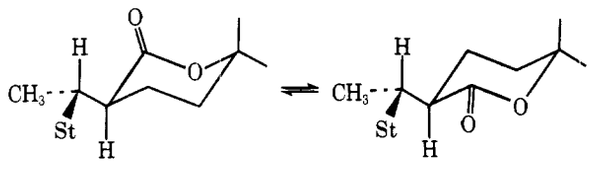

9a 9b

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.

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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.

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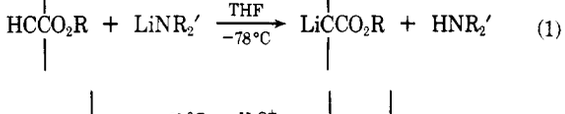
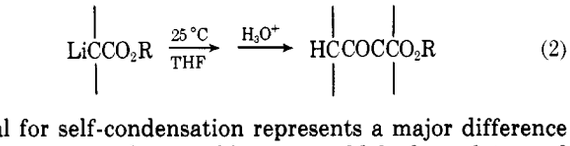
The Self-Condensation Reaction of Lithium Ester Enolates. Isolation of a Ketene Intermediate

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-



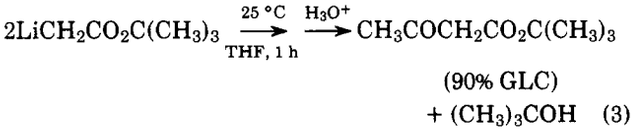
(1)



(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)

Similar condensations have been observed with zinc ester enolates (Reformatsky reagents).[3] Vaughan suggested a ketene intermediate for the self-condensation of the reagent prepared from ethyl α-bromoisobutyrate and zinc metal as shown in eq 4.[4]

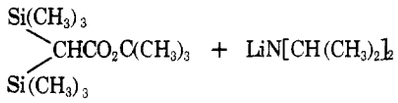
$$BrZnC(CH_3)_2CO_2C_2H_5 \rightarrow (CH_3)_2C{=}C{=}O + BrZnOC_2H_5 \quad (4)$$

$$(CH_3)_2C{=}C{=}O + BrZnC(CH_3)_2CO_2C_2H_5 \xrightarrow{H_3O^+} (CH_3)_2CHCOC(CH_3)_2CO_2C_2H_5 \quad (5)$$

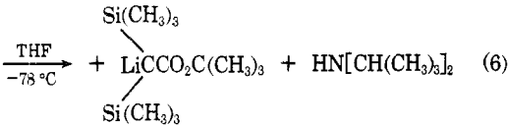
Ketene intermediates have also been proposed for the E_1CB mechanism of hydrolysis of malonic and β-keto esters.[5,6]

We report here what is to our knowledge the first isolation of a ketene from the decomposition of an ester enolate.

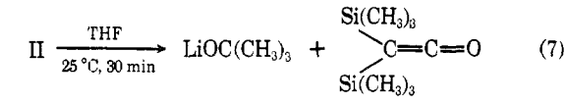
Addition of *tert*-butyl bis(trimethylsilyl)acetate, I, to an equivalent amount of lithium diisopropylamide gave the corresponding ester enolate, II (eq 6).[7] Warming solutions of



I



II to room temperature did not produce the usual yellow color indicative of ester condensation. Instead, the solution remained colorless and GLC analysis showed the presence of a single product, identified as bis(trimethylsilyl)ketene, III (eq 7). Vacuum distillation of the reaction mixture gave pure samples of III [60%, bp 20 °C (2 mm)].

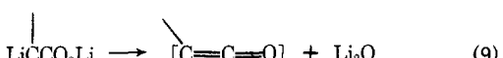


III (85%, GLC)

Bis(trimethylsilyl)ketene has previously been obtained as a side product of a Grignard synthesis of trimethylsilyl butoxyacetylene.[8] The present assignment of structure rests on a comparison of IR bands [2085, 1295 cm^{-1} (lit.[8] 2085, 1295 cm^{-1})], the ^1H NMR spectrum (CCl_4) δ 0.25(s), and ethanolysis with acidic ethanol to give ethyl bis(trimethylsilyl)acetate.[9]

The ability to isolate ketene rather than condensation product in the present case is clearly due to the steric hindrance to further reaction presented by the bulky trimethylsilyl groupings in III.[10] We are now attempting to obtain evidence for the formation of ketene intermediates in the self-condensation of simple aliphatic lithium ester enolates. We note that a ketene mechanism provides a simple explanation for the much greater stability (compared to lithium ester enolates) reported for the enolates of *N,N*-dialkylamides[11] and lithium carboxylates,[12] both of which have exceptionally poor leaving groups (eq 8, 9).

(8)



(9)

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References and Notes

(1) M. W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).
(2) (a) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973); (b) L. Lochmann and D. Lim, *J. Organometal. Chem.*, **50**, 9 (1973).
(3) R. L. Shriner, *Org. React.*, **1**, 1 (1942).
(4) W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965).
(5) (a) W. A. Remero, R. H. Roth, and M. J. Weiss, *J. Org. Chem.*, **30**, 2910 (1965); (b) B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, **91**, 2993 (1969); (c) R. F. Pratt and T. C. Bruice, *ibid.*, **92**, 5956 (1970); (d) J. Rebek, D. Brown, and S. Zimmerman, *ibid.*, **97**, 454 (1975).
(6) The lithium enolate of a 1,3-oxazine was reported to form a ketenimine on warming to 0–25 °C: A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973).
(7) S. L. Hartzell and M. W. Rathke, *Tetrahedron Lett.*, **32**, 2737 (1976).
(8) L. L. Shchukovskaya, A. I. Koltsov, A. N. Lazarev, and R. I. Palchick, *Dokl. Akad. Nauk, SSSR*, **179**, 892 (1968).
(9) ^1H NMR spectrum (CCl_4): δ 0.23 (s, 18 H), 1.3 (t, 3 H), 1.6 (s, 1 H), 4.1 (q, 2 H).
(10) For example, III appears to be inert to the methyl Grignard reagent and reacts only sluggishly with *n*-butyllithium at 25 °C.
(11) For example, THF solutions of α-lithio-*N,N*-dimethylacetamide are stable for several days at 25 °C: R. P. Woodbury and M. W. Rathke, *J. Org. Chem.*, in press.
(12) (a) D. O. DuPree and R. D. Closson, *J. Am. Chem. Soc.*, **80**, 2311 (1958); (b) P. L. Creger, *ibid.*, **92**, 1396 (1970).

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Oxazoles in Organic Chemistry. Synthesis of the Antitumor Agent Ellipticine

Summary: An efficient total synthesis of the alkaloid ellipticine through the intermediacy of a substituted oxazole has been achieved. The versatility of this intermediate for the preparation of peripherally modified analogues is emphasized.

Sir: The chemistry of oxazoles was first seriously investigated when the antibiotic penicillin was believed to contain this heterocyclic moiety.[1] More recently, the Diels–Alder reaction of substituted oxazoles has been found to provide a convenient method for the preparation of pyridoxine (vitamin B_6) and its analogues and homologues.[2] The azadiene component of the oxazole generally condenses with a dienophile in a highly regiospecific fashion to furnish a substituted pyridine base of the isonicotinic acid series (the electron-withdrawing group of the dienophile assumes position 4 of the pyridine ring[3]).

Our interest in the development of a general strategy for the preparation of several therapeutically important alkaloids led us to further pursue the chemistry of this class of heterocycles. Ellipticine (**6**), an alkaloid present in plants of genera *Ochrosia* and *Aspidosperma*, has stimulated numerous synthetic efforts because of its potent antitumor activity.[4] We chose this molecule as the first simple target in our pursuit of a general oxazole based strategy for alkaloid synthesis.

The key intermediate in our planned scheme, the 5-substituted oxazole **4**, was synthesized starting from gramine. Thus, following a general method for the preparation of indolyl aliphatic acids reported by Suvorov,[5] indoleacetonitrile (from gramine, KCN, CH_3I)[6] was dicarbomethoxylated (dimethyl carbonate, NaOMe, benzene) to give **1**. Further treatment with NaOMe/CH_3I proceeded with loss of the *N*-carbomethoxy group and C-methylation to yield the re-