orientationally nonspecific. The singlet S adds to olefins with high cis stereospecificity, as expected, but also with high regiospecificity for the fused type of cycloadduct (F). We suggest that the cause of the striking and unanticipated regiospecificity is that S has a "bisected" geometry, like that predicted[10–12] for the parent trimethylenemethane. This would produce a low bond order at the developing π bond in the transition state leading to bridged adduct B (Scheme II) but not in that leading to fused adduct F. One might expect a tendency for the regiospecificity to be reversed in reactions of a planar singlet trimethylenemethane (Scheme II).

(10) M. J. S. Dewar and J. S. Wasson, *J. Amer. Chem. Soc.*, **93**, 308 (1971).
(11) W. T. Borden and L. Salem, *J. Amer. Chem. Soc.*, **95**, 932 (1973).
(12) D. R. Yarkony and H. F. Schaefer, III, *J. Amer. Chem. Soc.*, **96**, 3754 (1974).
(13) National Institute of General Medical Sciences Predoctoral Fellow, 1969–1973 (4-F01-GM-46,047-04).

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Regiospecificity in Enolate Reactions with α-Silyl Vinyl Ketones. An Application to Steroid Total Synthesis

Sir:

Recently, α-silylated vinyl ketones have been introduced as useful reagents for annelation reactions under strongly basic conditions.[1] These reagents have also been utilized in conjunction with diorganocuprate reagents in an efficient conjugate addition annelation sequence.[2] The observed successful trapping of the enolate intermediate in organocuprate additions under aprotic conditions, even in situations where rapid equilibration to a more stable enolate (eq 1) is possible, led us to investigate this process further.
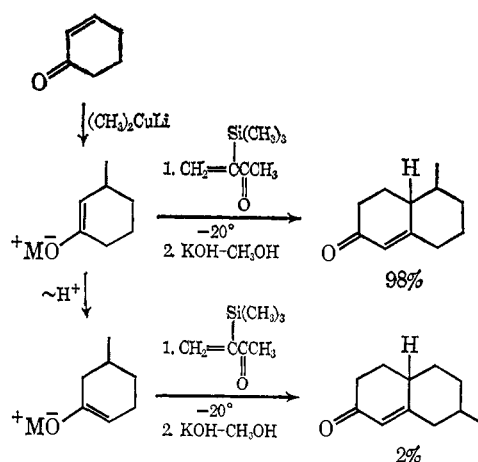
The high regiostability of this enolate intermediate could conceivably result from the incorporation of a copper atom, and we therefore set out to discover whether there was a dependence upon the presence of copper species in the reaction medium. Enol silyl ether **1** was prepared from cyclohexenone by addition

(1) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, **95**, 6152 (1973).
(2) R. K. Boeckman, Jr., *J. Amer. Chem. Soc.*, **95**, 6867 (1973).

of lithium dimethyl cuprate in ether followed by quenching with trimethylsilyl chloride.[3a] The required lithium enolate was regenerated with methyl lithium (1.1 equiv) in ether (2–3 hr at room temperature or 1 hr at reflux). As the results in Table I indicate, reaction of the lithium

Table I

substrate[a]	products[b]	Yield, %[c]
1	99:1	85 (50)
2 + CuI (1 equiv)	75:25	30
3 + CuI + CH₃Li (1 equiv each)	75:25	50
4 + (CuCH₃)ₙ (1 equiv preprepared)	98:2	50
5 (DME)	80:20	64
6 (THF)	95:5	48

[a] Reactions were run in dry ether unless specified otherwise on a 1 mmol scale with a 1:1 molar ratio of silyl ether to α-silylvinyl ketone excepting case 1 which was run with 1.5 equiv of vinyl ketone. The yield with 1 equiv is given in parentheses. [b] Ratio of products determined by vpc (20% Carbowax-20-M, 10 ft at 170°) by comparison with authentic materials; cf. ref 2. [c] Yields of distilled materials.

enolate (1 equiv) with α-trimethylsilyl methyl vinyl ketone (1.5 equiv) at $-78°$ (initially) produced regiospecifically, the desired octalone in 85% yield.[4] The addition of CuI (1 equiv) in order to produce cuprous enolate (**2**), prior to the addition of silyl vinyl ketone, reduced the reactivity markedly and had a somewhat detrimental effect upon the regioselectivity. Further addition of an equivalent of methyl lithium to the cuprous enolate to produce a proposed "ate" enolate species (**3**) had no significant effect nor did the addition of independently prepared methyl copper (1 equiv). While these experiments do not rule out the intermediacy of a "copper" enolate, they indicate that the "copper" enolate is operationally indistinguishable in this case from a simple lithium enolate.
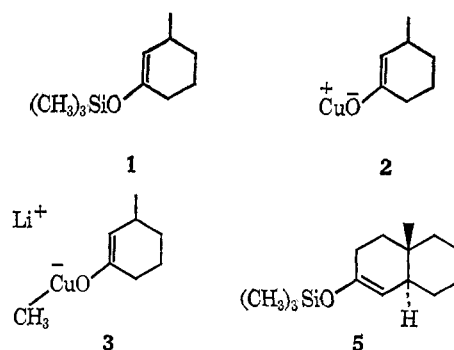
We have made the observation that the partial loss of regiospecificity[1,3a] may be eliminated by changing the solvent from 1,2-dimethoxyethane (DME)

(3) (a) B. Ganem, Ph.D. Thesis, Columbia University, 1972. (b) The results reported by Professor Stork and his coworker in the accompanying communication indicate that this conclusion may not be entirely valid (G. Stork and J. Singh, *J. Amer. Chem. Soc.*, **96**, 6181 (1974)). Traces of protic impurities may be the cause of the observed partial equilibration in our experiments. However, we find that DME seems to offer no particular advantage over ether, and parenthetically, ether is easier to prepare and keep anhydrous. We thank Professor Stork for making his results available to us prior to publication.
(4) Distilled yield and identified by comparison with authentic material (cf. ref 2).

to ether. The results indicate that the preferred solvent for these reactions is ether. As more ionizing solvents are utilized (*e.g.*, DME and THF), the effective basicity of the enolate increases sufficiently to promote some proton transfer between the enolate and annelating agent or product ketone leading to partial equilibration.[3b]
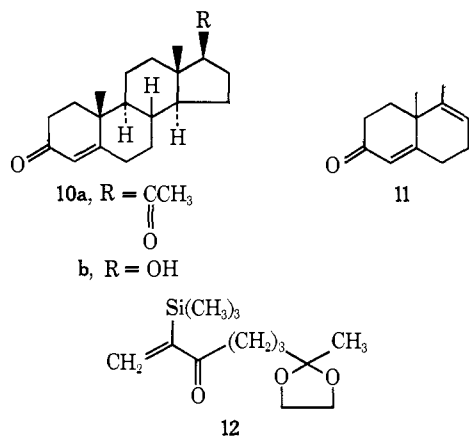
As a further test, enol silyl ether (5) derived from 10-methyl-$\Delta^{1,9}$-octal-2-one (6)[3] was treated similarly to afford tricyclic enone (7) (mp 124–126°) in 69% yield.[5] Less than 5% of the isomeric linear tricyclic was observed.[6] The enolate derived from 5 is particularly sensitive to equilibration due to the steric inhibition of reactions of C-1 by the angular methyl group and the considerably higher stability of the isomeric $\Delta^{2,3}$ enolate.[7] This result has important implications for steroid total synthesis, since it allows for the first time direct functionalization of C-1 in a C/D ring precursor with a vinyl ketone derivative.

Direct generation of the lithium enolate *via* reduction of an α,β-unsaturated ketone is also feasible, although the result is slightly lowered overall yields. Reduction

6   7   8   9
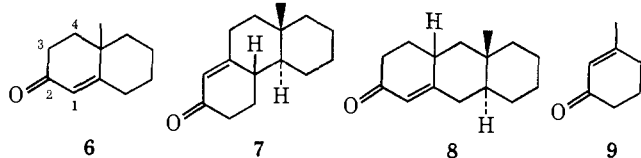
of unsaturated ketones 6 and 9 with lithium in liquid ammonia, exchange of the solvent for ether, addition of the annelating agent, and work-up as before affords ketones 4 and 7 in ~50–60% yield in each case.[8]

To demonstrate the utility of the above procedure for steroid total synthesis, we have employed this transformation to complete the efficient total synthesis of intermediates convertible to *dl*-progesterone (10a) and *dl*-testosterone (10b).

10a, R = CCH₃
       ‖
       O
b, R = OH

11

12

Dienone 11[9] (nmr (δ): 1.68, d, J = 2 Hz (3 H); 1.35, s (3 H)) was reduced (lithium–ammonia) and the

resulting enolate treated with α-silylated vinyl ketone 12[1,10] (−78 → −20°, 2 hr) in ether. Subsequent treatment with aqueous methanolic potassium hydroxide afforded as the only annelated product 13 (nmr (δ): 1.60, d, J = 2 Hz (3 H); 1.27, s (3 H); 1.08, s (3 H)) in a 51% yield. No equilibrated material was detected during purification of 13 by chromatography. Enone 13 was further reductively alkylated (lithium–ammonia; excess methyl iodide) producing 14 (nmr (δ): 1.60, d, J = 2 Hz (3 H); 1.28 s (3 H); 1.03 s (3 H), 1.00 s (3 H)) in 67% yield.[11] Exposure of 14 to aqueous acid (10% hydrochloric acid–acetone) then hot methanolic potassium hydroxide resulted in the isolation of 15 (mp 141–

13   14

15
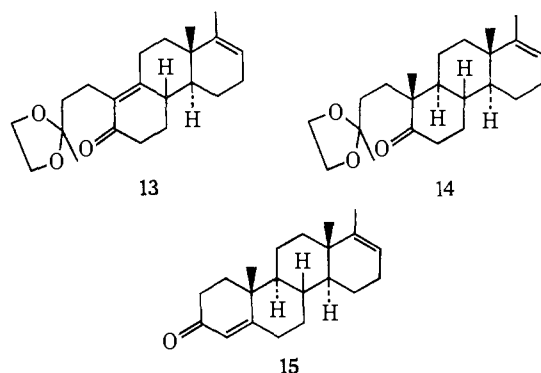
143°) in ~80% yield. Mixture melting point, spectral, and tlc comparison with authentic *dl*-15[5] established the regiospecificity of the reductive annelation. Since 15 has been transformed into *dl*-progesterone (10a) in three steps,[11] this constitutes a formal total synthesis of the latter substance. In the same manner, beginning with enone 16,[12] enone 17 (nmr: 1.34, s (3 H), 1.00, s (3 H)) and ketone 18 (nmr: 1.34, s (3 H), 1.08, s (3 H), 0.90, s (3 H)) were produced in 50 and 75% yield, respectively. Removal of the protecting groups and cyclization as before afforded *dl*-D-homotestosterone (19) (mp 155–158°).[11] *dl*-D-homotestosterone

OTHP

16   17

OTHP   OH

18   19

has been converted to *dl*-testosterone (10b) in five steps, utilizing procedures in the literature.[13,14]

(5) Thanks are due Professor Gilbert Stork for authentic samples of 7, 8, and 15.

(6) Authentic mixtures of 7 and 8 were prepared and ~5% of 8 was detectable by nmr.

(7) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 87, 275 (1965).
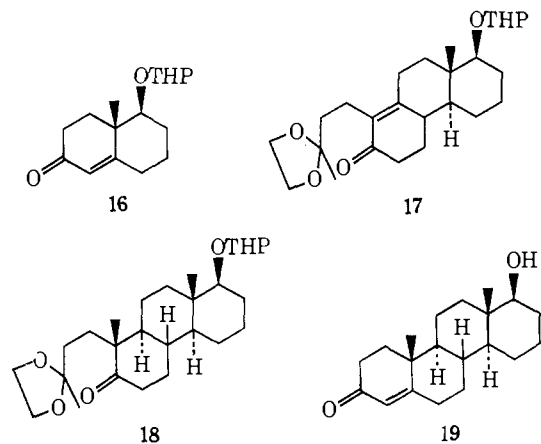
(8) In the case of 6, some unreacted unsaturated ketone was recovered (~20%) plus a small amount of reduced but unalkylated ketone.

(9) Prepared from 10-methyl-$\Delta^{1,9}$-octalin-2,5-dione by successive treatment with pyrrolidine (1 equiv) in benzene, methyllithium (3 equiv) in ether at 0°, hydrolysis (sodium acetate–acetic acid–methanol), and dehydration (thionyl chloride–pyridine–ether at 0°). A minor amount of the exo double bond isomer was also produced.

(10) Prepared by addition of the Grignard reagent from α-bromovinyltrimethylsilane in tetrahydrofuran to 5-ethylenedioxyhexanal, followed by careful Jones' oxidation at 0° in ether.

(11) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, 89, 5464 (1967).

(12) Prepared by reduction of 1-methyl-$\Delta^{1,9}$-octalin-2,5-dione (sodium borohydride–ethanol) followed by conversion to the tetrahydropyranyl ether; *cf.* T. A. Spencer, *et al.*, *J. Org. Chem.*, 33, 712 (1968).

(13) W. S. Johnson, B. Bannister, and R. Pappo, *J. Amer. Chem. Soc.*, 78, 6331 (1956).

(14) W. S. Johnson, B. Bannister, R. Pappo, and J. E. Pike, *J. Amer. Chem. Soc.*, 78, 6354 (1956).

We have demonstrated in this report that (1) α-silylated vinyl ketones successfully trap even readily equilibrated lithium enolates under aprotic conditions; (2) the presence of copper is not required to account for the observed results, the "copper" enolate being indistinguishable in this case from the lithium enolate; and (3) an efficient synthesis of steroids is possible utilizing the reductive annelation procedure. This procedure seems to be amenable to large scale application bound by the costs of the silicon reagents, and the need to shrink ring D to obtain steroids of the natural series.

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Regiospecific Michael Reactions in Aprotic Solvents with α-Silylated Electrophilic Olefins. Application to Annelation Reactions

Sir:

The discovery that lithium enolates of asymmetric ketones can be generated regiospecifically[1,2] coupled with the original demonstration that such *lithium* enolates could be alkylated and carboxylated (*cf.* 1 → 2, 3)

1

2, R = CH₃
3, R = CO₂H
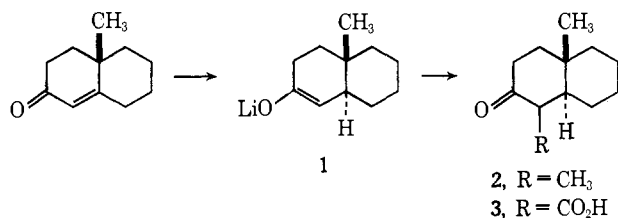
more rapidly than they undergo equilibration *via* proton transfers[1] greatly extended the synthetic possibilities for the construction of complex structures.

Our original work was confined (if one excepts the carboxylation reactions) to the use of reactive alkyl halides[3] and it became increasingly evident that important progress would result if regiospecifically generated lithium enolates could be used in two of the other fundamental processes for forming carbon–carbon bonds, the aldol and the Michael reactions. We deal elsewhere with the regiospecific aldol condensation[4] and wish to report here on the regiospecific Michael reaction with lithium enolates.

We have recently taken the first step in the solution of this problem with the demonstration that α-trialkylsilyl vinyl ketones such as 4 can be condensed with some regiospecifically generated lithium enolates in aprotic solvents (*e.g.*, 5 → 6)[5]

(1) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem, Soc.*, 83, 2965 (1961).
(2) G. Stork, P. Rosen, N. L. Goldman, R. V. Coombs, and J. Tsuji, *J. Amer. Chem. Soc.*, 87, 275 (1965).
(3) For applications to reactive, functionally substituted halides, *cf.*, *inter alia*, G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, 89, 5459 (1967); G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Labovitz, *J. Amer. Chem. Soc.*, 93, 4945 (1971); G. Stork and M. Jung, *J. Amer. Chem. Soc.*, 96, 3682 (1974).
(4) (a) G. Stork and J. D'Angelo, in preparation; (b) G. Stork and G. Kraus, in preparation.

4   5

6
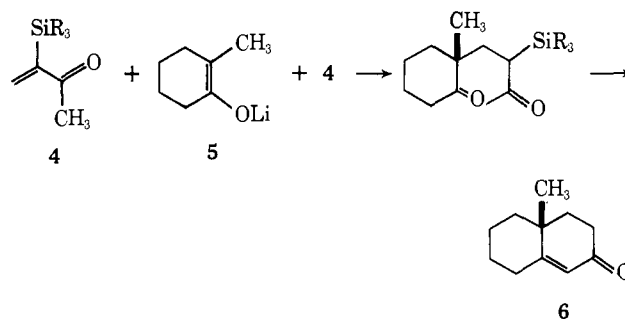
We initially considered, as did Boeckman,[6] that the enolate equilibration we had encountered, might be suppressed by making the enolate metal bond less easily dissociated. We were indeed successful with diethyl aluminum enolates (from addition of one equivalent of diethylaluminum chloride to the lithium enolate) but eventually realized that with careful attention to details[7] the original procedure[5] is in fact applicable and leads in high yield to regiospecific Michael reactions. Because of the importance of the reaction we report it here in detail.

The most general procedure involves trapping of a regiospecifically generated enolate (*e.g.*, from lithium–ammonia reduction in the presence of 0.8 equiv of *tert*-butyl alcohol) with trimethylchlorosilane, and regenerating the lithium enolate from the isolated enol silyl ether.[8] This procedure has the advantage that the silyl ether can be examined spectrally, to establish its structural homogeneity, before proceeding with the Michael reaction. We illustrate this for the annelation of 1 to 8.[9]

1

7

8
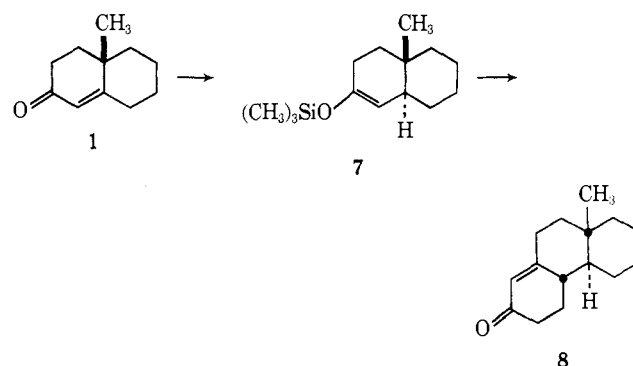
To a solution of 3 g-atoms lithium in dry, distilled liquid ammonia was added dropwise a solution of 1 equiv of enone 1 in tetrahydrofuran (4 ml/mmol) containing 0.8 equiv of *tert*-butyl alcohol. Excess lithium was destroyed after 5 more minutes with isoprene. Removal of the ammonia, finally under oil pump vacuum at ~40° for *ca.* 10 min, gave a residual white

(5) G. Stork and B. Ganem, *J. Amer. Chem. Soc.*, 95, 6152 (1973).
(6) We now believe that earlier difficulties were due to the adventitious presence of traces of protic impurities in the medium. The glyme used in the present experiments was distilled from fresh lithium aluminum hydride and great care was used to prevent access of moisture to the system at all times.
(7) Professor R. K. Boekman, Jr. (*J. Amer. Chem. Soc.*, 96, 6179 (1974)) reports, his successful, independent, efforts to ensure regiospecificity in annelation with the silyl vinyl ketone reagents. We thank him for communicating his results to us in advance of publication.
(8) G. Stork and P. F. Hudrlik, *J. Amer. Chem. Soc.*, 90, 4462, 4464 (1968).
(9) All operations were conducted under nitrogen. Base-catalyzed cyclizations were carried out in deoxygenated media.