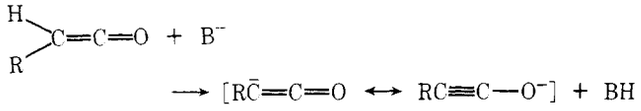
Reaction of Trimethylsilylketene with Strong Base. Evidence for Ketene Enolate Formation

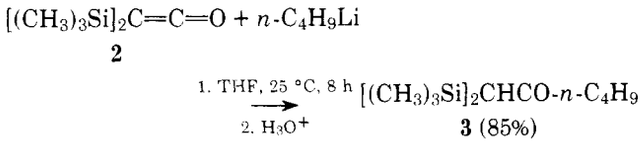
Summary: Evidence for the formation of a ketene enolate of trimethylsilylketene, based on trapping experiments with trimethylchlorosilane, is described.

Sir: The β hydrogens of aldoketenes are potentially acidic and it is possible to conceive of base-promoted ketene enolate formation in a fashion analogous to that for the familiar aldehyde or ketone enolates. Indeed, Bryce-Smith obtained insoluble, presumably polymeric materials on treatment of ketene with copper or silver salts in the presence of weak

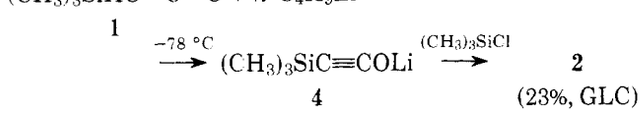


bases.[1] The products were formulated as metal ketenides, $M_2C{=}C{=}O$ (M = Cu^I, Ag^I). We present here evidence for the formation of a lithium enolate derived from trimethylsilylketene (**1**).

The reaction of bis(trimethylsilyl)ketene (**2**) with *n*-butyllithium proceeds normally, if somewhat sluggishly, at room temperature. The reaction mixture remains colorless and quenching gives good yields of the expected addition product **3**. In contrast, when *n*-butyllithium was added to **1** under the same conditions, the solution turned black immediately and quenching after periods of 5 min to 24 h gave trimethylsilylcarbinol as the only GLC mobile product of longer retention time than the solvent. The complete absence of the following addition products was established: $(CH_3)_3SiCH_2CO$-*n*-C_4H_9, $(CH_3)_3SiCH_2COH(n\text{-}C_4H_9)_2$, CH_3CO-*n*-C_4H_9, and $CH_3COH(C_4H_9)_2$.

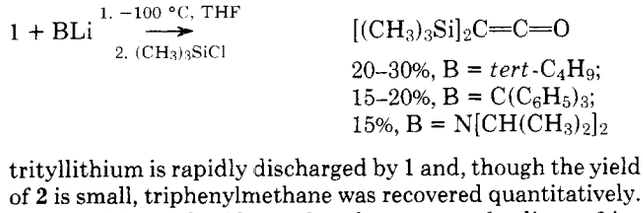


Addition of 1 equiv of **1** to a 0.5 M THF solution of *n*-butyllithium at −78 °C gave a colorless solution. Quenching this solution after 5 min with an equivalent amount of trimethylchlorosilane gave a 23% yield of **2**, presumably by formation of the ketene enolate **4**.



Addition of **1** to solutions of *n*-butyllithium at −100 °C increased the yield of **2** to 60–65%. Finally, addition of **1** to 0.1 M solutions of *n*-butyllithium at −100 °C gave 80–90% yields of **2**. Reaction mixtures obtained by this latter procedure turned black when allowed to warm to 0 °C for 15 min prior to the addition of trimethylchlorosilane and only 15–20% yields of **2** were obtained.

Similar results were obtained using other bases, although somewhat lower yields of **2** were obtained. The red color of



tritylllithium is rapidly discharged by **1** and, though the yield of **2** is small, triphenylmethane was recovered quantitatively. This is additional evidence that the sequence leading to **2** involves a simple acid–base reaction.

Attempts to trap the enolate **4** with other electrophiles, ϵ^+, have so far been unsuccessful. No GLC mobile products were obtained by quenching reaction mixtures of **1** and *n*-butyllithium with methyl iodide, benzyl bromide, acetone, or acetic anhydride. In addition, quenching with a variety of proton acids including water, acetic acid, or methanesulfonic acid returned only trace amounts of **1**. These negative results may simply be due to the instability of **4** or the instability of the product alkynol ethers **5** or ketenes **6**.

The following procedure describes a typical trapping experiment using trimethylchlorosilane. A 50-mL flask equipped with septum inlet, mercury bubbler, and magnetic stirrer was flushed with argon and immersed in a −100 °C cooling bath (liquid nitrogen and ethanol). The flask was charged with 10 mL of THF followed by 0.67 mL (1.0 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. After 15 min of stirring, 0.114 g (1.0 mmol) of trimethylsilylketene[2] was injected over a 5-min period. The colorless solution was stirred an additional 15 min and then 0.131 g (1.2 mmol) of trimethylchlorosilane was injected all at once. The solution was allowed to reach room temperature and analyzed by GLC (6 ft × 0.25 in. Carbowax 20 M column). The presence of 0.9 mmol (90%) of bis(trimethylsilyl)ketene[3] was established. Evaporation of the solvent at 25 °C gave a residue (0.16 g, 85%) of pure **2** based on either ^1H NMR [δ 0.25 (s)] or IR [2085, 1295 cm^{-1} (lit.[4] 2085, 1295 cm^{-1})] spectral examination.

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References and Notes

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An Approach to Cytochalasins: Diels–Alder Addition of α,β-Unsaturated Imides

Summary: Diels–Alder reactions of α,β-unsaturated imides are considerably accelerated relative to the reaction of the parent amides. This activating effect is used for the synthesis of a cytochalasin precursor.

Sir: Weinreb and Auerbach have described an elegant synthetic approach[1] to cytochalasins[2] by internal Diels–Alder addition of the diene ester **3**. This interesting reaction controls the regiochemistry of cycloaddition and defines four asymmetric centers in the adduct **4**. However, the problem of C-3 benzyl stereochemistry and the correct C-3 oxidation level remains unsolved.

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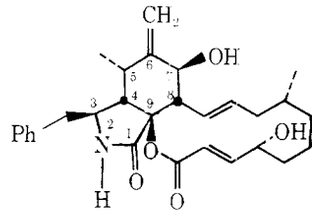
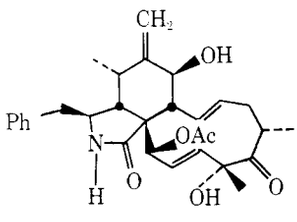
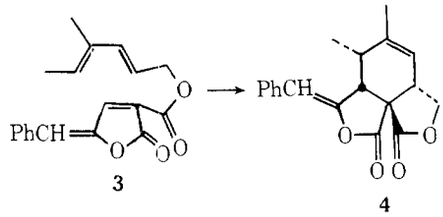
We report here the alternative approach using an intermolecular Diels–Alder reaction. Assuming the usual preference for an endo transition state a diene **5** would be expected to approach α,β-unsaturated lactam dienophiles such as **6** from the side opposite to the C-3 benzyl substituent.[3] A bicyclic adduct **7** would be formed with cytochalasin stereochemistry at C-3, C-4, C-5, and C-8. Subsequent functionalization at C-7 and C-9 should then be feasible from the less-hindered β face of the Diels–Alder product, and would allow entry into the lactone (**1**) or carbocycle (**2**) series.



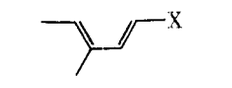
1
cytochalasin B
(phomin)



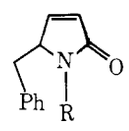
2
cytochalasin D



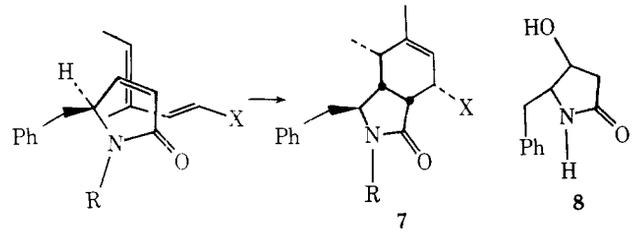
3 **4**



5a, X = $CH_2OCOC_2H_5$
b, X = CH_2CH_2OAc
c, X = CH_2OAc
d, X = CH_2OCH_3
e, X = CO_2CH_3



6a, R = H
b, R = $COCH_2Cl$



7 **8**

The parent dienophile **6a** does not survive the conditions of Diels–Alder addition.[4] Double-bond migration in similar pyrrolinones is well known in the literature,[5] and has been verified in our laboratory with 3-substituted dervatives of **6a**.[6] The double-bond migration presumably involves the formation of a hydroxypyrrole tautomer as the crucial intermediate.

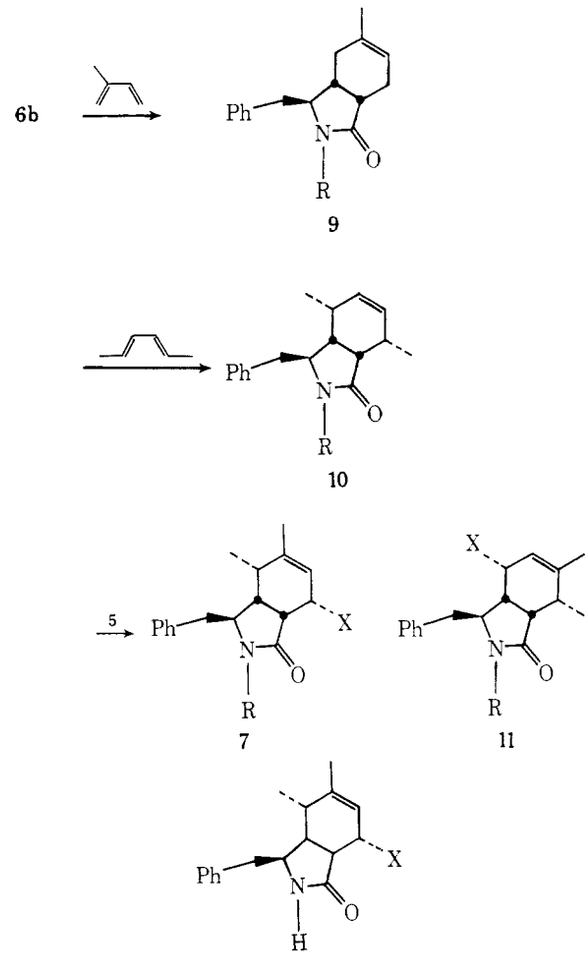
To avoid formation of tautomers from pyrrolinone dienophiles, it is desirable to introduce an electron-withdrawing N substituent which destabilizes the aromatic hydroxypyrrole intermediate. An *N*-chloroacetyl derivative **6b** is ideal in several respects. First, examples of relatively stable *N*-acetylpyrrolinones are already in the literature.[7] Furthermore, we have observed that simple α,β-unsaturated imides are considerably more reactive as dienophiles than the related esters, and much more reactive than the parent amides (Table I). Finally, *N*-acylpyrrolinones are easily cleaved by sodium carbonate in aqueous methanol to give the parent pyrrolinone.[7]

Reaction of **8** (easily available from phenylalanine ethyl ester)[9] with chloroacetic anhydride/lutidine in toluene affords **6b** in 74% isolated yield. The *N*-acylpyrrolinone **6b** is quite stable at 150 °C in hydrocarbon solvents and does not appear

Table I. Diels–Alder Reactivity of α,β-Unsaturated Imides [a] and Related Dienophiles [b]

Dienophile	% isolated yield of adduct
CH_2=$CHCO_2CH_3$	7
CH_2=$CHCONMe_2$	5
CH_2=$CHCONH\,CH_3$	<1
CH_2=$CHCON(CH_3)COCH_3$	56
CH_2=$CHCON(CH_3)COCH_2Cl$	81
CH_2=$CHCON(CH_3)COCHCl_2$	92
CH_3CH=$CHCON(CH_3)COCHCl_2$	Trace [c]

[a] All imides prepared by acylation of the *N*-trimethylsilylamide.[8] [b] Reaction at 60 °C, 24 h, in benzene, with 2,3-dimethylbutadiene in excess. [c] Reaction of α,β-unsaturated imides in the acrylate, crotonate, or tiglate series occurs at 25 °C in the presence of $TiCl_4$ catalyst (2,3-dimethylbutadiene substrate).



9 **10** **7** **11**

12a X = $CH_2OCOC_2H_5$
R = $COCH_2Cl$

to form double-bond isomers. Upon reaction with isoprene or 1,4-dimethylbutadiene at 150 °C, **6b** affords a single adduct in each case. The regiochemistry of **9** follows from 270-MHz decoupling studies, while the stereochemistry of **10** is in accord with observed coupling relationships between adjacent methine protons.[11,12]

The formation of a single adduct **10** from 1,4-dimethylbutadiene is taken as evidence that our assumption of the less hindered endo transition state is correct. Given the strong directive effect of methyl in the condensation between **6b** and isoprene, we expected that directive effects from the terminal substituents in diene **5** would tend to cancel provided that substituent X does not encounter unfavorable steric or dipole interactions with dienophile substituents. In fact, the Diels–

Alder reaction between **5a** or **5b** and dienophile **6b** (120–150 °C) is selective in favor of **7a** and **7b** by a ca. 2:1 ratio relative to the undesired regioisomer **11**. However, dienes **5c** and **5d** afford approximately 1:1 mixtures of both regioisomers, while **5e** reacts slowly to give a 4:1 mixture in favor of the wrong isomer **11e**.

With the proper choice of diene substituents, a synthetically useful ratio of adducts **7** can now be obtained by the intermolecular Diels–Alder route. Furthermore, cleavage of the activating *N*-chloroacetyl group is easily accomplished with methanolic carbonate. Thus, crystalline **12a** can be obtained in ~50% overall yield from **6b**.

Methods for introduction of cytochalasin ring A functionality are under active investigation and will be described in due course.

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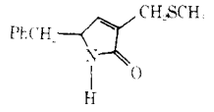
(6) Compound i decomposes within 12 h at 80 °C in toluene, and gives no Diels–Alder adduct with 2,3-dimethylbutadiene.



i

(7) H. Plieninger and M. Decker, *Justus Liebigs Ann. Chem.*, **598**, 198 (1956); T. W. Guentert, H. H. A. Linde, M. S. Ragab, and S. Spengel, *Helv. Chim. Acta*, **59**, 2138 (1976).
(8) J. S. Davies, C. H. Hassall, and K. H. Hopkins, *J. Chem. Soc., Perkin Trans.*, **7**, 2614 (1973).
(9) The sequence involves acylation of phenylalanine ethyl ester with the acid chloride of monoethyl malonate, Dieckmann cyclization[10] (sodium ethoxide, ethanol, room temperature), decarboxylation of the neutralized Dieckmann product (CH_3CN/H_2O, 1.5 h, 70 °C), and reduction (Na $CNBH_3$, $ClCH_2CO_2H$ in MeOH, 1 h, room temperature) to give **8**.
(10) H. Yuki, Y. Tohira, B. Aoki, T. Kano, S. Takama, and T. Yamazaki, *Chem. Pharm. Bull.*, **15**, 1107 (1967).
(11) NMR spectrum of **10** (R = $COCH_2Cl$): 270-MHz NMR ($CDCl_3$) δ 7.32 (5 H, m), 5.64 (1 H, dt, *J* = 9, 3 Hz), 5.56 (1 H, dt, *J* = 9, 3 Hz), 4.65 (2 H, s), 4.32 (1 H, ddd, *J* = 8, 3, 2 Hz), 3.07 (1 H, dd, *J* = 13, 3 Hz), 2.75 (1 H, dd, *J* = 13, 8 Hz), 2.71 (1 H, dd, *J* = 9, 6 Hz), 2.52 (1 H, br t, *J* = 9 Hz), 2.31 (1 H, m), 2.13 (1 H, m), 1.40 (3 H, d, *J* = 7 Hz), 0.83 (3 H, d, *J* = 7 Hz). NMR spectrum of **10** (R = H): 270-MHz NMR ($CDCl_3$) δ 7.22 (5 H, m), 5.77 (1 H, dt, *J* = 9, 3 Hz), 5.65 (1 H, dtd, *J* = 9, 3, 1 Hz), 5.48 (1 H, br s), 3.41 (1 H, ddd, *J* = 10, 5, 4 Hz), 2.96 (1 H, dd, *J* = 14, 4 Hz), 2.76 (1 H, dd, *J* = 10, 7 Hz), 2.57 (1 H, m), 2.52 (1 H, dd, *J* = 14, 10 Hz), 2.34 (2 H, m), 1.36 (3 H, d, *J* = 7 Hz), 1.22 (3 H, d, *J* = 7 Hz).
(12) Compound **10** has been prepared by a different route by G. Stork et al. (personal communication, G. Stork).
(13) NSF Predoctoral Fellow, 1975–1978.

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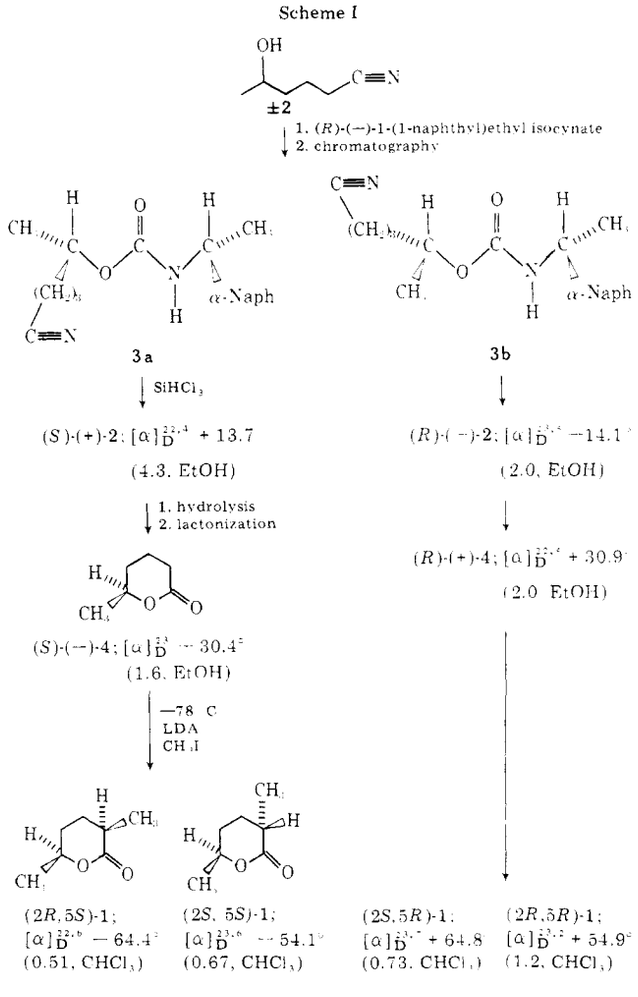
Synthesis of the Carpenter Bee Pheromone. Chiral 2-Methyl-5-hydroxyhexanoic Acid Lactones

Summary: 5-Cyanopentan-2-ol was resolved by chromatographic separation of diastereomeric carbamate derivatives. Hydrolysis and lactonization of each enantiomer afforded optically pure δ-methyl-δ-valerolactone, which was methylated to give cis and trans isomers of 5-hydroxyhexanoic acid lactone. One of the cis enantiomers is the carpenter bee pheromone.

Sir: As a prelude to a future account of a convenient and general synthetic approach to enantiomerically pure γ-substituted γ-lactones or δ-substituted δ-lactones, we describe the synthesis of all four stereoisomers of 2-methyl-5-hydroxyhexanoic acid lactone (**1**). One (presumably)[1] of the enantiomers of the *cis*-lactone is the major volatile component of the carpenter bee sex attractant.[2]

Our synthetic approach was designed to utilize a racemic intermediate that could be predictably and conveniently resolved into its enantiomers using our recently described broad-spectrum chromatographic method.[3] As shown in Scheme I, racemic 5-cyanopentan-2-ol (**2**), prepared by the method of Colonge et al.,[4] was converted to diastereomeric cyanocarbamates **3a** and **3b** by reaction with (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate.[5] These diastereomers are easily separable by automated multigram HPLC[6] (acidic alumina; 2:1 $CHCl_3$–hexane) and the enantiomerically pure cyano alcohols were retrieved quantitatively by silanolysis with trichlorosilane.[7] Basic hydrolysis of the enantiomeric cyano alcohols and subsequent lactonization afforded the corresponding enantiomers of δ-methyl-δ-valerolactone **4**. Low-temperature methylation (LDA–methyl iodide) of the enan-

Scheme I



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