in the rotation of **5a** and **5b** suggests an important role for lithium in this isomerization. Ultimately, significant changes in the overall stereoselectivity in electrophilic substitution reactions of azaallyllithium reagents may result from such equilibrations. For example, Meyers et al. have observed dramatic increases in diastereoselectivity when they alkylated chiral az-

(6) Binsch, G. *Mol. Phys.* **1968**, *15*, 469–476. *J. Am. Chem. Soc.* **1969**, *91*, 1304–1309.
(7) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959–3960.
(8) *N*-Cyclohexylbutanaldimine similarly gives only the E_{C-C} azaallyllithium reagent when deprotonated with LDA.[3c]
(9) For a recent discussion of this effect, see: Davenport, K. G.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1981**, *46*, 3143–3144.
(10) Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088–3093.
(11) Thompson, T. B.; Ford, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 5459–5464.

aallyllithium reagents *after* the intermediates were thermally equilibrated.[10]

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[(Trimethylsilyl)acetyl]trimethylsilane, a Versatile Synthon for Stereoselective Syntheses of Functionalized Trisubstituted Olefins

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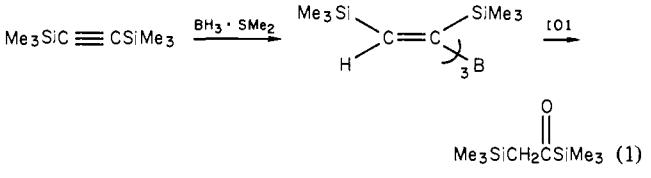
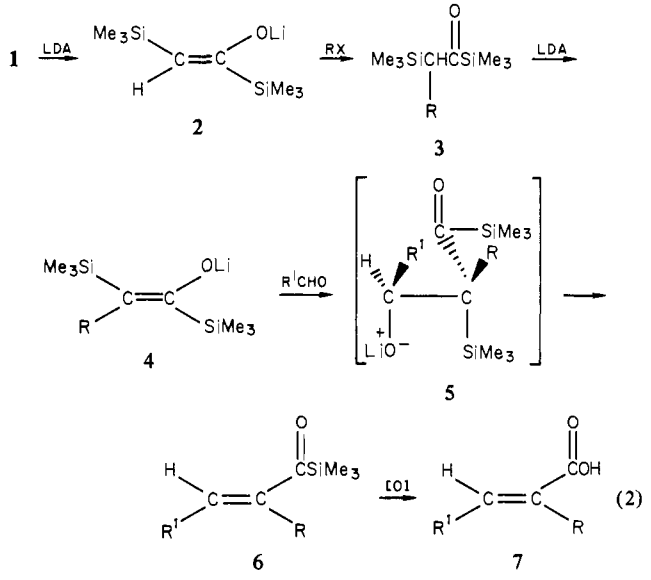
Recently we reported that monohydroboration of bis(trimethylsilyl)acetylene with borane–methyl sulfide complex followed by oxidation of the resultant trivinylborane with anhydrous trimethylamine oxide and a hydrolytic workup affords [(trimethylsilyl)acetyl]trimethylsilane (**1**, eq 1).[1] Compound **1** is



(1)

1

unique in that it contains both the α- and β-ketosilane structural features which endow it with considerable potential value as a synthon for a wide variety of transformations. Thus, we describe here its efficient elaboration into trisubstituted olefins of defined stereochemistry via sequential deprotonation–alkylation–deprotonation–aldolization reactions (eq 2). Such transformations are of special importance in that many biogenetically interesting isoprenoid molecules and insect pheromones embody trisubstituted olefinic moieties.[2]



(2)

2 **3** **4** **5** **6** **7**

Treatment of **1** in THF with lithium diisopropylamide (LDA) resulted in the nearly exclusive formation of the (*E*)-enolate **2** as evidenced by its conversion into the (*E*)-alkenylsilyl ether on treatment with chlorotrimethylsilane.[3] The formation of the (*E*)-enolate **2** reflects the known tendency of the trimethylsilyl group in vinylsilanes to occupy the sterically more favorable trans positions.[4] Alkylation of **2** with reactive alkyl halides proceeded readily to furnish the α-substituted [(trimethylsilyl)acetyl]trimethysilane **3**. Deprotonation of **3** with LDA produced the new enolate **4**. When **4** (R = CH_3) was treated with chlorotrimethylsilane, the 360-MHz ^1H NMR spectrum of the resultant alkenylsilyl ether exhibited only one CH_3 singlet (δ 1.60). Moreover, its examination on a 96-m SE-30 glass capillary column revealed the presence of a single product. Thus, by analogy with **2** it appears that the trans arrangement of the bulky trimethylsilyl moieties also prevails in the enolate **4**, at least when it contains an R group with moderate steric requirements.

The last step in the olefin synthesis (eq 2) involved treatment of **4** with an appropriate aldehyde. Elimination of the oxygen and trimethylsilyl moieties from the resultant crossed aldol condensation product **5** proceeded spontaneously at −78 °C and produced the *E*-disubstituted α,β-unsaturated acylsilane **6**.[5] For establishment of the stereochemistry and the isomeric purities of the olefins obtained, the acylsilane group in **6** was oxidized to the carboxylic acid with alkaline hydrogen peroxide.[6] It has been shown that (*E*)- and (*Z*)-2,3-dialkyl-substituted acrylic acids of the type **7** exhibit distinct chemical shifts for the vinyl protons.[7] On the basis of spectral and GLC data of the α,β-unsaturated acylsilanes **6** and the corresponding acids **7** it was concluded that they also possess the *E* configuration and that they were at least 98% isomerically pure.

Typical procedures for the preparation of **6** and **7** (R = CH_3, R^1 = *sec*-C_4H_9) are as follows. To a solution of diisopropylamine (22.0 mmol) in 40 mL of THF at −78 °C was added a solution of *n*-butyllithium (20.0 mmol, 2.4 M) in hexane. The mixture was stirred for 15 min at 0–5 °C, treated at −78 °C with a solution of **1**[8] (20.0 mmol) in 5 mL of THF, warmed to 0–5 °C, and stirred at this temperature for 30 min to obtain the enolate **2**. Alkylation of **2** was achieved by addition at −25 °C of a solution of methyl iodide (20.0 mmol, 2 M) in THF. The mixture was stirred for 4 h at −25 °C and then let warm to 25 °C. The resultant solution of α-methylated acylsilane **3** was added via an addition funnel to a solution of LDA (20.0 mmol, prepared as described above) maintained at 0–5 °C. The mixture was stirred for 1 h at 25 °C, and then the enolate **4** formed was treated at −78 °C with a solution of 2-methylbutyraldehyde (22.0 mmol) in THF (20 mL) over a 30-min period. The resultant yellow slurry was stirred for an additional 15 min at −78 °C, warmed to 25 °C, and poured into a separatory funnel containing 25 mL of 1 N HCl. After extraction with ether the combined organic phases were washed with saturated aqueous NaCl and dried over $MgSO_4$. Distillation

(1) Miller, J. A.; Zweifel, G. *Synthesis* **1981**, 288.

(2) For a recent summary of trisubstituted olefin syntheses, see: Marfat, A.; McGuirk, P. R.; Kramer, R.; Helquist, P. *J. Am. Chem. Soc.* **1977**, *99*, 253.

(3) The ^1H NMR (360-MHz) spectrum of the silyl enol ether showed only one singlet at 5.0 ppm in the vinyl proton region. A similar vinyl proton chemical shift for the silyl enol ether derived from propionyltrimethylsilane has been observed by: Kleschick, W. A. Ph.D. Thesis, University of California, Berkeley, 1977.

(4) Zweifel, G.; On, H. P. *Synthesis* **1980**, 803. Zweifel, G.; Murray, R. E.; On, H. P. *J. Org. Chem.* **1981**, *46*, 1292.

(5) For the preparation of monosubstituted α,β-unsaturated acylsilanes, see: Minami, N.; Abe, T.; Kuwajima, I. *J. Organomet. Chem.* **1978**, *145*, Cl. Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423.

(6) Zweifel, G.; Backlund, S. *J. Am. Chem. Soc.* **1977**, *99*, 3184.

(7) For 7, R = CH_3; R^1 = C_2H_5, *n*-C_4H_9, *sec*-C_4H_9, C_6H_5, the IR and NMR spectral data were in good agreement with those reported in the literature for these compounds.

(8) The original procedure reported for the preparation of **1**[1] was modified in that after oxidation of the trivinylborane (20 mmol) with anhydrous trimethylamine oxide[9] the reaction mixture was poured into a mixture of ether (60 mL) and water (30 mL) maintained at 0–5 °C. The reaction mixture was stirred vigorously at this temperature for 15 min and then worked up in the usual way. It should be noted that **1** has to be used shortly after its preparation since it isomerizes to the silyl enol ether even when stored at low temperatures.

(9) Köster, R.; Morita, Y. *Liebigs Ann. Chem.* **1967**, *704*, 70.

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