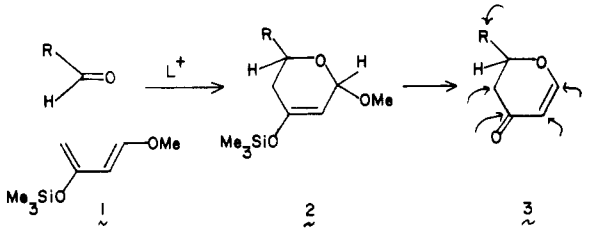
Cram Rule Selectivity in the Lewis Acid Catalyzed Cyclocondensation of Chiral Aldehydes. A Convenient Route to Chiral Systems of Biological Interest

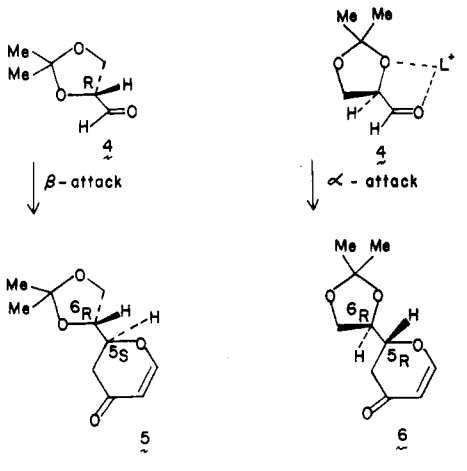
Summary: High Cram rule selectivity was observed in the zinc chloride catalyzed reaction of (*E*)-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadienes with glyceraldehyde acetonide and with *N*-Boc-substituted leucinal. Conversion of the resultant dihydropyrones to other products of interest is described.

Sir: Recently we described some Lewis acid (L^+) catalyzed cyclocondensation reactions of aldehydes with the parent *trans*-1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (1) and derivatives thereof.[1-3] The catalyst–solvent systems which we have most commonly employed are zinc chloride in benzene and boron trifluoride etherate in ether. The dihydropyrones (3) which are isolated may well arise via 1:1 cycloadducts of the type 2, though, in fact, no such intermediates have been experimentally detected.



As we have shown, such dihydropyrones can be very useful in a variety of synthetic undertakings. The arrows in structure 3 indicate convenient access points for heteroatom or carbon functionality which have been experimentally realized[1-3] either through incorporation into the "R" function of the aldehyde, by substitutions at the 2- or 4-positions of the diene, or by operations performed subsequent to formation of the dihydropyrone.

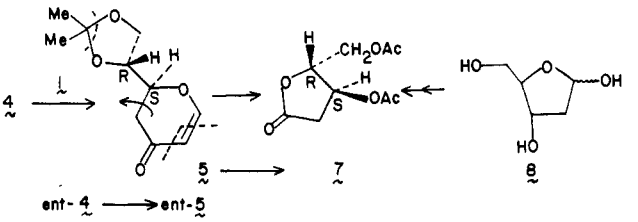
In the study which is described below, we investigated the outcome of using the chiral aldehyde 4 in such a reaction. It is seen that a classical Cram rule formulation of the problem[4] would predict that the (*R*)-aldehyde 4,[5]



would give rise to the (5*S*,6*R*)-heptulose 5. Alternatively, in a chelation model,[6,7] wherein L^+ imposes a syn relationship between the formyl and neighboring oxygen functions, the (5*R*,6*R*)-heptulose would be expected.

In this paper we report that with this aldehyde, the cyclocondensation[8] reaction occurs cleanly with no detectable erosion of optical integrity. We have also found that the process exhibits a high adherence to the classical Cram's rule model.[4] Combining these two findings, a versatile entry to a variety of modified carbohydrate system is now available. Finally, we have used this methodology to achieve a stereospecific synthesis of the biologically important amino acid statine as its *N*-Boc derivative.

The cyclocondensation of 1 (1.5 equiv) with aldehyde 4 (1 equiv) in the presence of anhydrous zinc chloride (0.6 equiv) was carried out in benzene (4 mL/mmol of 4) at room temperature overnight. There was thus obtained



a 72% yield of 5,[9] $[\alpha]^{20}_D$ + 120.6° (*c* 0.5, MeOH). *Similarly, reaction of ent-4,*[10] *obtained from the readily available* L-*arabinose, gave rise to ent-5. A pathway to a wide variety of difficulty available* L-*heptose and* L-*hexoses is thus available.* The optical purities of 5 and *ent*-5 were vouchsafed through NMR analysis by using $Eu(hfc)_3$ as a chirally discriminating shift reagent.[11]

The 5*S* configuration of 5 follows from its correlation with 2-deoxyribonolactone. This was accomplished by ozonolysis (O_3/MeOH, −78 °C) followed by oxidative

(1) Danishefsky, S.; Kerwin, J. F., Jr.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.
(2) Danishefsky, S.; Kato, N.; Askin, D., Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 360.
(3) Danishefsky, S.; Kerwin, J. F., Jr. *J. Org. Chem.*, in press.
(4) Cram, D. J.; Elhafez, F. *J. Am. Chem. Soc.* **1952**, *74*, 5828.
(5) Baer, E.; Fisher, H. O. L. *J. Biol. Chem.* **1939**, *128*, 463.
(6) Cram, D. J.; *Kopecky*, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748.
(7) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, 1031. Still, W. C.; Schneider, J. A. *ibid.* 1035.
(8) The term cyclocondensation as we use it here has no implication with respect to degree of concertedness.
(9) All new compounds gave satisfactory NMR (*J* values given in hertz), IR, and mass spectra, representative data follow. **5**: IR (CCl_4) $\bar{\nu}$ 1690, 1605 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.33 (d, *J* = 6.25, 1 H), 5.43 (d, *J* = 6.25, 1 H), 4.25–4.37 (m, 2 H), 4.14 (dd, *J* = 5.9, 8.8, 1 H), 3.95 (dd, *J* = 4.4, 8.8, 1 H), 2.5–2.7 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H); mass spectrum, *m/e* 198 (M^+), 183, 101. **9**: IR (CCl_4) $\bar{\nu}$ 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.35 (dd, *J* = 1, 4.0, 1 H), 4.0–4.2 (m, 3 H), 3.8–3.9 (m, 2 H), 2.4–2.7 (m, 4 H), 1.42 (s, 3 H), 1.37 (s, 3 H), 1.19 (d, *J* = 6, 3 H), 1.14 (d, *J* = 6 Hz, 3 H); mass spectrum, *m/e* 258 (M^+), 243, 157. **10**: IR $\bar{\nu}$ 3540 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.76 (br s, 1 H), 3.80–4.15 (m, 6 H), 1.85–2.0 (m, 2 H), 1.55–1.67 (m, 2 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.25 (d, *J* = 6.3, 3 H), 1.15 (d, *J* = 6.3, 3 H); mass spectrum, *m/e* 245 (M^+ − 15), 159, 141, 99. **12**: IR $\bar{\nu}$ 3450–3600 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (br quintet, *J* = 3.5, 1 H), 4.98 (br d, *J* = 4.0, 1 H), 4.20 (m, 1 H), 3.85 (heptet, 1 H), 3.64–3.80 (m, 3 H), 2.21 (s, 3 H), 1.7–2.0 (m, 4 H), 1.20 (d, *J* = 6, 3 H), 1.10 (d, *J* = 6, 3 H); mass spectrum, *m/e* 261 (M^+ − 1), 201, 141, 99. **13**: IR $\bar{\nu}$ 3500, 1740 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (br quintet, *J* = 3.4, 1 H), 5.02 (br d, *J* = 3.7, 1 H), 4.2 (m, 1 H), 3.89 (heptet, *J* = 6.1, 1 H), 3.67 (dd, *J* = 4.2, 11.5, 1 H), 3.53 (dd, *J* = 6.1, 11.5, 1 H), 2.05 (s, 3 H), 1.6–2.1 (m, 4 H), 1.21 (d, *J* = 6.1, 3 H), 1.11 (d, *J* = 6.1, 3 H); mass spectrum, *m/e* 231 (M^+ − 1), 201, 141, 113. **15** (major diastereomer): IR $\bar{\nu}$ 1720, 1680, 1600, 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.35 (d, *J* = 6.0, 1 H), 5.40 (dd, *J* = 1.1, 6.0, 1 H), 4.71 (br d, *J* = 9.6, 1 H), 4.41 (br dd, *J* = 2, 12.5, 1 H), 3.89 (br m, 1 H), 2.69 (dd, *J* = 15.0, 17.0, 1 H), 2.38 (dd, *J* = 2.0, 17.0, 1 H), 1.68 (m, 1 H), 1.60 (m, 1 H), 1.44 (br s, 9 H), 1.35 (m, 1 H), 0.95 (2 d, *J* = 6.5, 6 H); mass spectrum, *m/e* 228 (m^+ − 57), 210, 186. **5** (minor diastereomer): IR $\bar{\nu}$ 1710, 1680, 1600, 1520 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.37 (d, *J* = 6.0, 1 H), 5.41 (d, *J* = 6.0, 1 H), 4.54 (m, 1 H), 4.35 (br d, *J* = 15.0, 1 H),, 3.92 (m, 1 H), 2.60 (dd, *J* = 14.0, 16.0, 1 H), 2.42 (dd, *J* = 3.6, 16.0, 1 H), 1.60–1.80 (m, 2 H), 1.44 (br s, 9 H), 1.35–1.40 (m, 1 H), .96 (d, *J* = 6.5, 3 H), .94 (d, *J* = 6.5, 3H); *m/e* 228 (M^+ − 57), 210, 186.
(10) Cf.: Baker, S. B. *J. Am. Chem. Soc.* **1952**, *74*, 827.
(11) Using $Eu(hfc)_3$ as the chiral shift reagent, we observed a shift of one methyl resonance (1.43 ppm) to 2.26 and 2.32 ppm in the complex [1 equiv of Eu(hfc)] ^1H NMR spectrum of racemic 5. Performing the same routine with 5 shifted the resonance only to 2.32 ppm (no detectable peak at 2.26 ppm). Likewise, with *ent*-5 the resonance was shifted to 2.26 ppm (no detectable peak at 2.32 ppm). All complexed ^1H NMR spectra showed a shift of the other methyl resonance from 1.37 to 2.00 ppm.

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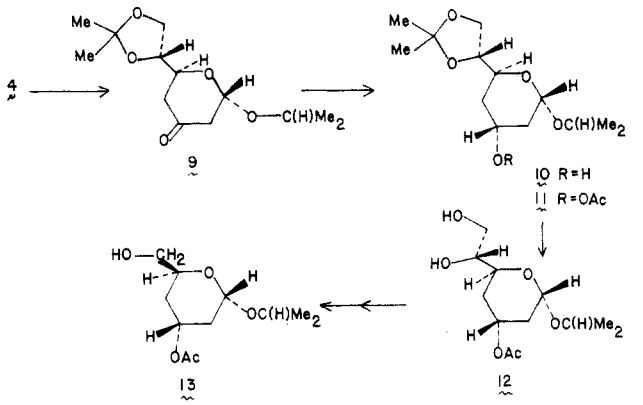
(H_2O_2–NaOH) fragmentation of the dihydropyrone ring as previously described.[2] Acetylation of the synthetic 2-deoxyribonolactone afforded **7** which was identical with authentic material prepared from 2-deoxyribose (**8**) by oxidation (aqueous bromine) of the anomeric hydroxyl, followed by acetylation (pyridine–acetic anhydride).[12a]

We also demonstrated the convertibility of **5** to the chiral 2,4-dideoxy-D-glucose **13**.[12b] In this process, C_7 of the

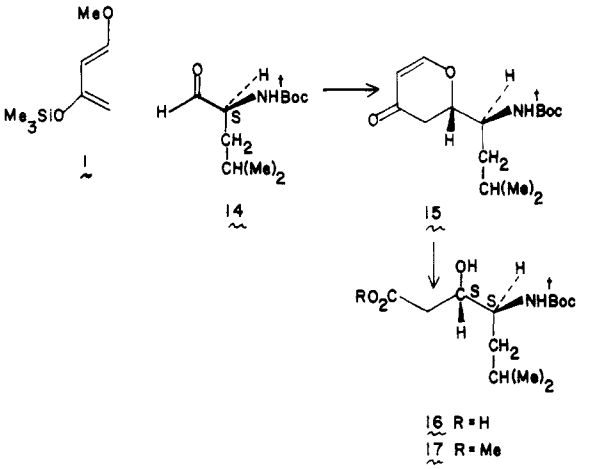


9 **10** R=H **11** R=OAc **12** **13**

heptulose system is excized. Stereoselective addition of 2-propanol to the enone system was accomplished (2-propanol–acetone, 4-Å molecular sieves, room temperature) in 54% conversion[13] to afford **9**[9] ($[\alpha]^{30}_D$ +85.2° (*c* 1.50, MeOH)) which is conformationally defined. Stereoselective reduction of the keto group was achieved[1] (L-Selectride; THF, −78 °C), giving **10**,[9] ($[\alpha]^{30}_D$ +96.0° (*c* 1.11, MeOH)), and upon acetylation this gave **11**: $[\alpha]^{20}_D$ +127.5° (*c* 1.65, MeOH); 95% yield (from **9**).

Under mild hydrolytic conditions (30% aqueous AcOH, room temperature), the side-chain acetonide was selectively cleaved, affording the heptulose derivative **12**:[9] $[\alpha]^{20}_D$ +143.8° (*c* 1.26, MeOH); 71% yield. The latter was converted [(1) $NaIO_4$, (2) $NaBH_4$] quantitatively to **13**:[9] $[\alpha]^{20}_D$ +158.4° (*c* 167, MeOH). *It is seen that **13** is a unit which corresponds in its relative and absolute configurations to the pyranose portion of the antihypocholestemic agent compactin.*[14-16]

We now describe the application of this methodology to a stereoselective synthesis of the novel β-hydroxy-γ-amino acid statine in the form of its *N*-Boc derivative **16**. Interest in this problem arises from the appearance of two statine residues in the acid protease inhibitor pepstatin.[17] There is a great deal of activity involving incorporation of statine units in a variety of synthetic peptides. The currently known syntheses of statine are stereorandom.[18] Recently[19] Rich has achieved the very difficult separation of diastereomers in the statine series via the *N*-Boc ethyl esters and described a protocol for determining diastereomeric purity through GLC analysis of the corresponding methyl esters. A simple and highly stereoselectivity entry to the statine series was accomplished through our cyclocondensation methodology.



1 **14** **15** **16** R=H **17** R=Me

N-Boc-Leu (**14**)[20] (0.1 M in benzene) reacted with diene **1** (3.5 equiv) in the presence of zinc chloride (2.8 equiv) to give a 68% yield of pyrones as a 9:1 mixture of diastereomers. These could be separated by HPLC[21] to afford the "threo" isomer **15**[9] (mp 70–71 °C) as the major product. The minor "erythro" isomer was also fully characterized by spectral methods.[9] Ozonolysis of **15** followed by oxidative fragmentation with hydrogen peroxide in the usual way[2] afforded *N*-Boc-substituted statine (**16**) which upon esterification (diazomethane) gave **17**. Comparison with authentic samples of **17**[22] by ^1H NMR and gas chromatography[19] confirmed its configuration as that of statine.

Of course, the high stereoselectivity obtained in this process does not per se prove or disprove the involvement of chelation as a conformation-determining influence.[23] It may well be that the isobutyl group is substantially larger than the *N*-Boc function. However, it is tempting to invoke such a chelation effect to account for the superior Cram's rule fidelity in the Lewis acid catalyzed process observed here, relative to previous carbanionic cases which evidence essentially no selectivity. Studies directed toward understanding these subtle effects and exploiting them more fully are in progress.

Acknowledgment. This research was supported by PHS Grant HL48136-02. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University which was supported by the NSF Chemistry Division Grant CHE-7916210.

(12) (a) For a very recent conversion of aldehyde 4 to the deoxyribose series using, for this purpose, the "allyl" specie derived from the reaction of allyl iodide with stannous fluoride see: Harada, T. and Mukaiyama, T. *Chem. Lett.* **1981**, 1109. (b) For a recent paper bearing on the syntheses of deoxyhexoses see: Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843.

(13) The reaction also provided a 6% yield of the β anomer and 21% recovered starting material.

(14) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.

(15) Wang, N.-Y.; Hsu, C.-T.; Shih, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 6538.

(16) Prugh, J. D.; Deana, A. A. *Tetrahedron Lett.* **1982**, 281.

(17) Umezawa, H.; Aoyagi, T.; Morishima, H.; Matzusaki, M.; Hamada, H.; Takeuchi, T. *J. Antibiot.* **1970**, *23*, 259.

(18) Morishima, H.; Takita, T.; Umezawa, H. *J. Antibiot.* **1973**, *26*, 115. Kinoshita, M.; Hagiwara, A.; Aburaki, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 570. Steulmann, R.; Klostermeyer, H. *Justus Liebigs Ann. Chem.* **1975**, 2245. Liu, W. S.; Glover, G. I. *J. Org. Chem.* **1978**, *43*, 754.

(19) Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.

(20) For most recent synthesis of amino acid aldehydes, cf.: Stanfield, C. F.; Parker, J. E.; Kanellis, P. *J. Org. Chem.* **1981**, *46*, 4797. In this case leucinal was racemic and was prepared by oxidation of the alcohol. cf.: Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(21) Separated on a Waters μ-Porasil column (3.9 mm i.d. × 30 cm) by using a solution of 15% ethyl acetate in hexane as the eluant.

(22) An authentic sample of **16** purchased from Sigma which was esterified with diazomethane to afford **17**.

(23) A referee has suggested that a chelation model in which the Lewis Acid is coordinated to the β-substituted oxygen and the carbonyl oxygen of glyceraldehyde also explains the formation of observed products. He cites previous work in which this possibility may be relevant (cf.: Ohgo, Y.; Yoshimura, J.; Kono, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1969**, *43*, 2957. Deton, M. H.; Yuen, G. U. *J. Org. Chem.* **1968**, *33*, 2473). Since the ratio of products in the aforementioned work approaches unity, we do not find these arguments to be definitive. We note, however, that in a very recent paper the same possibility has been invoked by Mukaiyama et al. with supporting data which is quite similar to our own (Cf.: Suzuki, K.; Yuki, Y.; Mukaiyama, T. *Chem. Lett.* **1981**, 529).

Registry No. 4, 15186-48-8; *ent*-4, 22323-80-4; 5, 81277-28-3; *ent*-5, 81277-29-4; 9, 81277-30-7; 10, 81277-31-8; 11, 81277-32-9; 12, 81277-33-0; 13, 81277-34-1; 14, 58521-45-2; 15 (major isomer), 81277-35-2; 15 (minor isomer), 81277-36-3; 16, 58521-49-6; 17, 81277-37-4.

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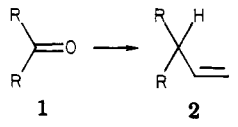
[β-(Trimethylsilyl)ethyl]lithium: A New Reagent for Carbonyl Reductive Vinylation

Summary: The direct transformation of a carbonyl compound into a vinyl compound (i.e., cyclohexanone → vinylcyclohexane) is now possible with use of the new reagent described in this paper: [β-(trimethylsilyl)ethyl]lithium, followed by protodesilylation.

Sir: The direct transformation of a carbonyl group **1** into a vinyl compound **2** (eq 1) has not been possible directly.[1] This transformation can now readily be accomplished with use of the new reagent reported in this paper: [β-(trimethylsilyl)ethyl]lithium (**3a**).



(1)

1 **2**

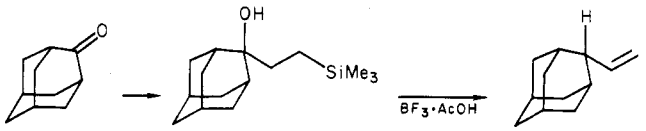
$Me_3SiCH_2CH_2M$ $Me_3SiCH_2\dot{C}H_2$ $Me_3SiCH_2\bar{C}H_2$

3a, M = Li
3b, M = MgBr

4 **5**

These reagents correspond to an "umpolung"[3] of the well-recognized[4] β-(trimethylsilyl) carbonium ion chemistry (cf. **4**), since they formally represent β-(trimethylsilyl) anions **5**.[5,9-11] As such, ready and high yield addition to carbonyl electrophiles is observed.

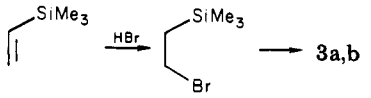
For example, addition of 2-adamantanone (**6**) to **3a** in ether (−78 °C) gives alcohol **7** quantitatively (72% isolated).[12] Our expectation[13] that acid treatment of **7** would lead to dehydration to an allylsilane and subsequent protonolysis to vinyl compound **8** was indeed the case. BF_3·AcOH treatment of **7** gives olefin **8** (100%, CH_2Cl_2, 25 °C, 5 min). Other results with aldehydes and ketones



6 **7** **8**

are collected in Table I. In most cases the alcohols were purified by column chromatography. NMR signals at δ = 0 (Me_4Si) and a multiplet at δ 0.2–0.8 (CH_2CH_2) were observed.

This compound is readily prepared from the corresponding bromide[14] **9** and *tert*-butyllithium at −78 °C (eq 2). For large-scale preparations the Grignard reagent **3b**



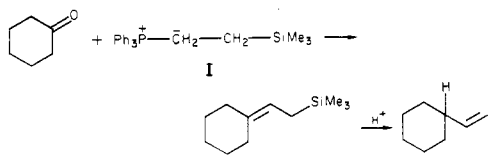
(2)

9

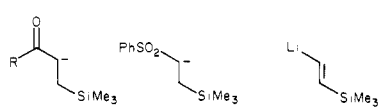
is more convenient (Mg, ether, 25 °C). While lithium reagent **3a** has been generated and used in situ, Grignard **3b** has been prepared on a 0.5-mol scale, and stock solutions have been stored at 0 °C for weeks. Compound **9** is labile, decomposing to Me_3SiBr and (presumably) ethylene on standing at 25 °C overnight. It is best used immediately after washing with H_2O and drying over silica gel (which also removes Me_3SiBr seen as a singlet at δ 0.2).

An interesting observation of possible theoretical interest is the behavior of Grignard **3b** with hindered ketones. The known ketone reduction[15] by the Grignard reagent via β-hydrogen transfer is particularly pronounced in the case of **3b** wherein 35% **7** and 65% **10** are produced. However, Grignard **11**, sterically similar to **3b**, gave no reduction of **6**. Thus it seems that the β-hydrogen transfer from a carbon bearing a Me_3Si group is especially favorable.

(1) This transformation via the Wittig reagent I[2] has been reported; however, the reagent I reacts in good yield only with aldehydes and cyclohexanone. Fleming, I.; Paterson, I. *Synthesis* **1979**, 446–448. This general transformation is known for arylation: Hall, S. S.; McEnroe, F. J. *J. Org. Chem.* **1975**, *40*, 271–275.



(2) Seyferth, D.; Wursthorn, K. R.; Mammarella, R. E. *J. Org. Chem.* **1977**, *42*, 3104–3106.
(3) Seebach, D.; Kolb, M. *Chem. Ind. (London)* **1974**, 687–692.
(4) (a) Jarvie, A. W. P. *Organomet. Chem. Rev., Sect. A.* **1970**, *6*, 153–207. (b) Chan, T. H. *Acc. Chem. Res.* **1977**, *10*, 442–448.
(5) Other anions β to silicon have been reported. A variety of ketone stabilized β-(trimethylsilyl) anions such as II have been produced by the conjugate addition of Me_3SiLi to enones.[6] Sulfone anion III has been reported[7] as well as ylide I.[2] [β-(Trimethylsilyl)vinyl]lithium (IV) is known.[8]

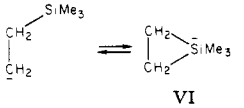


II III IV

(6) Still, W. C. *J. Org. Chem.* **1976**, *41* 3063–3064.
(7) Kocienski, P. J. *Tetrahedron Lett.* **1979**, 2649–2650.
(8) Cunico, R. F.; Clayton, J. F. *J. Org. Chem.* **1976**, *41*, 1480–1482.
(9) β-(Triphenylsilyl)ethyl Grignard V has been studied: (a) Bourne,

$Ph_3SiCH_2CH_2MgBr$
V

A. J.; Rowley, R. J. *J. Org. Chem.* **1972**, *39*, 93–97. (b) Jarvie, A. W. P.; Bourne, A. J.; Rowley, R. J. *J. Organomet. Chem.* **1972**, *39*, 93–97.
(10) Cf. a series of papers on β-substituted organolithium compounds: Barluenga, J.; Fananas, F. J.; Yus, M. *J. Org. Chem.* **1979**, *44*, 4798–4801 and references cited.
(11) The actual structures of **3a** and **3b** are unknown. They are only represented as **3a** and **3b**. Structures such as VI, however, have precedence in silicon and especially tin chemistry: cf. Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1290–1303.



VI

(12) All new compounds reported in this paper possessed spectral data and combustion analysis in accord with their structures.
(13) While this work was in progress a report appeared of a similar dehydration/rearrangement of a large set of γ-(trimethylsilyl) carbinols. These alcohols were made by "classical" methods: Fleming, I.; Patel, S. K. *Tetrahedron Lett.* **1981**, 2321–2324.
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