phthalamic acid, evident in Figure 1, must be attributed to electrostatic inhibition by the carboxylate. An alternative explanation, namely hydrogen bonding of the carboxylate to the labile N proton, is unlikely in view of the unfavorable seven-membered ring geometry of such an interaction. Our results suggest that a peptide linkage lying in proximity to anionic side chains might exchange only slowly despite being neither "buried" nor internally hydrogen bonded within the protein.[13]

Acid-catalyzed proton exchange is *not* accelerated by the ortho hydroxy group of *N*-methylsalicylamide. Thus, the coalescence pH is approximately 1.4 for both *N*-methylbenzamide and *N*-methylsalicylamide. Apparently, the phenol is too weak an acid to assist in the formation of a protonated amide intermediate assumed to be involved in the exchange.[14,15]

Intramolecular catalysis is even more effective in aprotic solvents than in water. For example, 0.02 *M* *n*-butylamine causes doublet-to-singlet coalescence of 0.1 *M* *N*-methylsalicylamide in dry acetonitrile at 25°. In contrast, a distinct doublet was still observed with 1.6 *M* *n*-butylamine and 0.1 *M* *N*-methylbenzamide in acetonitrile. We surmise that the ortho hydroxyl group stabilizes the anionic portion of an ion pair intermediate *via* chelation to the amide carbonyl. Full details will be reported later.

Acknowledgment. This work was supported in part by the National Science Foundation.

(13) H. A. Scheraga, "Protein Structure," Academic Press, New York, N. Y., 1961, p 192.
(14) A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, **81**, 62 (1959).
(15) R. B. Martin and W. C. Hutton, *ibid.*, **95**, 4752 (1973).
(16) Recipient of a Camille and Henry Dreyfus Foundation Teacher Scholar Grant and a National Institutes of Health Research Career Development Award.

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New Synthetic Reactions. Sulfenylation–Dehydrosulfenylation as a Method for Introduction of Unsaturation

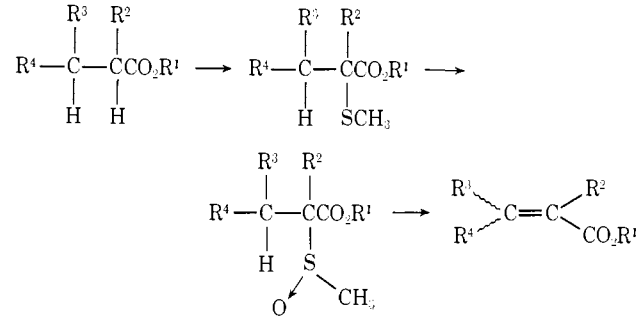
Sir:

Introduction of unsaturation α,β to a carbonyl group serves as a major method for elaboration of organic structures. Invariably, the basic approach involves bromination followed by dehydrobromination. The wide diversity of brominating agents and "bases" attests to the capriciousness of the method. Application of this method to esters and lactones[1] becomes even more difficult because of the lack of general methods to effect direct α halogenation.[2] Because of our needs to carry out such a transformation under very mild conditions, we developed a new method based upon the facile direct sulfenylating of enolates.[3,3g]

(1) (a) A. E. Greene, J. C. Miller, and G. Ourisson, *Tetrahedron Lett.*, 2489, 3375 (1972); (b) T. R. Kastur, G. R. Pettit, and K. A. Jaeggi, *Chem. Commun.*, 644 (1967); (c) for a new approach see G. Cainelli, G. Cardillo, and A. Umani-Ronchi, *J. Chem. Soc., Chem. Commun.*, 94 (1973).
(2) For some recent developments see P. L. Stotter and K. A. Hill, *Tetrahedron Lett.*, 4067 (1972); M. W. Rathke and A. Lindert, *ibid.*, 3995 (1972).

Addition of an ester to a tetrahydrofuran solution containing 1 equiv of lithium *N*-cyclohexyl-*N*-isopropylamide[4] at −78° followed by inverse quenching into a tetrahydrofuran solution containing a 15% excess of freshly distilled dimethyl disulfide[5a] led to 79–100% isolated yields of pure 2-methylthio esters. Oxidation with sodium metaperiodate[6] in aqueous methanol at room temperature followed by heating neat at 120° or in refluxing toluene led to exceptionally high isolated yields of α,β-unsaturated ester.[7] Scheme I and Table

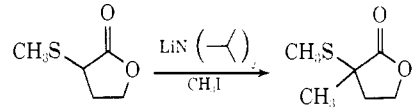
Scheme I. General Scheme for Introduction of Unsaturation into Esters



I exemplify the process.[8] No attempt has been made to optimize the yields listed.

The thermolysis of the α-methylsulfinyl derivative of ethyl decanoate was studied in some detail. At temperatures below 120°, elimination was sluggish. At 120° 5 hr was required. In refluxing toluene, completion occurred in about 14 hr. No difference in yield was noted for the two methods. Following the reaction by nmr revealed the exclusive formation of the *E* isomer during the entire course of the elimination.

Entry 5 illustrates the utility of a lactone as substrate. The same α-methylthiolactone (**1**) is also available by the methylation of α-methylthio-γ-butyrolactone.[9] This

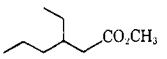
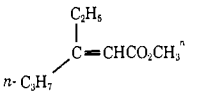
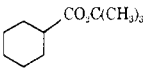
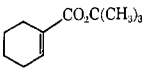
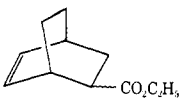
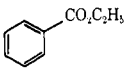
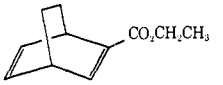
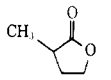
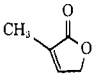
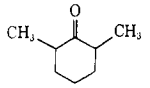
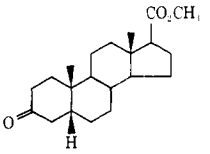
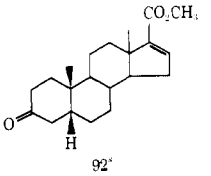
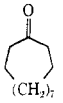
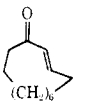


1

facile alkylation illustrates the utility of the intermediate

(3) For alternative sulfenylation methods and reagents see (a) M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966); (b) M. Ohno and I. Terasawa, *ibid.*, **88**, 5683 (1966); (c) M. Ohno, N. Naruse, S. Torimitsu, and M. O. Kamoto, *Bull. Chem. Soc. Jap.*, **39**, 1119 (1966); (d) R. L. Autry and P. W. Scullard, *J. Amer. Chem. Soc.*, **87**, 3284 (1965); (e) R. L. Autry and P. W. Scullard, *ibid.*, **90**, 4917, 4924 (1968); (f) S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972); T. Mukaiyama, S. Kobayashi, and T. Kumamoto, *Tetrahedron Lett.*, 5115 (1970).
(3g) NOTE ADDED IN PROOF. Professor D. Seebach has informed us of his independent efforts in sulfenylating ketone enolates with diphenyl disulfide.
(4) M. W. Rathke and A. Lindert, *J. Amer. Chem. Soc.*, **93**, 2318 (1971).
(5) (a) Available from Aldrich Chemical Co.; (b) available from Eastman Kodak Co.
(6) C. R. Johnson and J. E. Keiser, *Org. Syn.*, **46**, 18 (1966).
(7) (a) C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960); (b) C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964); (c) D. N. Jones and M. A. Saeed, *Proc. Chem. Soc., London*, 81 (1964); (d) S. I. Goldberg and M. S. Sahli, *J. Org. Chem.*, **32**, 2059 (1967); (e) D. W. Emerson and T. J. Korniski, *ibid.*, **34**, 4115 (1969); (f) D. N. Jones, E. Helmy, and A. C. F. Edmonds, *J. Chem. Soc. C*, 833 (1970), and references therein, (g) N. Grabowsky, *Justus Liebigs Ann. Chem.*, **175**, 348 (1875).
(8) A similar sequence involving the synthesis and elimination of α-phenylselenoxy esters has been independently developed. See H. J. Reich, I. Reich, and J. Renga, *J. Amer. Chem. Soc.*, **95**, 5813 (1973).
(9) B. M. Trost and H. Arndt, *J. Org. Chem.*, **38**, 3140 (1973).

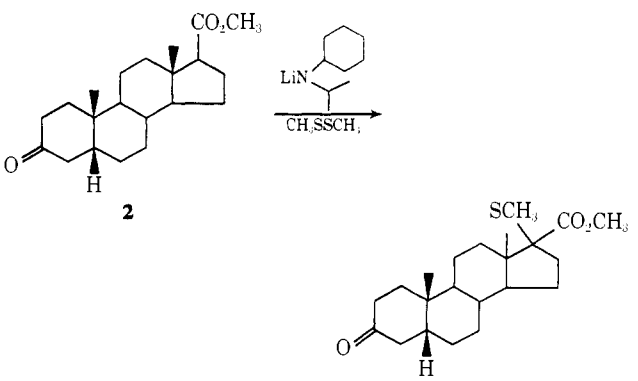
Table I. General Examples[a]

Entry no.	Saturated carbonyl	Thioether[b,c]	Sulfoxide[d]	Unsaturated carbonyl[b]	Overall yield[b,e]
1[f]	$CH_3(CH_2)_6CH_2CH_2CO_2C_2H_5$	92	97[i,k]	$CH_3(CH_2)_6CH{=}CHCO_2C_2H_5$[m] 96[k]–98[i]	86–88
2[f]		88	92[i]	 92	72
3[f]		98	93[i]	 88	80
4		a[f] 94	100[i]	 96	90
		b[g] 91	98[i]	 86	77
5[f]		79	94[i]	 95[n,p,q]	71
6		a[f] 0			
		b[g] 94	93[i]	 90[r]	79
7[f]		100[h]	98[k]	 92[s]	90
8[g]		93[h]	95[l]	 93[m]	82

[a] No attempt has been made to optimize yields. All compounds were completely characterized by spectroscopic methods. [b] Yields are for isolated pure products. [c] The major by-product is unreacted starting material. [d] Yields are based on material isolated directly from work-up. [e] Yield represents overall transformation of saturated ester to unsaturated ester. [f] Enolate quenched with dimethyl disulfide; therefore, this sequence involves methylthio derivatives. [g] Enolate quenched with diphenyl disulfide; therefore, this sequence involves phenylthio derivatives. [h] Two equivalents of base utilized. [i] Pyrolysis of sulfoxide performed neat at 120°. [j] Pyrolysis of sulfoxide performed neat at 50°. [k] Pyrolysis of sulfoxide performed in refluxing toluene. [l] Pyrolysis of sulfoxide performed in carbon tetrachloride at 50°. [m] Nmr indicates the presence of only the *E* isomer. [n] Vpc indicates an approximately 1:1 mixture of *E* and *Z* isomers. [o] Contains 13% exocyclic double bond isomer. [p] Yield and product ratio determined by nmr. [q] See also C. J. Cavallito and T. H. Haskel, *J. Amer. Chem. Soc.*, 68, 2332 (1946). [r] Contains 6% of exocyclic double bond isomer. [s] Mp 170.5–171.5°.

α-methylthio esters for elaboration of more complex structures.

Application of the method to ethyl bicyclo[2.2.2]-oct-5-ene-2-carboxylate (entry 4a) led to retro Diels–Alder of the initially formed ethyl bicyclo[2.2.2]octa-2,5-diene-2-carboxylate at 120°. Alternatively, quenching the ester enolate with diphenyl disulfide[5b] and subsequent oxidation allows elimination to proceed at 50° (*vide infra*) without this undesirable complication (entry 4b). A quantitative recovery of starting material was obtained after quenching of the enolate of 2,6-dimethylcyclohexanone with the dimethyl disulfide. Since this result indicated that ketone enolates are not sufficiently reactive to attack this sulfenylating reagent, the feasibility of selectively introducing unsaturation α to an ester in a keto ester appeared promising. Thus, steroidal keto ester **2** was treated with 2.2 equiv of lithium *N*-cyclohexyl-*N*-isopropylamide at −78°, allowed to



2

Communications to the Editor

warm to 25°, and quenched with 2 equiv of dimethyl disulfide. Aqueous acid work-up gave an essentially quantitative yield of the α-methylthio ester with no detectable sulfenylation α to the ketone. This material was carried on in the usual manner (Table I, entry 7) to give a 90% overall yield of the conjugated ester.

When simple ketone enolates (generated as in the case of ester enolates) were quenched at 25° with a 15% excess of diphenyl disulfide,[5b,10] the corresponding α-phenylsulfenyl ketones (Table I, entries 6b and 8) were isolated in high yield. For α-methylene ketones a ratio of ketone:amide based:isulfide of 1:2:1.1 was required. Surprisingly, after oxidation to the sulfoxide as previously, facile elimination occurred at 50° either neat or in carbon tetrachloride solution. The fact that benzenesulfenic acid should be a better leaving group than methylsulfenic acid accounts for this 70° temperature lowering for elimination of the aryl *vs.* alkyl sulfoxides.[3e]

The method is quite mild as the compatibility with *tert*-butyl esters (Table I), acetals,[11] allylic alcohols,[11] and epoxides[11] demonstrates. The fact that all intermediates in the sequence are stable, easily isolable compounds allows for the possibility of other structural modification prior to thermolysis. The commercial availability and ease of handling of dimethyl and diphenyl disulfides and the ability of dimethyl disulfide to sulfenylate in a chemospecific[12] reaction further illustrates the synthetic potential of the above reaction sequence.

Acknowledgment. We wish to thank the National Science Foundation and the National Institutes of Health (General Medical Sciences) for their generous support of our programs.

(10) *Cf.* T. Fujisawa, K. Hata, and T. Kojima, *Chem. Lett.*, 278 (1973).

(11) T. N. Salzmann and B. M. Trost, unpublished results.

(12) The term chemospecific is introduced to define a reaction which is specific for a given structural unit even in the presence of other functionality that might have appeared to be as or more reactive. For example, the ability to brominate α to a ketone in the presence of a double bond (or *vice versa*) would also constitute a chemospecific reaction.

(13) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

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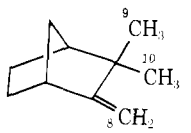
Received June 29, 1973

An Analysis of the Acid-Catalyzed Racemization of (−)-Camphene-^{13}C. Is *endo*-Methyl Migration Necessary?[1]

Sir:

In a recent ^{13}C nmr study[2] of the racemization of camphene-*8*-^{13}C (1.71 *M* camphene, 6.59 *M* pyruvic acid in acetonitrile at 137–138°), during which the extent of isotopic labeling in all three methyls was determined after partial racemization, the authors claim to have detected a small fraction of 3,2-*endo*-methyl shift. We doubted this conclusion, since 3,2-endo shifts in bicyclo-



camphene and numbering system

[2.2.1]heptyl compounds are, in general, inhibited.[3,4] In addition, these authors[2] reported that their results were compatible with three competing racemization processes, one of which (k_1) was *endo*-methyl migration, and then stated "the assignment of zero values to α does not give a good agreement of experimental mole fractions of X/X_0 with the predicted value." In their[2] notation, α is the fraction proceeding with *endo*-methyl migration and X/X_0 signifies the mole fractions (above normal abundance) of ^{13}C at C_8 after reaction times of 1.5 and 3.0 hr.

The mathematical method employed[2] seemed to us to be unnecessarily cumbersome. In addition the authors,[2] after calculating the fractions of reaction proceeding through the three competing processes from their individual experimental runs, averaged these fractions "to give single experimental values" from which theoretical curves for these "experimental" values *vs.* time were computed. Thus the individual fits for each of the four experimental runs were not compared with and then without *endo*-methyl migration, but rather the fit was determined with the synthetically averaged values.

The average of the four derived α values calculated by Vaughan, Stothers, and coworkers[2] is 0.026, from which we determine a standard deviation[5] of ±0.023 and a 95% confidence level[5] of about ±0.046, a value greater than the presumed fraction (α = 0.026) of *endo*-methyl migration. If we consider that there are only four observations, then the limits of error would be even greater.

For all of the above-mentioned reasons, we reanalyzed the data[2] using a more direct method, and demonstrate unequivocally and beyond any doubt that these data are fit equally well by a mechanism in which k_1 is omitted. Thus, by Occam's razor,[6] we conclude that endo migration of methyl should not be included in the mechanism.

There is at least one other way to treat their data.[2] We replaced their scheme[7] with the model shown in Scheme I, in which the appropriate intermediates are also considered. In our model A is (−)-camphene-*8*-^{13}C, B is (+)-camphene-*9*-^{13}C, C is (−)-camphene-*10*-^{13}C, D is (+)-camphene-*10*-^{13}C, E is (−)-camphene-*9*-^{13}C, F is (+)-camphene-*8*-^{13}C, a–f are the protonated forms of A–F; k_1 is the racemization process 3,2-*endo*-Me, k_2 is the racemization process Wagner–Meerwein, 6,2-hydride shift Wagner–Meerwein, k_3 is the racemiza-

(1) Research sponsored by the U. S. Atomic Energy Commission under contract with the Union Carbide Corp.

(2) C. W. David, B. W. Everling, R. J. Kilian, J. B. Stothers, and W. R. Vaughan, *J. Amer. Chem. Soc.*, **95**, 1265 (1973).

(3) C. J. Collins, Z. K. Cheema, R. G. Werth, and B. M. Benjamin, *ibid.*, **86**, 4913 (1964); P. von R. Schleyer, *ibid.*, 89, 701 (1965). There are only two documented cases of 3,2 endo hydride migration: A. W. Bushell and P. Wilder, Jr., *ibid.*, **89**, 5720 (1967); P. Wilder, Jr., and W. C. Hsieh, *J. Org. Chem.*, **36**, 2552 (1971).

(4) See also C. J. Collins and C. K. Johnson, *J. Amer. Chem. Soc.*, **95**, 4766 (1973).

(5) See, for example, D. J. Finney, "Experimental Design and Its Statistical Basis," University of Chicago Press, Chicago, Ill., 1955, p 35.

(6) "Pluralitas non est ponenda sine necessitate," a dictum posed by the Franciscan philosopher, William Ockham (or Occam, c. 1280–1349). "Encyclopedia Britannica," Vol. 16, Wm. Benton, Publisher, London, 1966, p 858.

(7) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *J. Amer. Chem. Soc.*, **85**, 2282 (1963).