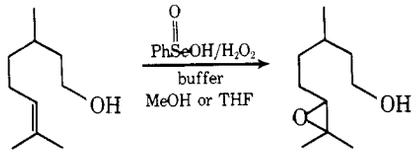
drogen peroxide in tetrahydrofuran buffered at pH 7 revealed on TLC analysis after ~20 min the complete conversion of starting olefin to the desired epoxide **9**. NMR analysis of the



8 **9**

crude product after workup revealed that >90% of the starting olefin remained. If, however, after initial mixing of reagents (~20 min) one pours the reaction contents onto a silica gel plate (for convenience) and elutes after ~60 min, an 85% yield of pure epoxide **9** can be realized. In buffered methanol solution using 1.2 equiv of benzeneseleninic acid and 1.2 equiv of 50% hydrogen peroxide citronellol gave, using the same silica gel treatment, a 75% isolated yield of pure epoxide.

The stereoselectivity observed in the epoxidation of olefinic alcohols with benzeneperoxyseleninic acid complements that observed in the transition metal catalyzed epoxidations of olefinic alcohols by *tert*-butyl hydroperoxide.[11] Geraniol and linalool are selectively oxidized in the presence of vanadium or molybdenum catalysts by alkyl hydroperoxides to 2,3-epoxygeraniol and 1,2-epoxylinalool, respectively. In contrast, linalool and geraniol were epoxidized with benzeneperoxyseleninic acid predominantly at the olefin furthest removed from the hydroxyl group (see Table I).[12]

The following experimental procedure indicates the simplicity of the method. A solution of benzeneseleninic acid (454 mg, 2.4 mmol) in 4 mL of methanol was treated with 160 μL (2.4 mmol) of 50% hydrogen peroxide. After ~5 min, 1.5 mL of phosphate buffer (pH 7) was added followed by the addition of citronellol (312 mg, 2.0 mmol) in 2 mL of methanol. The reaction was quenched after 20 min with 20 g of silica gel. After 60 min the silica gel was washed with a 1:1 mixture of ether and hexane leaving 302 mg of crude product. Purification on 15 g of silica gel gave 264 mg (75%) of pure epoxide (**9**) as a colorless liquid.

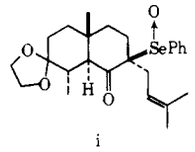
In summary, benzeneperoxyseleninic acid represents a new reagent for the facile, rapid, high yield conversion of substituted olefins into epoxides. The syn-directive effect observed in both the peracid and the transition metal/hydroperoxide epoxidation of allylic alcohols does not appear to play a major role in epoxidation with benzeneperoxyseleninic acid.

Acknowledgment. We thank the National Institutes of Health (CA 13689-05), Glidden Organics, and Shell Development Co. for support of this research. We thank Mr. George Majetich for providing us with a sample of 10-hydroxymethyl-$\Delta^{1,9}$-octalin.

References and Notes

(1) For the use of α-phenylseleno carbonyl compounds as precursors to α,β-unsaturated ketones and esters, see H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973).

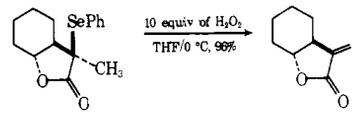
(2) During the elimination of benzeneselenenic acid from selenoxide i in the



i

presence of excess hydrogen peroxide we have observed epoxidation of the prenyl double bond.

(3) We have previously demonstrated [P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974)] that α-methyl-α-phenylselenolactones undergo



ii iii

oxidation with excess hydrogen peroxide providing after elimination of benzeneselenenic acid near-quantitative yields of α-methylene lactones (cf. ii → iii).

(4) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

(5) $PhSeO_3H$ has been proposed as the active reagent in hydrogen peroxide oxidations of divalent selenium compounds.[6b]

(6) (a) K. B. Sharpless and K. M. Gordon, R. F. Lauer, D. W. Patrick, S. P. Singer, and M. W. Young, *Chem. Scr.*, **8A**, 9 (1975); (b) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975); (c) D. L. Klayman and W. H. H. Gunther, "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973.

(7) Hydrogen peroxide in the presence of selenium dioxide has been reported to hydroxylate olefins [N. Sonoda and S. Tsutsumi, *Bull. Soc. Chem. Jpn.*, **38**, 958 (1965)].

(8) J. D. McCullough and E. S. Gould, *J. Am. Chem. Soc.*, **71**, 674 (1949).

(9) Use of diphenyl diselenide in place of benzeneseleninic acid during epoxidation of citronellol in tetrahydrofuran with excess hydrogen peroxide gave a 69% yield of epoxide **9**.

(10) The epoxidation reaction appears to be catalytic with respect to benzeneseleninic acid; however, the reaction requires very long reaction times during which diol formation predominates.

(11) K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).

(12) Epoxidation of geraniol and linalool with standard peracids (e.g., *m*-chloroperbenzoic acid) results in poor selectivity.

(13) Fellow of the Alfred P. Sloan Foundation.

Paul A. Grieco,*[13] Yuusaku Yokoyama
Sydney Gilman, Mugio Nishizawa
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

Received February 8, 1977

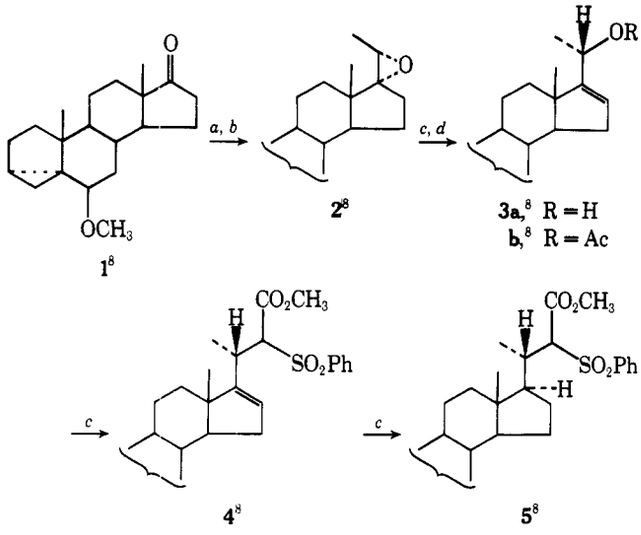
Stereocontrolled Synthesis of the Ecdysone Side Chain via Organopalladium Chemistry

Summary: Two stereocontrolled syntheses of (22*R*)-25-dihydroxycholesterol and one of the 22*S* isomer from 6β-methoxy-3,5-cycloandrostan-17-one are reported.

Sir: The ability to introduce a cholesterol-type side chain with stereochemical control continues as a major challenge that has been heightened by the importance of natural products containing modified side chains.[1-5] Most noteworthy are the hydroxylated side chains that appear in the ecdysones[2,3] and the metabolites of vitamin D.[4,5] We wish to report the stereocontrolled synthesis of (22*R*)-25- and (22*S*)-25-dihydroxycholesterol which, by known procedures,[3] could be converted into the insect molting hormones. This approach demonstrates the use of the palladium-based alkylations for control of acyclic stereochemistry,[6] the versatility of the α-sulfonyl esters, and the introduction of a vinyl group at an allylic carbon with control of stereochemistry at that carbon.

The key intermediate is the sulfone ester 4 available from 6β-methoxy-3,5-cycloandrostan-17-one (**1**),[7,8] mp 65–66 °C, as outlined in Scheme I. Condensations with ethylidenetriphenylphosphorane followed by epoxidation gave **2**,[8] mp 97–98 °C. Treatment with 10 equiv of lithium diisopropylamide in 4:1 hexane–DME initially at −78 °C and subsequently warming to room temperature gave in 77% isolated yield the desired allylic alcohol **3a**, oil, $[\alpha]^{25}_D$ +38.4° ($CHCl_3$, *c* 0.742).[9] Addition of a solution of methyl phenylsulfonylsodioacetate in THF to a solution of **3b**[8] and 9 mol % tetrakis(triphenylphosphine)palladium in THF at room temperature and subsequent reflux led to an 85% yield of **4**,[8] mp 166–167

Scheme I. Preparation of Sulfone Ester 5



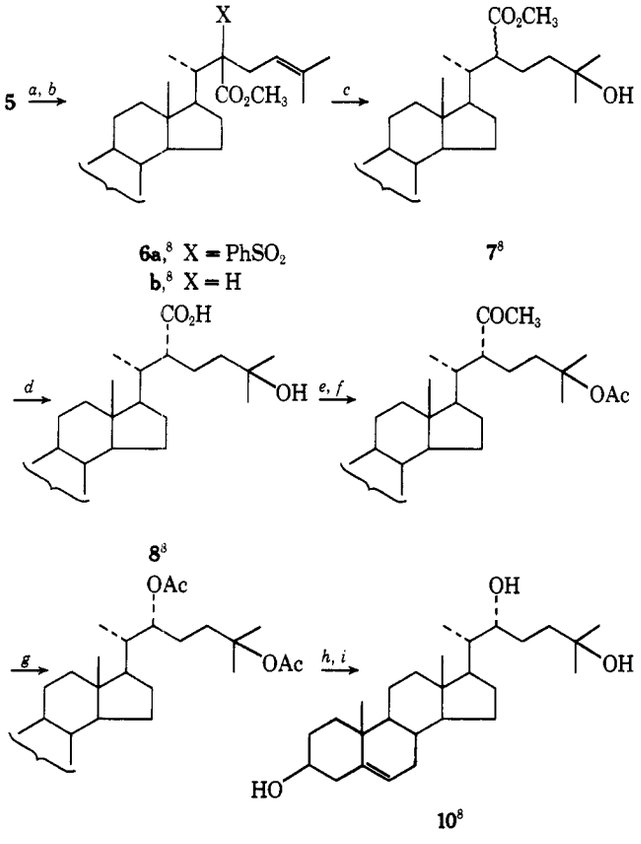
1[8] 2[8] 3a,[8] R = H; b,[8] R = Ac 4[8] 5[8]

[a] $Ph_3P^+CH_2CH_3$, Br^-, KOC_4H_9-*t*, THF, reflux, 76%. [b] MCPBA, $CHCl_3$, −10 °C, 74%. [c] See text. [d] Ac_2O, pyridine, room temperature, 97%.

°C, presumably as a diasteromeric mixture at C(22) but a single stereochemistry at C(20) (vide infra). Hydrogenation over 5% Pd–$BaCO_3$ gave **5**,[8] mp 180–183 °C, quantitatively.

In the first conversion of **5** to the desired dihydroxy compound (see Scheme II), alkylation to **6a**[8] gave an isomeric mixture at C(22) which could be separated.[10] However, separation of isomers is unnecessary and undesired. Hydration of the double bond introduced the 25-hydroxyl group (i.e., **7**). The key step in this sequence is the base-catalyzed hydrolysis of the hydroxy ester [isomeric at C(22)] which leads to a single hydroxy acid **8**.[8] Assignment as **8** was established by reesterification with diazomethane back to one epimer of **7**.[8] Each epimer of **7** had, in turn, been correlated with the known (22*R*)- and (22*S*)-hydroxycholesterols. Thus, the configuration at C(22) is *R* and that at C(20) is confirmed as *S* as depicted. That epimerization at C(22) involved participation of the hydroxy group at C(25) via the lactones **9a** and **9b** was

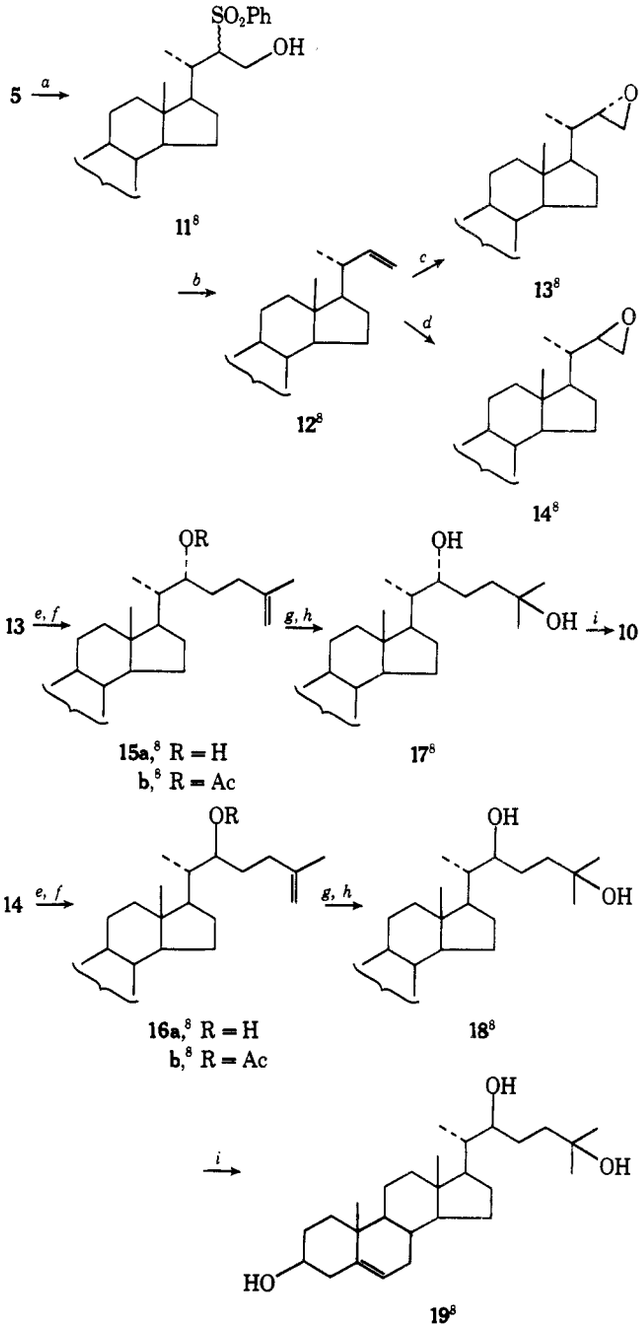
Scheme II. Preparation of (22*R*)-25-Dihydroxycholesterol



6a,[8] X = $PhSO_2$; b,[8] X = H 7[8] 8[8] 10[8]

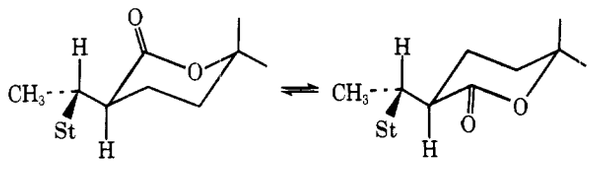
[a] NaH, PhH, DMF, γ,γ-dimethylallyl bromide, room temperature, 80%. [b] 6% Na(Hg), CH_3OH, Na_2HPO_4, −10 °C. [c] $Hg(OAc)_2$, THF, CH_3CN, H_2O, room temperature, 71%. [d] NaOH, CH_3OH, reflux, 96%. [e] CH_3Li, ether, −10 °C, 53%. [f] 4-$(CH_3)_2NC_5H_4N$, Ac_2O, $CHCl_3$, room temperature, 66%. [g] MCPBA, $CHCl_3$, $NaHCO_3$, room temperature, 34%. [h] $LiAlH_4$, ether, room temperature, 93%. [i] TsOH, H_2O, DME, reflux, 81%.

Scheme III. Preparation of (22*R*)-25- and (22*S*)-25-Dihydroxycholesterol



11[8] 12[8] 13[8] 14[8] 15a,[8] R = H; b,[8] R = Ac 17[8] 16a,[8] R = H; b,[8] R = Ac 18[8] 19[8]

[a] $LiAlH_4$, ether, room temperature, 94%. [b] 6% Na(Hg), CH_3OH, room temperature, 77%. [c] I_2, AgOAc, CH_2Cl_2, $NaHCO_3$, −10 °C, then CH_3OH, K_2CO_3, reflux, 83%. [d] MCPBA, $CHCl_3$, $NaHCO_3$, −20 °C, 79%. [e] See text. [f] Ac_2O, C_5H_5N, reflux, 93–100%. [g] See *d*, 65–66%. [h] See *a*, 87–98%. [i] TsOH, DME, H_2O, reflux, 81–96%.



9a 9b

St = steroid nucleus

supported by the complete absence of epimerization upon hydrolysis of the epimerially pure unsaturated esters **6b**. Since the *A* value of an ethyl group (1.75) is larger than that for a carboalkoxy group (~1-1.2),[11] **8b** would be expected to be the more stable isomer as observed. Conversion of the carboxy group to an hydroxy group employed the Baeyer–Villiger procedure and allowed obtention of the pure (22*R*)-25-dihydroxycholesterol,[8] mp 253–255 °C, which, owing to its insolubility, was further characterized as its 3,22-diacetate,[8] mp 150 °C, $[\alpha]^{25}_D$ −25.5° ($CHCl_3$, *c* 0.51).

Scheme III outlines a synthesis of both the 22*R* and 22*S* isomers and demonstrates the use of the sulfone ester in synthesis. Conversion of this group to a terminal vinyl group [**12**,[8] mp 39–40 °C, $[\alpha]^{25}_D$ +36.2° ($CHCl_3$, *c* 1.190)] proceeded smoothly via the hydroxy sulfone **11**[8] (mp 98–103 °C) by direct reductive elimination.[12] Formation of the epoxide via the iodohydrin[13] gave **13**[8] (mp 90–91 °C) contaminated by a small amount of **14**, whereas, direct epoxidation with MCPBA gave predominantly **14**,[8] mp 119–120 °C.[14] Coupling of each epoxide with methallylmagnesium chloride in THF at room temperature (93%), acetylation, epoxidation, and reduction completed the synthesis of each epimerically pure 6β-methoxy-22,25-dihydroxy-3,5-cyclocholesterol. **17**[8]: foam; $[\alpha]^{25}_D$ +46.4° ($CHCl_3$, *c* 0.86); NMR δ 1.32 (s, 6 H), 1.05 (s, 3 H), 0.96 (d, *J* = 7 Hz, 3 H), 0.77 (s, 3 H). **18**:[8] mp 111–113 °C; $[\alpha]^{25}_D$ +30.3° ($CHCl_3$, *c* 0.93); NMR δ 1.25 (s, 6 H), 1.04 (s, 3 H), 0.92 (d, *J* = 7 Hz, 3 H), 0.74 (s, 3 H). Solvolytic cyclopropyl ring opening of **17** produced (22*R*)-25-dihydroxycholesterol (**10**) identical with the previously prepared sample. Identical treatment of **18** produced the corresponding 22*S* isomer **19**,[8] mp 186–187 °C, $[\alpha]^{25}_D$ −34.4° (methanol, *c* 0.72).

Since the cholesterol nucleus has been converted to the ecdysone nucleus,[3] these intermediates can serve as precursors to the commercially important ecdysones. Furthermore, the nature of the side-chain substitution provides great flexibility for the synthesis of many other important side-chain modified steroids. More generally, this strategy can be envisioned as an approach to attach an acylic side chain in a stereocontrolled fashion onto a ring system.

Acknowledgment. We wish to thank the National Institutes of Health, the National Science Foundation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of our programs. We express our deep gratitude to Roussel-Uclaf for a generous gift of 3β-hydroxyandrost-5-en-17-one.

References and Notes

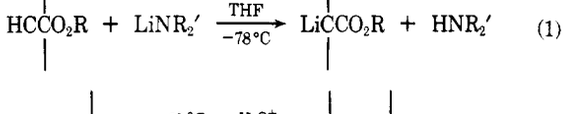
(1) For some recent work in this area, see N. K. Chaudhuri, R. Nickolson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767, 3759 (1969); E. E. van Tamelen and R. J. Anderson, *J. Am. Chem. Soc.*, **94**, 8225 (1972); Y. M. Shiekh and C. Djerassi, *J. Org. Chem.*, **38**, 3545 (1973); J. Wicha and K. Bal, *Chem. Commun.*, 968 (1975); J. P. Schmit, M. Piraux, and J. F. Pilette, *J. Org. Chem.*, **40**, 1586 (1975); T. C. McMorris and S. R. Schow, *J. Org. Chem.*, **41**, 3759 (1976). For a conflict, see W. R. Nes, T. E. Varkey, and K. Krevitz, *J. Am. Chem. Soc.*, **99**, 260 (1977).
(2) K. Nakanishi, *Pure Appl. Chem.*, **25**, 167 (1971); H. Hikino and Y. Hikino, *Fortschr. Chem. Org. Naturst.*, **28**, 256 (1970).
(3) J. B. Siddall, J. P. Marshall, A. Bowers, A. D. Cross, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, **88**, 379 (1966); J. B. Siddall, A. D. Cross, and J. H. Fried, *ibid.*, **88**, 862 (1966); A. Furlenmeier, A. Fürst, A. Langemann, G. Waldvogel, P. Hocks, U. Kerb, and R. Wiechert, *Helv. Chem. Acta*, **50**, 2387 (1967); H. Mori, K. Shibata, K. Tsuneda, and M. Sawai, *Tetrahedron*, **27**, 1157 (1971); D. H. R. Barton, P. G. Feakins, J. P. Poyser, and P. G. Sammes, *J. Chem. Soc. C*, 1584 (1970); E. Lee, Y.-T. Liu, P. H. Solomon, and K. Nakanishi, *J. Am. Chem. Soc.*, **98**, 1634 (1976).
(4) M. F. Holick and H. F. DeLuca, *Ann. Rev. Med.*, **25**, 349 (1974); *Adv. Steroid Biochem. Pharmacol.*, **4**, 111 (1974).
(5) I. J. Bolton, R. G. Harrison, and B. Lythgoe, *J. Chem. Soc. C*, 2950 (1971); J. J. Partridge, V. Toome, and M. R. Uskoković, *J. Am. Chem. Soc.*, **98**, 3739 (1976).
(6) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, **98**, 630 (1976).
(7) Cf. P. Lenkowski, *Rocz. Chem.*, **35**, 1323 (1961); J. J. Partridge, S. Faber, and M. R. Uskoković, *Helv. Chim. Acta*, **57**, 764 (1974).
(8) Spectroscopic data and elemental composition in full accord with the assigned structure have been obtained.
(9) 6β-Methoxy-17α-hydroxy-17β-vinyl-3,5-cycloandrostane is obtained as a by-product whose amount varies with the choice of lithium dialkylamide.
(10) Correlation of each epimer of **6b** to (22*R*)- and (22*S*)-hydroxycholesterol allowed determination of configuration at C(22). See E. P. Burrows, G. M. Hornby, and E. Caspi, *J. Org. Chem.*, **34**, 103 (1969); T. A. Wittstruck, *ibid.*, **38**, 1426 (1973). Full details of this correlation will be published in our full account.
(11) J. A. Hirsch, *Top. Stereochem.*, **1**, 199 (1967).
(12) M. Julia and J. M. Paris, *Tetrahedron Lett.*, 4833 (1973).
(13) Cf. J. P. Poyser, F. R. Hirtzbach, and G. Ourisson, *Tetrahedron*, **30**, 977 (1974); D. H. R. Barton, J. P. Poyser, and P. G. sammes, *J. Chem. Soc., Perkin Trans. 1*, 53 (1972). Also see M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro, and L. Mangoni, *Tetrahedron Lett.*, 3661 (1976).
(14) Confirmation of the stereochemical assignment was obtained by hydrogenation of **15a** and **16a**, respectively, and subsequent solvolytic opening of the cyclopropyl ether to (22*R*)- and (22*S*)-hydroxycholesterol. See ref 9.

Barry M. Trost*, Yoshihiro Matsumura
Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706
Received February 22, 1977

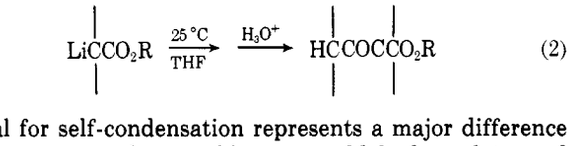
The Self-Condensation Reaction of Lithium Ester Enolates. Isolation of a Ketene Intermediate

Summary: Warming a tetrahydrofuran solution of lithio *tert*-butyl bis(trimethylsilyl)acetate to 25 °C produces bis(trimethylsilyl)ketene.

Sir: Solutions of ester enolates prepared by addition of esters to lithium amide bases in tetrahydrofuran (THF) are stable indefinitely at −78 °C[1] (eq 1). However, such solutions normally turn yellow upon warming to room temperature and quenching produces β-keto esters (eq 2).[2] This inherent po-



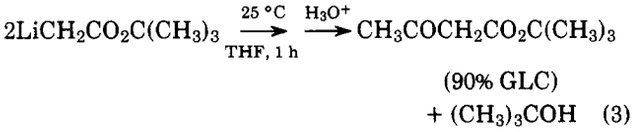
(1)



(2)

tential for self-condensation represents a major difference between ester enolates and ketone or aldehyde enolates and is perhaps a primary reason for the relatively late development of the chemistry of the aliphatic ester enolates.

A simple mechanism for the formation of condensation products is reversal of eq 1 to give small amounts of starting ester which then condenses with ester enolate. However, solutions of lithio *tert*-butyl acetate, which are prepared free of amine,[2a] nevertheless form condensation products at room temperature (eq 3).



(90% GLC)
+ $(CH_3)_3COH$ (3)