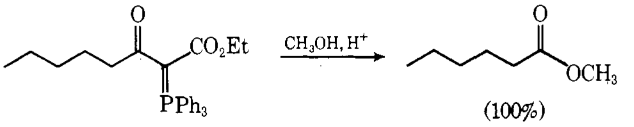
Additions are successful with a variety of substituted acceptors (entries 7-10). It is interesting to note that the diene system of entry 10 suffers exclusive β-carbon addition as opposed to the terminal additions observed in similar systems with Gilman reagents.[11] We have encountered difficulty only in the case of β,β-disubstituon (entry 11) where γ-proton abstraction predominates. This substitution pattern is often observed to interfere with Michael-type additions.[1b]

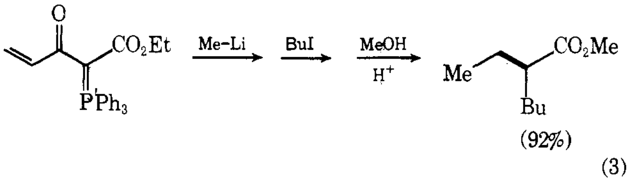
In all cases observed to date involving additions of organolithium derivatives, the resulting adducts (**2a**) undergo facile alkylation with common alkyl halides. Methylations with methyl iodide occur rapidly at 0 °C and *n*-alkyl iodides are consumed within 0.5 h at room temperature.[12] This high reactivity is in sharp contrast with the low reactivity of enolates generated through the use of Gilman reagents.[13]

While the acylphosphorane moiety in **3a** is highly resistant to attack by nucleophiles, the phosphonium salts resulting from treatment of these ylides with mineral acids are readily cleaved by nucleophilic solvents.[14] The acyl ylides **3a** obtained from the conjugate addition-alkylation process are readily converted into simple esters merely by heating in the presence of the desired alcohol containing an equivalent amount of concentrated hydrochloric acid. An example of this highly efficient conversion is shown in eq 2.[15]



(2)

An overall transformation may be envisioned involving sequentially: derivatization of unsaturated carboxylic acids, β-alkylation by charge directed conjugate addition, α-alkylation of the resulting anionic adducts with electrophiles, followed by terminal manipulation of the control element Z. The potential utility of such a sequence is enhanced by the ability to conduct high yield "one pot" conversions without the isolation of intermediates as illustrated in eq 3.



(3)

Preliminary experiments have shown that the principle of charge-directed conjugage addition is applicable to a number of systems where carbonyl interaction with an adjacent charge center suppresses 1,2-carbonyl addition. These studies will be detailed in future reports.

Acknowledgment. The authors wish to thank the Research Corporation and the Washington State University Research Committee for support of this work.

References and Notes

(1) (a) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10,** 179 (1959); (b) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", McGraw-Hill, New York, N.Y., 1968, p 604; (c) H. O. House, "Modern Synthetic Reactions", 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9.

(2) G. H. Posner, *Org. React.*, **19,** 1 (1972).

(3) Thio-substituted anions as donors: (a) J. L Herrman, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 2599, 3271, 3278 (1973). Ortho-esters as donors: (b) A. B. Manas and R. A. J. Smith, *J. Chem. Soc., Chem. Commun.*, 216 (1975). Metalated thioacetal anions as donors: (c) D. Seebach and R. Burstinghaus, *Angew. Chem., Int. Ed. Engl.*, **14,** 57 (1975). Thio-substituted acceptors: (d) R. J. Cregge, J. L. Herrman, and R. L. Schlessinger, *Tetrahedron Lett.*, 2603 (1973); J. L. Herrman, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo, and R. L. Schlessinger, *Ibid.*, 4711 (1973); J. L. Herrman, G. R. Kieczykowski, R. F. Romanet, and R. L. Schlessinger, *ibid.*, 4715 (1973); K. Iwai, H. Kosugi, and H. Uda, *Chem. Lett.*, 981 (1975). Ketene thioacetals as acceptors: (e) D. Seebach, M. Kolb, and B. T. Grobel, *Angew. Chem., Int. Ed. Engl.*, **14,** 57 (1975). Unsaturated oxazines as acceptors: (f) A. I. Meyers and C. E. Whitten, *J. Am. Chem. Soc.*, **97,** 6266 (1975). For a recent example of the discrete addition of an oxygenated enolate donor: (g) R. E. Damon and R. H. Schlessinger, *Tetrahedron Lett.*, 4551 (1975).

(4) T. M. Harris and C. M. Harris, *Org. React.*, **17,** 155 (1969); P. L. Greger, *J. Am. Chem. Soc.*, **89,** 2500 (1967); **92,** 1396, 1397 (1970).

(5) Highly delocalized enolates are slowly attacked by strong nucleophiles: T. P. Murray and T. M. Harris, *J. Am. Chem. Soc.*, **94,** 8253 (1972).

(6) M. P. Cooke, Jr., *J. Org. Chem.*, **38,** 4082 (1973); J. D. Taylor and J. F. Wolf, *J. Chem. Soc., Chem. Commun.*, 876 (1972); M. P. Cooke, Jr, and R. Goswami, *J. Am. Chem. Soc.*, **95,** 7891 (1973).

(7) Under vigorous conditions certain Grignard reagents have been observed to give 1,4-addition as well as 1,2-addition with certain α,β-unsaturated carboxylic acids and related derivatives: J. Klein, *Tetrahedron*, **20,** 465 (1964). Using similar conditions of high temperature and large excess of reagent, methyllithium has been reported to add in a conjugate manner to phenylpropiolic acid derivatives: J. Klein and N. Aminadav, *J. Chem. Soc. C*, 1380 (1970).

(8) For example, using a modification of a reported procedure (S. T. D. Gough and S. Tripett, *J. Chem. Soc.*, 2333 (1962) treatment of 2 equiv of carboethyxymethylenetriphenylphosphorane with 1 equiv of crotonyl chloride for 15 min in benzene at 0 °C gave the corresponding ylide in 86% isolated yield. In the preparation of the acroyl derivative, lower yields result owing to polymerization. This derivative is conveniently prepared in high yield from 2-chloroacetyl chloride as above followed by treatment of the β-chloro ylide with sodium methoxide in methanol at 25 °C.

(9) Cuprates from α-methoxyvinyllithium (entry 3) have recently been shown useful for the introduction of the acetyl unit in a conjugate manner: C. G. Chavdarian and C. H. Heathcock, *J. Am. Chem. Soc.*, **97,** 3822 (1975); R. K. Boeckman, Jr., and K. J. Bruza, *J. Chem. Soc., Chem. Commun.*, 519 (1975).

(10) While cuprate derivatives of dithiane are not useful for conjugate additions, it has been reported that cuprates from substituted phenylthioacetals are successfully employed in this manner: see T. Mukaiyama, K. Narasaka, and M. Furusato, *J. Am. Chem. Soc.*, **94,** 8641 (1972).

(11) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, 1611 (1973).

(12) Separate experiments have shown that these same anions, prepared by deprotonation of the corresponding saturated acyl ylides with BuLi, are readily alkylated by a variety of alkyl bromides (unpublished results with D. Majumdar).

(13) R. D. Boeckman, Jr., *J. Org. Chem.*, **38,** 4450 (1973).

(14) P. A. Chopard, R. J. G. Searle, and F. H. Devitt, *J. Org. Chem.*, **30,** 1015 (1965).

(15) In a typical procedure a solution of **3a** in the appropriate alcohol was treated with 1.05 equiv of concentrated hydrochloric acid and heated at reflux for 5 h followed by removal of excess alcohol by distillation, addition of water, and extraction of the ester with pentane. Yields were determined by GLC after workup.

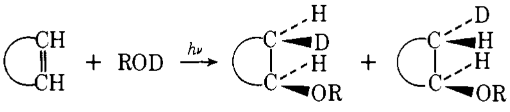
Manning P. Cooke, Jr.,* Ramanuj Goswami
Department of Chemistry, Washington State University
Pullman, Washington 99164

Received January 26, 1976

Stereochemistry and Mechanism of the Photochemical Addition of Methanol to Cycloheptenones

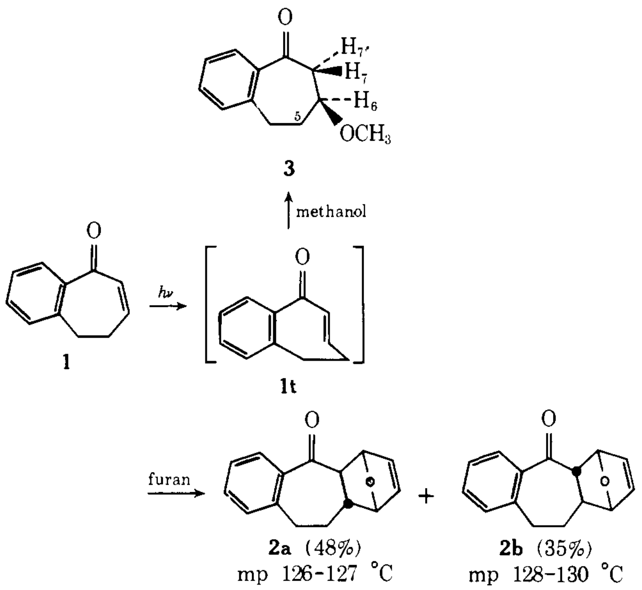
Sir:

The photochemical addition of alcohols to cycloalkenes (C_6-C_8) has been extensively investigated.[1] The reaction proceeds via carbocations formed by protonation of the double bond in a highly strained "trans" intermediate.[1,2] The additions are *not* stereospecific, since mixtures of cis and trans adducts are formed.

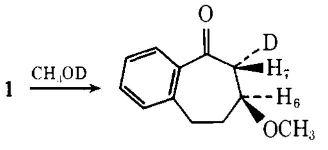


Cycloheptenones and cyclooctenones undergo a formally similar photoaddition of alcohols and other nucleophiles.[3] We have investigated their stereochemistry for the first time, and wish to report that *these additions are stereospecific.* Our results have important mechanistic consequences.

Irradiation[4] of **1**[5] in furan (0.05 M, 8 h) gave an 83% yield[6] of the trans adducts **2a** and **2b**.[7,8] We infer from this result that **1** photoisomerizes to **1t** which is trapped by the furan.[9] Irradiation of **1** in methanol (0.05 M, 6.5 h) gave ether **3** as the sole product,[8] in 61% (73%) yield.[6] In the NMR spectrum of **3**, H_6 appeared as a doublet of quartets (δ 3.68) showing that one of the four possible coupling constants (with methylene protons at C5 and C7) was unique. Decoupling by irradiation at δ 2.00 (C5 methylene) gave H_6 as a doublet of doublets, J = 7.5 and 5.0 Hz. Thus H_6 was coupled differently with the two protons at C7.

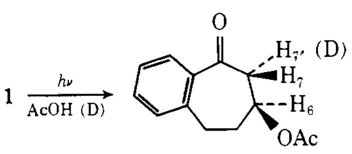


To obtain stereochemical information, **1** was irradiated in CH_3OD. The NMR spectrum of the adduct **3d** showed that the addition was stereospecific. H_6 appeared as a doublet of triplets (J = 8 and 5 Hz) and irradiation at δ 2.02 (C5 methylenes) converted the signal for H_6 to a doublet ($J_{6,7}$ = 8 Hz).[10]



3d

The photoaddition of methanol to **1** is unequivocally stereospecific, but the assignment of trans geometry to the methoxyl and deuterium (in **3d**) rests on the premise (considered reasonable[11]) that $J_{trans} > J_{cis}$. To obtain further support for this assignment, we studied the addition of acetic acid to **1**. Irradiation of **1** in acetic acid (0.05 M, 15 h) proceeded slowly to give **4**[8] in 30% (65%) yield.[6,12] The NMR spectrum of **4d** showed H_6 as a doublet of triplets (J = 7.5 and 6.0 Hz) which, after decoupling by irradiation of the C5 methylene protons, collapsed to a doublet ($J_{6,7}$ = 7.5 Hz). Thus the coupling pattern was similar to that of **3**, but with a smaller difference between J_{trans} and J_{cis}.



4 (**4d**)

It was anticipated and found that **4** readily eliminates acetic acid thermally (200 °C) to give **1**. This elimination is expected to be syn.[13] However, the analogous electron-impact 1,2-elimination is expected to be nonconcerted and much less stereoselective.[14] The mass spectral results for the elimination of AcOH/AcOD from **4d** as a function of inlet temperature are shown in Table I. As the inlet temperature is raised, more of the elimination should occur thermally (syn). As expected for the stereochemistry in **4d**, preferential loss of AcOH is favored.[15] Interestingly, a similar trend was seen with **3d**, accompanied as expected by a decrease in the intensity of M^+.

Table I

	Inlet temp, °C	M^+ (%)	$(M^+ - ROH)/(M^+ - ROD)$
4d (R = Ac)	rt[a]	<0.5	0.98
	150	<0.5	2.63
	160	<0.5	3.7
3d (R = CH_3)	rt[a]	40	1.49
	150	17	5.88

[a] rt = room temperature.

We conclude that the moieties of the addend in **3** and **4** are trans to one another. This result suggests that **1** photoisomerizes to **1t** which then adds methanol or acetic acid in what is effectively a concerted, regio- and stereospecific syn manner.[16,17]

Acknowledgment. We are indebted to the National Science Foundation (GP 43659-X) and the National Institutes of Health (GM 15997) for financial support of this research.

References and Notes

(1) For reviews, see P. J. Kropp, *Pure Appl. Chem.*, **24**, 585 (1970); J. A. Marshall, *Acc. Chem. Res.*, **2**, 33 (1969). For more recent results and additional references, see P. J. Kropp, E. J. Reardon, Jr., Z. L. F. Gaibel, K. F. Williard, and J. H. Hattaway, Jr., *J. Am. Chem. Soc.*, **95**, 7058 (1973).

(2) For direct evidence concerning a trans cyclohexene, see R. Bonneau, J. Joussot-Dubien, L. Salem, and A. J. Yarwood, *J. Am. Chem. Soc.*, **98**, 4329 (1976).

(3) H. Nozaki, M. Kurita, and R. Noyori, *Tetrahedron Lett.*, 2025, 3635 (1968); R. Noyori, A. Watanabe, and M. Katô, *ibid.*, 5443 (1968); J. K. Crandall and R. P. Haseltine, *J. Am. Chem. Soc.*, **90**, 6251 (1968); T. S. Cantrell and J. S. Solomon, *ibid.*, **92**, 4656 (1970); R. Noyori, H. Inoue, and M. Katô, *Chem. Commun.*, 1695 (1970); N. Miyamoto, S. Isiyama, K. Utimoto, and H. Nozaki, *Tetrahedron*, **29**, 2365 (1973); G. L. Lange and E. Neidert, *Can. J. Chem.*, **51**, 2215 (1973); R. Noyori and M. Katô, *Bull Chem. Soc. Jpn.*, **47**, 1460 (1974).

(4) All irradiations were carried out under nitrogen with a Hanovia 450-W lamp using a Uranium glass filter (>350 nm).

(5) Prepared by a modification of the procedure described by E. W. Collington and G. Jones, *J. Chem. Soc. C*, 2656 (1969).

(6) All yields are of pure isolated products; yields in parentheses are calculated on the basis of reacted starting material.

(7) The trans ring juncture in **2a** and **2b** was established by NMR using methods similar to those used previously for a series of analogous adducts; H. Hart and M. Suzuki, *Tetrahedron Lett.*, 3447, 3451 (1975).

(8) A correct elemental analysis was obtained.

(9) Photolysis of **1** in cyclohexane gave a mixture of dimers whose structures are under investigation.

(10) The J's were slightly different for the protium and deuterium compounds.

(11) S. Kabuss, H. G. Schmid, H. Friebolin, and W. Faisst, *Org. Magn. Reson.*, **1**, 451 (1969); M. St-Jacques and C. Vaziri, *ibid.*, **4**, 77 (1972).

(12) Although **4** was the major product, small amounts of dimers were also formed.

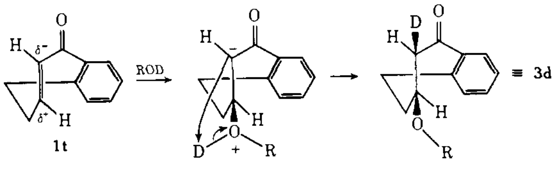
(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Wiley, New York, N.Y., 1965, p 102.

(14) G. Eadon, P. Gold, and E. Bacon, *J. Am. Chem. Soc.*, **97**, 5184 (1975); for reviews, see H-F. Grützmacher, *Suomen Kemistilehti*, **46**, 50 (1973), and M. M. Green in *Top. Stereochem.*, **9**, 35 (1976).

(15) **4d** and **3d** apparently underwent rapid epimerization in purification attempts by GLC. Thermal elimination of acetic acid from **4d** on GLC gave an AcOH/AcOD ratio of approximately 1. However, in the high vacuum of the mass spectrometer inlet system the thermal elimination was apparently highly stereoselective.

(16) For examples of syn addition to *trans*-cyclooctene, see K. T. Burgoine, S. G. Davies, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc., Perkin Trans. 1*, 2629 (1974).

(17) A conventional Michael-type addition mechanism is ruled out, since there is no reason why the enolate in such a mechanism should be protonated stereospecifically. We regard the carbon–carbon double bond in **1t** as highly polarized by the electron-withdrawing carbonyl group, but not appreciably



conjugated. Consequently, if the addition is stepwise, the intermediate carbanion is formed with charge localized on the α-carbon, and a proton must be transferred to it before any conformational change necessary for charge delocalization can occur.[18]

(18) Note Added in Proof. We have since obtained similar results with the photochemical addition of methanol to other seven- and eight-membered ring enones.

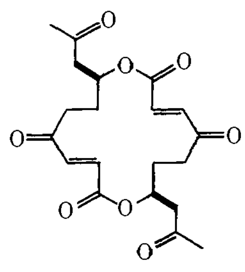
Ezra Dunkelblum, Harold Hart*
Department of Chemistry, Michigan State University
East Lansing, Michigan 48824

Received October 15, 1976

A Novel Synthesis of (±)-Vermiculine

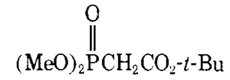
Sir:

The structure of the cytotoxic antibiotic vermiculine (**1**)[1] contains a 16-membered ring comprised of two identical C_{10} hydroxyacid units lactonized in head-to-tail fashion.[2] Recently, Corey has described a total synthesis of (±)-**1** via coupling of modified constituent halves as their pyridyl thioesters.[3] We now report a different synthesis of **1**, based on the alternative strategy of construction of a fully functionalized, acyclic hydroxyacid, which undergoes *intramolecular* lactonization to the completed macrolide.



1

Dienol acetate **3**[4] (1760, 1706 cm^{-1}; δ 5.72 (1 H, s)), prepared from Hagemann's ester (**2**) by treatment with isopropenyl acetate containing *p*-toluenesulfonic acid (reflux),[5] was reduced with sodium borohydride in aqueous dioxane (95 °C, 2 h) to hydroxy ester **4** (68%, 3500, 1710 cm^{-1}; δ 3.98 (1 H, m)) and a minor quantity of the isomeric, allylic alcohol.[6] Further reduction of **4** with lithium aluminum hydride (ether, 0 °C, 6 h) afforded diol **5** (82%; δ 3.99 (1 H, m), 4.14 (2 H, d)), which was smoothly oxidized with manganese dioxide (CH_2Cl_2, 18 h) to aldehyde **6** (83%, 1675 cm^{-1}; δ 2.15 (3 H, s), 10.16 (1 H, s)). Condensation of **6** with the phosphonate **7**, derived from *tert*-butyl α-bromoacetate[7] and trimethyl phosphite, in the presence of sodium hydride (THF, 0 °C, 0.5 h) gave the diene ester **8** (82%; 3500, 1705, 1630 cm^{-1}; δ 1.52 (9 H, s), 2.88 (3 H, s), 3.92 (1 H, m), 5.70 (1 H, d, J = 16 Hz), 7.75 (1 H, d, J = 16 Hz)). The desired E configuration of the αβ-unsaturated linkage is clearly established by the coupling constant of vinyl protons in **8**.[8]



$(MeO)_2\overset{\overset{\displaystyle O}{\|}}{P}CH_2CO_2\text{-}t\text{-}Bu$

7

Compound **8** contains the structural elements of the monomeric unit (vermiculinic acid) from which the diolide system of **1** is derived, with the 1,6-diketo functions coveniently masked at this stage as a cyclohexenyl double bond. Attachment of the second C_{10} component to **8** began with acylation using bromoacetyl bromide (pyridine-ether, 0 °C, 1 h) to yield **9** (89%; 1740, 1710 cm^{-1}; δ 3.82 (2 H, s), 5.06 (1 H, p, J = 5 Hz)), followed by conversion with trimethyl phosphite (neat, 110 °C, 1 h) to phosphonate **10** (88%; δ 3.01 (2 H, d, J = 21 Hz)). The latter underwent condensation with aldehyde **6** in the presence of sodium hydride (THF, 0 °C, 0.5 h) to give a 95% yield of **11**, which was an approximately 1:1 mixture of diastereomers with respect to the pair of asymmetric centers in the two cyclohexane rings (δ 3.92 (1 H, m), 5.10 (1 H, m), 5.75 (2 H, d, J = 16 Hz), 7.76 (1 H, d, J = 16 Hz), 7.81 (1 H, d, J = 16 Hz)).

The remaining synthesis operation, an oxidative deannulation of **11** to a tetraketone, was effected via bisepoxide **12** (δ 1.26 (6 H, s)), prepared in 91% yield from **11** by oxidation with *m*-chloroperbenzoic acid (CH_2Cl_2, 24 h). Selective epoxidation of the γ,δ-double bonds in **11** was anticipated on the basis of the greater nucleophilicity of these tetrasubstituted linkages,[9] a supposition which had been previously verified by a selective epoxidation of the monomeric system **8**. Hydrolytic opening of the two epoxide functions, without damage to the *tert*-butyl ester, was accomplished using 8% perchloric acid (THF, 25 °C) and gave pentahydroxy diester **13** in good yield as a mix-