eterization of the potential functions used by the different groups may explain the difference in their predictions, especially since these compounds are sterically hindered and sensitive to choice of van der Waals parameters. The structures of the two tripeptides Boc-Leu-Aib-Pro-OX (X = H, Bzl) and the published tetrapeptide,[9] (Z)-Aib-Pro-Aib-Ala-OMe, provide three examples of Aib residues preceding a proline. Theoretical calculations (Moore and Marshall, in preparation) suggest only a slight preference for the positive values of ϕ and ψ for Aib residues preceding a proline and both combinations are observed experimentally. Systematic calculation of the possible conformers of acetyl-Aib-Ala-Aib methylamide at 11.25° increments gave four conformers within 0.5 kcal/mol of the minimum as shown in Table X. Conformer R,L-A is very similar to the crystal structure observed for the fragment-Aib-Ala-Aib of the tetrapeptide, averaging only 8° deviation from the observed structure. This further supports the conclusion that the primary determinants of conformation in these molecules are intramolecular with crystal-packing forces selecting between energetically similar conformers. It should, therefore, be feasible to apply the constraints introduced by Aib residues to limit the possible conformations available to the alamethicin molecule. In addition, other antibiotics such as antiamoebin,[32] emerimicin,[33] and suzukacillin[34] have been shown to contain Aib residues. The name of peptaibophol antibiotics has been proposed[32] for this class which contains phenylalaninol as well as several residues of Aib. The unique properties associated with α-methyl substitution have been recognized by natural selection and have resulted in this class of compounds with unique membrane properties.

Acknowledgment. This investigation was supported in part by Grant No. GM-19684 from the National Institute of General Medical Sciences, DHEW (G.D.S. and W.L.D.), Grant No. PCM(74-03059) from the National Science Foundation (F.S.M. and E.W.C.), and Grant No. RR-00396 and Grant No. 5R01AI16182-02 from the National Institute of Allergy and Infectious Diseases (G.R.M. and T.M.B.).

Supplementary Material Available: Listings of atomic coordinates, bond distances and angles for the nonhydrogen and hydrogen atoms, and a tabulation of observed and calculated structure factors (71 pages). Ordering information is given on any current masthead page.

(32) R. C. Pandey, H. Meng, J. C. Cook, Jr., and K. C. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 5203 (1977).

(33) R. C. Pandey, J. C. Cook, Jr., and K. C. Rinehart, Jr., *J. Am. Chem. Soc.*, **99**, 5205 (1977).

(34) G. Jung, W. A. Konig, D. Leibfritz, T. Ooka, K. Janko, and G. Boheim, *Biochim. Biophys. Acta*, **433**, 164 (1976).

Synthesis and Reactions of Simple 3(2*H*)-Furanones

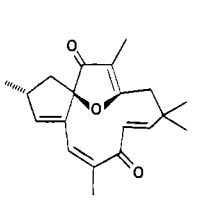
Amos B. Smith, III,*[1] Patricia A. Levenberg, Paula J. Jerris, Robert M. Scarborough, Jr., and Peter M. Wovkulich

Contribution from the Department of Chemistry, The Laboratory for Research on the Structure of Matter, and The Monell Chemical Senses Center, The University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received June 27, 1980*

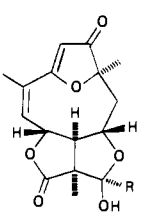
Abstract: Interest in the total synthesis of natural product antitumor agents which have as a central structural element the 3(2*H*)-furanone ring system has led to the development of an efficient general synthesis of a variety of simple 3(2*H*)-furanones. The strategy involves aldol condensation of aldehydes with the enolate derived from 3-methyl-3-(trimethylsiloxy)-2-butanone (**35**) followed by Collins oxidation to afford the 1,3-diketone. Acid-catalyzed cyclization–dehydration then leads to the corresponding 3(2*H*)-furanones. The availability of this facile approach to the 3(2*H*)-furanone ring system provided the opportunity to explore the chemistry of this increasingly important heterocycle. Three reactions were selected for initial study; they were (a) alkylation, (b) conjugate addition of organocuprate reagents, and (c) reaction with sulfur nucleophiles. The results of the latter vis-á-vis the mode of action of 3(2*H*)-furanone antitumor agents is discussed.

Introduction and Background

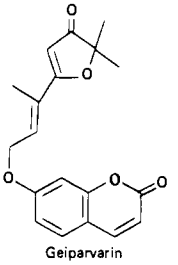
During the course of studies directed at devising a viable synthetic approach to jatrophone[2] (**1**) and related antitumor agents such as the eremantholides[3] (A, B, and C) (**2**) and geiparvarin[4] (**3**), each of which possesses as a central structural element the 3(2*H*)-furanone ring, we have had occasion to explore the synthesis and chemistry of a number of simple 3(2*H*)-furanones. We report here the results of that study.



Jatrophone
1



Eremantholide
2a: R = *i*-Pr
2b: R = *sec*-Bu
2c: R = CMe=CH$_2$



Geiparvarin
3

Our interest in simple 3(2*H*)-furanones was threefold. First, selection of the above synthetic targets demanded the availability of an efficient and hopefully general strategy for construction of

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983, and National Institutes of Health (National Cancer Institute) Career Development Awardee, 1980–1985.

(2) S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore, and R. F. Bryan, *J. Am. Chem. Soc.*, **98**, 2295 (1976). For the first total synthesis of normethyljatrophone see: A. B. Smith, III, M. A. Guaciaro, S. R. Schow, P. M. Wovkulich, B. H. Todu, and T. W. Hall, *J. Am. Chem. Soc.*, **103**, 219 (1981).

(3) P. W. Le Quesne, S. B. Levery, M. D. Menachery, T. F. Brennan, and R. F. Raffauf, *J. Chem. Soc., Perkin Trans. 1*, 1572 (1978).

(4) (a) F. N. Lahey and J. K. MacLeod, *Aust. J. Chem.*, **20**, 1943 (1967); (b) R. M. Carman, F. N. Lahey, and J. K. MacLeod, *ibid.*, **20**, 1957 (1967); (c) D. L. Dreyer and A. Lee, *Phytochemistry*, **11**, 763 (1972). (d) For the first total synthesis and assignment of olefinic configuration see P. J. Jerris and A. B. Smith, III, *Tetrahedron Lett.*, **21**, 711 (1980).

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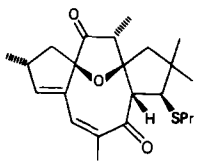
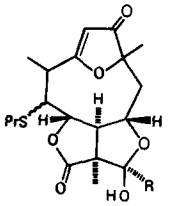
the 3(2*H*)-furanone ring; no such approach was available at the outset of our work.[5] In fact the chemistry of this increasingly important heterocycle had been little explored. Finally, it appeared that simple 3(2*H*)-furanones would be ideal substrates to model the mode of biological action of antitumor agents which possessed this structural element. In this regard, jatrophone and eremantholide A were reported, respectively by Kupchan[2] and Le Quesne,[3] to undergo facile conjugate addition of propanethiol to yield monoadducts **4** and **5**. Details of similar reactions with simple

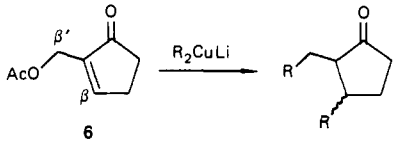


4



5

3(2*H*)-furanones, however, had not been investigated. Furthermore, the recent discovery in our laboratory of bis-β,β'-conjugate addition[6] of organocuprate reagents to substrates such as **6**[7] suggested that 3(2*H*)-furanones such as budlein A[8] or goyazensolide,[9] each of which possesses a potential leaving group in the



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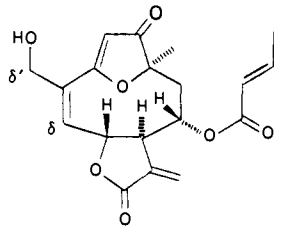
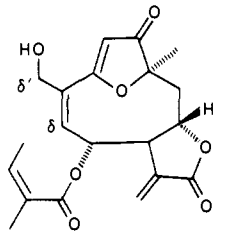
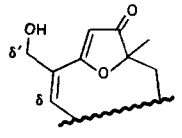


Budlein A



Goyazensolide

δ'-position, could undergo bis-δ,δ'-conjugate addition with an appropriate bionucleophile.[10] That is, budlein A and goyazensolide are vinylogues of enone **6**. Conjugate addition of propanethiol followed by loss of H_2O would lead to a new furanone (i.e., **7**), which in a subsequent step could accept a second equivalent of propanethiol to afford **8** via 1,6-conjugate addition. Such a



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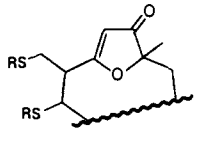


8

(5) For a recent elegant approach to a chiral 3(2*H*) and furanone see B. Fraser-Reid and T. F. Tam, *J. Org. Chem.*, **45**, 1344 (1980). For the syntheis of specific 3(2*H*)-furanone derivatives see: F. Sher, J. L. Isidor, H. R. Taneja, and R. M. Carlson, *Tetrahedron Lett.* 577 (1973); W. Ried and A. Marhold, *Chem. Ber.*, **107**, 1714 (1974); R. M. Carlson, R. W. Jones, and A. S. Hatcher, *Tetrahedron Lett.* 1741 (1975); A. S. Medvedeva, M. M. Demina, and V. I. Kaigorodova, *Zh. Org. Khim.*, **10**, 2280 (1974); P. K. Gupta, J. G. L. Jones, and E. Caspi, *J. Org. Chem.*, **40** 1420 (1975).

(6) A. B. Smith, III, B. A. Wexler, and J. S. Slade, *Tetrahedron Lett.*, in press.

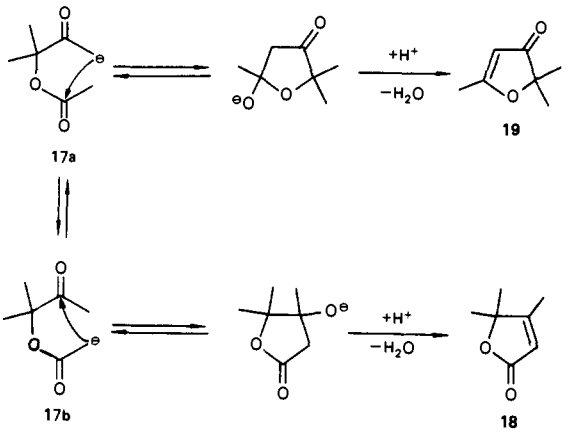
(7) M. A. Guaciaro, P. M. Wovkulich, and A. B. Smith, III, *Tetrahedron Lett.*, 4661 (1978).

(8) A. R. de Vivar, C. Guerrero, E. Diaz, and A. Ortega, *Tetrahedron*, **26**, 1657 (1970).

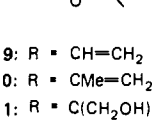
(9) W. Vichnewski, S. J. Sarti, B. Gilbert, and W. Herz, *Phytochemistry*, **15**, 191 (1976).

(10) Conjugate addition at the α-methylene functionality would also be expected.

Scheme I



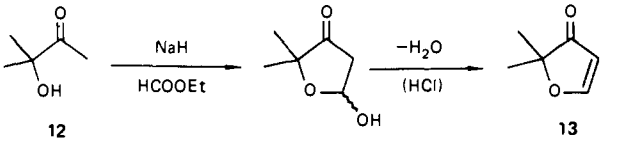
process in vivo would permit cross-linking, a process that has been suggested to enhance activity of many antitumor agents.[11] With these considerations in mind, we expanded the initial scope of our investigation to include the synthesis and chemistry of simple 5-vinyl-3(2*H*)-furanones **9–11**.



9: R = $CH{=}CH_2$
10: R = $CMe{=}CH_2$
11: R = $C(CH_2OH){=}CH_2$

Results and Discussion

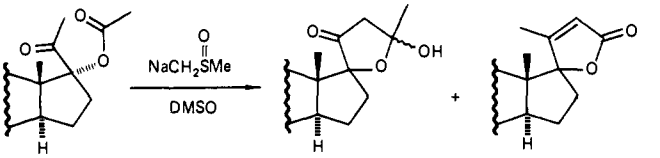
Synthesis of Simple 3(2*H*)-Furanones. In 1971 Margaretha[12] reported that the sodium hydride catalyzed acylation of hydroxy ketone **12** with ethyl formate follwed by an acid-promoted dehydration afforded furanone **13** in 50% yield. Unfortunately, all



12 **13**

attempts to exploit this transformation, for elaboration of 5-substituted 3(2*H*)-furanones, through utilization of an alkyl ester in place of ethyl formate proved fruitless.

Further consideration suggested that an intramolecular version of the Margaretha transformation might offer a general solution. In this regard Lehmann[13] as early as 1965 reported that α-acyloxy ketones such as **14**, when treated with sodium dimsyl in Me_2SO,



14 **15** **16**

afford a mixture of α-hydroxyfuranone **15** and butenolide **16**, with

(11) S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970).

(12) P. Margaretha, *Tetrahedron Lett.*, 4891 (1971).

(13) H. G. Lehmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 783 (1965). For additional examples of this reaction see: G. W. Moersch, D. E. Evans, and G. S. Lewis, *J. Med. Chem.*, **10**, 254 (1967); T. L. Popper, J. N. Gardner, R. Neri, and H. L. Herzog, *ibid.*, **12**, 393 (1969); N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 1841 (1966) S. J. Halkes, J. Hartog, L. Morsink, and A. M. de Wachter, *J. Med. Chem.*, **15**, 1288 (1972); G. Teutsch, L. Weber, G. Page, E. L. Shapiro, H. L. Herzog, R. Neri, and E. J. Collins, *ibid.*, **16**, 1370 (1973); J. R. Bull and A. Tuinman, *Tetrahedron Lett.* 4349 (1973); H. A. C. M. Keuss and J. Lakemann, *Tetrahedron*, **32**, 1541 (1976).

Scheme II

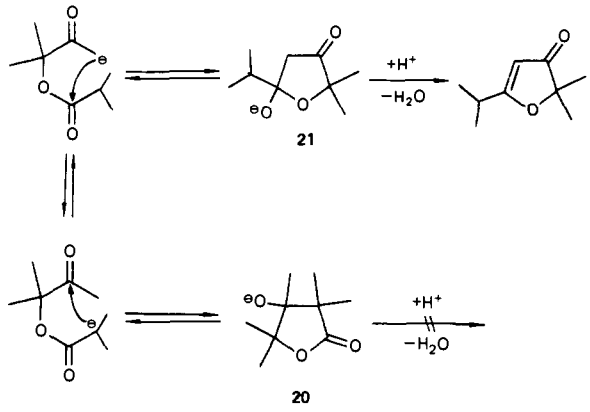
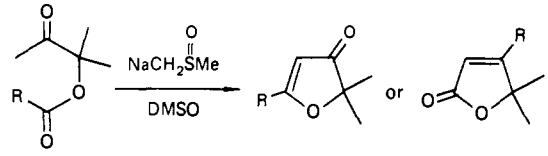


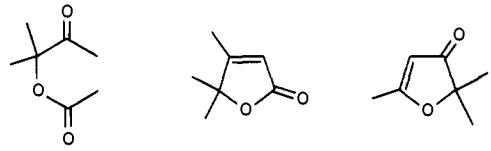
Table I. Synthesis of 3(2*H*)-Furanones from α-Acyloxy Ketones



Entry	α-Acyloxy ketone R		Product (percent yield)			
a	$CHMe_2$	22	26	(64)		—
b	Ph	23	27	(88)		—
c	*t*-Bu	24	28	(79)		—
d	Me	17		—	18	(20)
e	$CH{=}CMe_2$	25		—	30	(75)

the latter being the major product. The predominance of **16** was, however, troublesome in view of the well-known difference in acidity of ketones vs. esters (ca. 4–5 pK_a units).[14]

To explore the Lehmann transformation in detail, we subjected α-acyloxy ketone **17** to the NaH/Me_2SO reaction conditions; the result, albeit in low yield, was butenolide **18**. Even kinetic de-



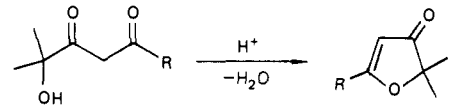
17 18 19

protonation (LDA/THF at −78 °C) followed by an acidic workup did not afford the desired furanone (i.e., **19**) in useful amounts. Instead, a complex mixture containing both **18** and **19** along with a number of unidentified components resulted.

Collectively these results suggest (see Scheme I) that an equilibrium is established between the ketone and ester enolates (**17a** and **17b**) at a rate that is fast relative to addition of the ketone enolate to the ester carbonyl. Furthermore, the greater facility with which ketones are known to undergo nucleophilic addition relative to ester carbonyls[15] leads to the prediction that butenolide **18** should in fact be the major product. However, if the system is so constructed (see Scheme II) such as to prevent elimination of water from the favored intermediate (**20**), the course of the reaction is expected to shift to formation of the 3(2*H*)-furanone ring system. That this rationale is correct was demonstrated by subjecting α-acyloxy ketones **22–24**, each of which bear at most one hydrogen in the α′-position of the ester substituent, to dimsyl sodium. As illustrated in Table I, 3(2*H*)-furanones **26–28** were obtained as the sole product in good to excellent yield. Particularly noteworthy here is the facile, highly efficient synthesis of bullatenone **27**, a natural 3(2*H*)-furanone isolated from blistered leaf myrtle (*Myrtus bullata*), a shrub endemic to New Zealand.[16]

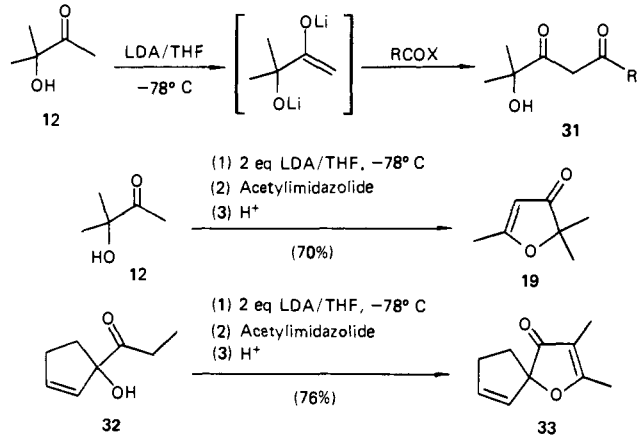
Alternatively, if the α-position of the ester substituent possesses more than one hydrogen or does so through the principle of vinylology (i.e., **17** and **25**, respectively), the corresponding butenolides **18** and **30** result. Thus, while we had succeeded in devising an efficient intramolecular cyclization–dehydration strategy for the synthesis of selected 3(2*H*)-furanones, the lack of generality of this approach left much to be desired.

Convinced that the most efficient general approach to the 3(2*H*)-furanone ring system would involve the acid-catalyzed cyclization–dehydration of an appropriately substituted α′-hydroxy 1,3-diketone **31**, we reexamined the intermolecular acylation of



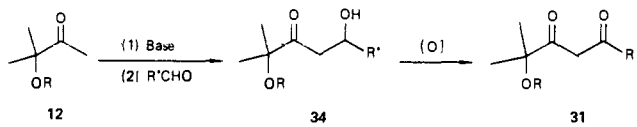
31

hydroxy ketone **12**, employing kinetic deprotonation under aprotic conditions. To this end, treatment of the dianions of **12** and **32** (2.3 equiv of LDA/THF, −78 °C) with the standard acylating agents EtOAc, Ac_2O, and AcCl again led only to complex mixtures. However, when the imidazole acyl transfer reagent[17] acetyl



imidazolide was employed, 3(2*H*)-furanones **19** and **33** accompanied only by starting hydroxy ketone were obtained. Although these tranformations were quite clean, conversions were only in the range of 30–40%. Presumably, the low conversions result from the acidic nature of the initially derived 1,3-diketone (e.g., **31**). Unfortunately, all attempts to increase the conversion either by inverse addition or by employing greater than 2 equiv (ca. 3–5 equiv) of base were counterproductive. The latter result is presumably due to the known base-catalyzed self-condensation of acetyl imidazolide.[17]

Thwarted by low conversions, we turned our attention to an alternative strategy. While our previous approach involved an electrophile in the oxidation state of a carboxylic acid, there appeared to be no reason that an aldehyde could not be employed for the initial carbon–carbon bond formation step (ca. an aldol condensation). Subsequent oxidation of the resultant β-hydroxy ketone **34** would then afford the desired 1,3-diketone (**31**).[18]



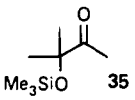
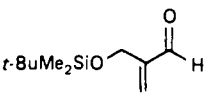
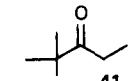
(14) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, p 494.

(15) Consider the ease with which ketones vs. esters react with HCN (i.e., cyanohydrin formation); see, for example, D. T. Mowry, *Chem. Rev.*, **42** (1948).

(16) (a) T. Brandt and W. I. Taylor, *J. Chem. Soc.*, 3425 (1954); (b) W. Parker, R. A. Raphael, and D. I. Wilkinson, *ibid.*, 3871 (1958).

(17) H. A. Staab, *Angew. Chem., Internat. Ed. Engl.*, **1**, 351 (1962).

Table II. Synthesis of Simple 3(2*H*)-Furanones

Entry	Ketone	Aldehyde RCHO (36)	Aldol (34) (percent yield)	1,3-Diketone (31) (percent yield)	3(2H)-Furanone (percent yield)
a	 35	CH_2=CHCHO	89[a]	57	9 50
b	35	CH_2=C(Me)CHO	92[a]	60	10 60
c	35		98[a]	90	11 43
d	35	PhCHO	100[a]	95	27 78
e	35	EtCHO	81[a]	86	37 66
f	35	*n*-BuCHO	77[b]	79	38 45
g	35	$Me(CH_2)_5CHO$	93[b]	80	39 62
h	35	$PhCH_2CHO$	86[b]	67	40 50
i	 41	$PhCH_2CHO$	82[a]	93	42 20

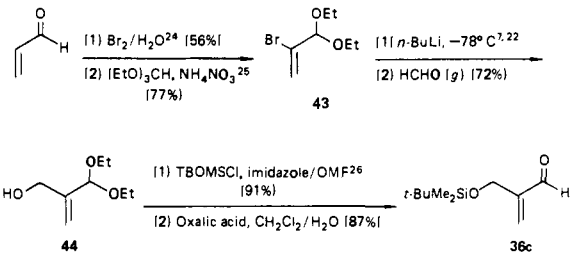
[a] Lithium enolate employed. [b] Zinc enolate employed.

Furthermore, if the oxidation were carried out under acidic conditions, it might be possible in "one pot" to effect direct cyclization to the desired 3(2*H*)-furanone.

Indeed, treatment of **35** (see Table II) with 1.1 equiv of LDA, followed by condensation at low temperature with a variety of aldehydes (i.e., **36a–h**), led to the desired β-hydroxy ketones **34**. Yields, in general, were good to excellent, except in the case of easily enolizable aldehydes (**36e–h**), where conversions were only modest (ca. 58%). Marked improvement here was realized by exploiting the zinc enolate prepared according to the method of House.[19,20]

Subsequent oxidation of the aldol products with Jones reagent[21a] resulted both in formation of the diketone and in cyclization–dehydration to the 3(2*H*)-furanone. Best results, however, were obtained when oxidations were effected using Collins' reagent,[21b] followed in a subsequent step by treatment of the derived 1,3-diketone with mild aqueous acid to effect cyclization–dehydration. *This two-step protocol for the elaboration of 1,3-diketones holds considerable promise, we believe, as a general synthetic method.*

Several additional comments are in order. First, the generality of this approach to 3(2*H*)-furanones disubstituted in the 2-position is illustrated by the variety of systems prepared. Even the very unstable 3(2*H*)-furadienones (Table II; entries a-c) could be prepared via this strategy in useful, albeit modest, yields. Furthermore, the method depends only on the availability of the appropriate aldehyde. In this regard, we note that *tert*-butyldimethylsiloxymethacrolein (**36c**) was previously an unknown compound. Its synthesis, modeled after previous work of Ficini[22] and that of this laboratory,[7] is depicted below.[23]



With a general approach to the 3(2*H*)-furanone ring system secure, we next turned our attention to the study of the chemistry of this heterocycle. Three reactions were selected; they were alkylation, conjugate addition of organocuprate reagents, and reaction with sulfur nucleophiles.

Alkylation of the 3(2*H*)-Furanone Ring System.[27] We initiated this study by examining the alkylation of a number of simple substituted 3(2*H*)-furanones. Our results are illustrated in Table III. As predicted, treatment of the kinetic lithium enolate of 2,5-dimethyl-3(2*H*)-furanone (**45**) with alkyl halides resulted in exclusive alkylation at the α′-position. On the other hand, reaction of α′,α′-disubstituted derivatives **19**, **22**, **46**, and **47** afforded excellent yields of only γ-alkylation. Of interest here is the fact that the reactivity of these furanones is not affected by the degree

(18) The oxidation of β-hydroxy ketones to 1,3-diketones, while not unprecedented, has not been widely exploited, presumably because of the enolic nature of the derived diketone and the potential of oxidative cleavage. Studies in our laboratory with simple β-hydroxy ketones and esters indicate that the latter is not a serious problem when Collins' or Swern's oxidation conditions are employed. (unpublished results of P. Levenberg).

(19) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).

(20) It is of interest that the lithium enolate derived from ketone **41**, unlike that of **35**, afforded an excellent conversion to aldol **34**l. Presumably, the added methyl group decreases the basicity of the lithium enolate such that proton transfer in this case is not a serious problem.

(21) (a) K. Bowden, I. M. Heilbroon, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); (b) J. C. Collins and W. W. Hess, *Org. Synth.*, **52**, 5 (1972).

(22) J. Ficini and J. C. Depezay, *Tetrahedron Lett.*, 4797 (1969).

(23) It is significant that the stability of **36c** differed considerably from that of α-hydroxymethylacrolein, the latter known to polymerize rapidly in the neat state; see: J. E. Vik, *Acta Chem. Scand.*, **27**, 239 (1973).

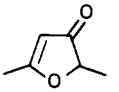
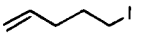
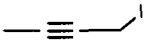
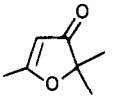
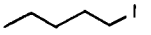
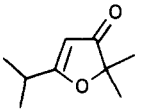
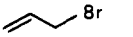
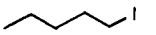
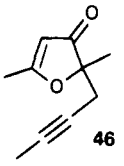
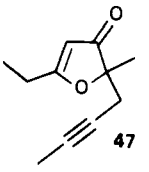
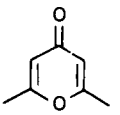
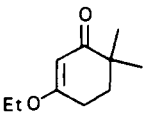
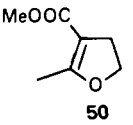
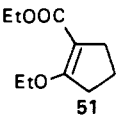
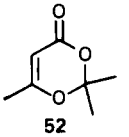
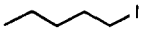
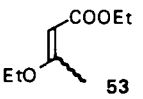
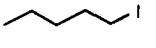
(24) R. H. Baker, S. W. Tinsley, Jr., D. Butler, and B. Riegel, *J. Am. Chem. Soc.*, **72**, 393 (1950).

(25) H. O. L. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 514 (1935).

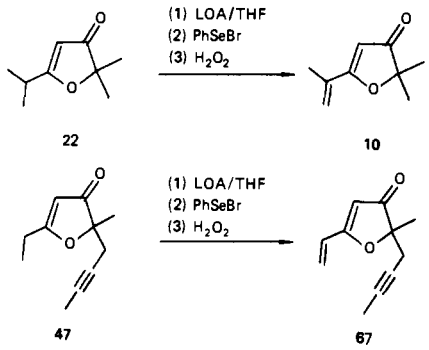
(26) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).

(27) For a preliminary account of this work see: R. M. Scarborough, Jr., and A. B. Smith, III, *Tetrahedron Lett.*, 4193 (1978).

Table III. Alkylation of 3(2*H*)-Furanones and β-Alkoxy-α,β-unsaturated Carbonyl Compounds

Entry	Substrate	Alkyl halide	Alkylation distribution (percent) α	Alkylation distribution (percent) γ	Product	Yield (percent)
1[33]	 **45**	MeI	100 (α′)	0	**19**	73
			100 (α′)	0	**54**	81
			100 (α′)	0	**46**	71
2[34]	 **19**	MeI	0	100	**37**	85
			0	100	**39**	80
3[35]	 **22**	MeI	0	100	**28**	93
			0	100	**55**	92
			0	100	**56**	83
		PhSeBr	0	100	**57**	75
4	 **46**	MeI	0	100	**47**	74
5	 **47**	PhSeBr	0	100	**58**	84
6[29]	 **48**	MeI	0	100	**59**	58
7[36]	 **49**	MeI	100	0	**60**	61
8[37]	 **50**	MeI	34	66	**61,62**	74
9[38]	 **51**	MeI	100	0	**63**	91
10	 **52**		33	67	**64, 65**	86
11	 **53**		100	0	**66**	88

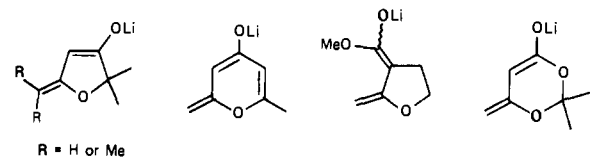
of either α or γ substitution. Furthermore, the utility of this process can be expanded to yield an alternative route to the furandienone system. For example, γ-alkylation of 3(2*H*)-furanones **22** and **47** with phenylselenenyl chloride followed by oxidative-elimination[31] affords furadienones **10** and **67** in 50–60% overall yield. Interestingly, the intermediate selenoxides displayed no propensity toward [2,3]-sigmatropic rearrangement, a known reaction of allylic selenoxides.[32]



To our knowledge, selective γ-alkylation of *lithium* dienolates is unprecedented.[28] Indeed, the only other reported example of selective γ-alkylation of a β-alkoxy-α,β-unsaturated carbonyl compound is that reported for 2,6-dimethyl-γ-pyrone **48**.[29,30] However, this vinylogous ester is exceptional in view of its aromatic nature. It is interesting in this regard to note that a wide variety of *copper* dienolates, derived from simple α,β-unsaturated esters, were recently observed to undergo selective γ-alkylation.[39]

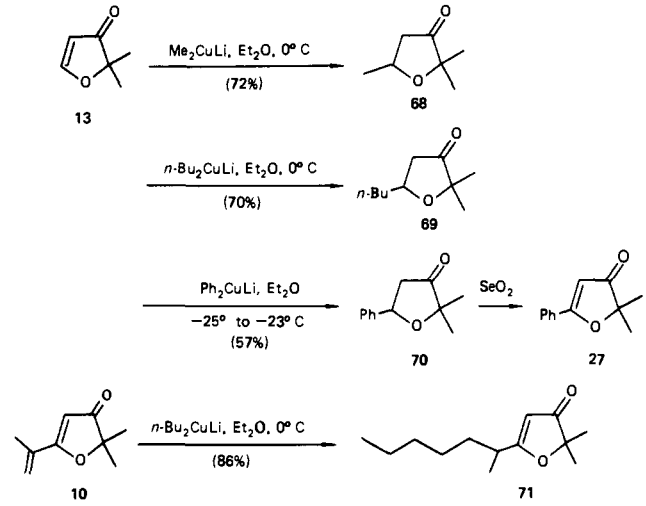
To evaluate the factors which determine the observed regiochemistry, we examined alkylation of a number of related β-alkoxy-α,β-unsaturated carbonyl substrates. Ideal candidates for this purpose appeared to be β-alkoxy-α,β-unsaturated esters since α'-alkylation would no longer be a concern. In the event, kinetic deprotonation of derivatives **49**, **51**, and **53**, employing the LDA–HMPA complex of Rathke[40] and Schlessinger[41] followed by reaction with alkyl halides afforded 100% α-alkylation, while similar treatment of substrates **50** and **52** led to a mixture of α- and γ-alkylated products, with the γ adduct predominating 3:2 in each case.

Although no definitive statement can, as yet, be made concerning the factors that govern α vs. γ selectivity, one consistent observation was noted. In those cases where the dienolate incorporates an exocyclic double bond, γ-alkylation is the preferred mode. Conversely, dienolates possessing an endocyclic olefin yield exclusively α adducts. Clearly, further structure–reactivity studies are required before the subtle features governing α vs. γ selectivity in the alkylation of β-alkoxy-α,β-enones can be fully appreciated.



Addition of Organocuprate Reagents to Simple 3(2*H*)-Furanones.[42] The second area investigated was that of addition of organocuprates[43] to 3(2*H*)-furanones. Such a study was anticipated not only to evaluate the reactivity of simple furanones with respect to conjugate addition but also to provide a test of the Baldwin rules for ring closure.[44] That is, if retro-5-endo-trigonal reactions are indeed disfavored processes as postulated by Baldwin, reaction of 3(2*H*)-furanones with excess cuprate should lead only to the mono-β-alkylated adduct, since expulsion of the β-alkoxy substituent by the initially formed enolate entails a retro-5-endo-trigonal process.[45]

In the event, treatment of 2,2-dimethyl-3(2*H*)-furanone (**13**) with 2.5 equiv of lithium dimethyl-, di-*n*-butyl-, and diphenylcuprates led in each case only to the monoalkylated adduct. Similarly, furadienone **10** afforded monoadduct **71** as the sole product.



Two experimental findings suggest that the α'-hydroxy enone is not formed. First, if such an intermediate were present, one would expect in the presence of excess reagent at least partial conversion to the β,β-dialkylated hydroxy ketone;[46] no such products (<1%) were observed. Second, furanone **68** would not yield to a retro-5-endo-trigonal opening upon prolonged treatment with excess base (i.e., LDA/THF).[47] Collectively, we take the

(28) (a) H. E. Zimmerman in "Molecular Rearrangements", P. de Mayo, Ed., Interscience, New York, 1963, p 345; (b) A. C. Cope, H. L. Holmes, and H. O. House, *Org. React.*, **9**, 102 (1957); (c) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9; (d) M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972); (e) J. L. Hermann, G. R. Kieczykowski, and R. H. Schlessinger, *ibid.*, 2433 (1973); (f) S. A. G. de Graaf, P. E. R. Osterhoff, and A. van der Gen, *ibid.*, 1653 (1974).

(29) M. Yamamoto and N. Sugiyama, *Bull. Chem. Soc. Jpn.*, **48**, 508 (1975).

(30) Regioselective γ-alkylation has been reported for vinylogous amides; see: M. Yoshimoto, N. Ishida, and T. Hiraoka, *Tetrahedron Lett.*, 39 (1973); T. A. Bryson and R. B. Gammill, *ibid.*, 3963 (1974).

(31) (a) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973); (b) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *ibid.*, **95**, 6137 (1973); (c) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973).

(32) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).

(33) C. Venturello and R. D'Aloisio, *Synthesis*, 754 (1977).

(34) Prepared by alkylation of **45**. For earlier preparation see I. I. Nazarova, B. P. Gusev, and V. F. Kucherov, *Isv. Akad. Nauk USSR*, 729 (1965).

(35) J. A. Rampes, S. Hoff, P. Montijn, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **88**, 1445 (1969).

(36) Ae. de Groot and B. J. M. Jansen, *Recl. Trav. Chim. Pays-Bas*, **93**, 153 (1974).

(37) F. Korte and H. Machleidt, *Chem. Ber.*, **90**, 2137 (1957).

(38) Prepared by the method of Stork and Kraus; see G. Stork and G. A. Kraus, *J. Am. Chem. Soc.*, **98**, 2351 (1976).

(39) J. A. Katzenellenbogen and A. L. Crumrine, *J. Am. Chem. Soc.*, **96**, 5662 (1974); also see J. A. Katzenellenbogen and A. L. Crumrine, *ibid.*, **98**, 4925 (1976).

(40) M. W. Rathke and D. Sullivan, *Tetrahedron Lett.*, 4249 (1972).

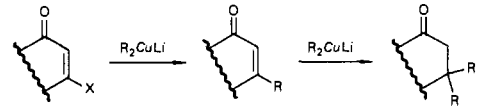
(41) J. L. Herrmann, G. R. Kieczykowski, and R. H. Schlessinger, *Tetrahedron Lett.*, 2433 (1973).

(42) For a preliminary account of this work see P. J. Jerris and A. B. Smith, III, *Synth. Commun.*, **8**, 421 (1978).

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

(44) (a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976); (b) J. E. Baldwin, J. Cutting, W. Dupont, L. Kruse, L. Silberman, and R. C. Thomas, *ibid.*, 736 (1976); (c) J. E. Baldwin, *ibid.*, 738 (1976); (d) J. E. Baldwin, R. C. Thomas, K. I. Kruse, and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

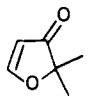
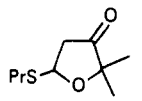
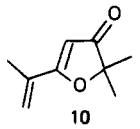
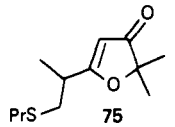
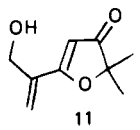
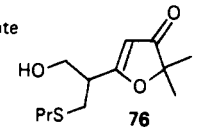
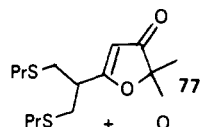
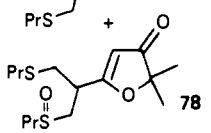
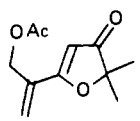
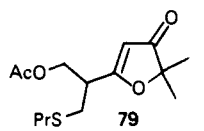
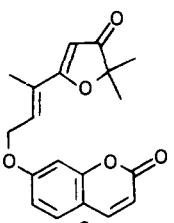
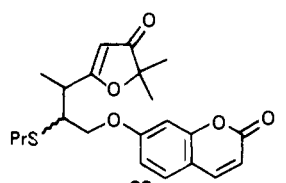
(45) It is now generally recognized that an enone possessing a good leaving group at the β-carbon affords mono-β-alkylated enone derivatives when 1 equiv of reagent is employed and β,β-dialkylated systems in the presence of excess reagent.



See, for example: (a) C. R. Casey, D. F. Marten, and R. A. Boggs, *Tetrahedron Lett.*, 2071 (1973); (b) R. M. Coates and R. L. Sowerby, *J. Am. Chem. Soc.*, **93**, 1027 (1971); (c) G. H. Posner and D. J. Brunelle, *J. Chem. Soc., Chem. Commun.*, 907 (1973); (d) S. Casschi, A. Caputo, and D. Misiti, *Indian J. Chem.*, **12**, 325 (1974); (e) E. Piers and D. I. Nagakura, *J. Org. Chem.*, **40**, 2694 (1975); (f) E. Piers, C. K. Lau, and I. Nagakura, *Tetrahedron Lett.*, 3233 (1976).

(46) H Mori, *Chem. Pharm. Bull.*, **12**, 1224 (1964).

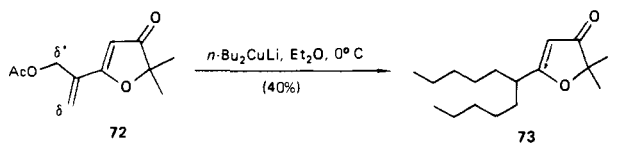
Table IV. Reactions of Simple 3(2*H*)-Furanones and Furandienones with Propanethiol

Entry	Substrate	Reaction conditions	Product	Yield (percent)
1 *(a)*	 13	Benzene/*i*-Pr_2NH	 74	54
(b)		Benzene		NR
(c)		Benzene/TsOH		48
2 *(a)*	 10	Benzene/*i*-Pr_2NH	 75	42
(b)		Benzene		NR
(c)		Benzene/TsOH		70
3 *(a)*	 11	Benzene/Et_3N or borate buffer (pH 9)	 76	62 57
(b)		Benzene	 77 +  78	32 22
(c)		Benzene/TsOH	77	60
4 *(a)*	 72	Benzene	 79	32
(b)		Benzene/TsOH	77	58
(c)		Benzene/Et_3N	77	30
5 *(a)*	 3	Benzene/*i*-Pr_2NH	 80	40
(b)		Benzene/TsOH		47

above results as further support of the Baldwin rules for ring closure.

Finally, we note that conjugate addition of lithium diphenylcuprate to **13**,[12] followed by selenium dioxide oxidation in *tert*-butyl alcohol,[48] provides a second approach to bullatenone (**27**).[16]

With these observations in hand, we next subjected furadienone **72**, which possesses on the δ' carbon a good leaving group, to excess lithium di-*n*-butylcuprate. Our intention here was to effect a δ,δ'-conjugate addition; indeed, furanone **73** was obtained in 40% yield. To the best of our knowledge this is the *first example of a δ,δ'-conjugate addition.*



72 73

(47) This result is consistent with the Baldwin observation that the 5-phenyl derivative **70** undergoes complete deuterium exchange at the α-position with no appreciable elimination to the corresponding hydroxyenone; see ref 44d.

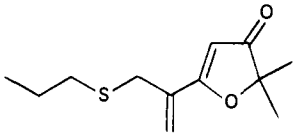
(48) S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **82**, 1235 (1960).

Conjugate Addition of Propanethiol to Simple 3(2*H*)-Furanones. Persuant to our interest in the mode of action of the antitumor agents possessing the 3(2*H*)-furanone ring system, we examined the reactivity of several of the above model systems with excess propanethiol, employing acidic, neutral, and basic reaction conditions. In addition to defining the site and degree of reactivity in simple 3(2*H*)-furanones, we were particularly interested in establishing the feasibility of a bis-β,β'-conjugate addition of propanethiol to a furadienone such as **11**. Our results are illustrated in Table IV.

Several comments are in order. First, the simple 3(2*H*)-furanone **13** and furadienone **10** underwent, respectively, 1,4- and 1,6-conjugate addition of propanethiol under acidic and basic conditions, but not under neutral conditions. This general reactivity of the 3(2*H*)-furanone system to propanethiol further supports the suggestion of Le Quesne,[3] that the γ position of eremantholide A serves as the electrophilic site for bionucleophiles. *Significant in this regard is the fact that our model 3(2H)-furadienone **10** was shown by the NCI to possess presumptive antitumor activity.*[49]

(49) Furandienone **10** displayed presumptive activity against P-388 lymphocytic leukemia (T/C = 128 at 100 mg/kg).

The reactivity of furadienone **11**, on the other hand, was found to be quite dependent upon the reaction conditions: protocols employing basic conditions afforded only monoadduct **76**, while reactions effected under neutral or acidic conditions led only to bis-adducts **77** and **78**, the latter demonstrated to arise via air oxidation. Presumably basic conditions inhibit loss of water, thereby preventing addition of a second equivalent of propanethiol. However, under acidic or neutral conditions loss of water is not precluded, the result being generation of a new furadienone system (i.e., **81**) capable of accepting a second equivalent of propanethiol.



81

We were concerned, however, that a free radical mechanism might play a significant role in these reactions, particularly those carried out under neutral conditions, since propanethiol is known to undergo facile free radical addition to olefins.[50] To explore this possibility, we examined the addition of propanethiol to **11** and **72** in the presence of the free radical inhibitor 2,5-di-*tert*-butylhydroquinone. As foreshadowed above, the presence of this inhibitor under neutral conditions resulted in complete recovery of starting furanone. No change in product formation occurred, however, when acidic or basic catalysis was employed. This result is consistent with the predominance of a free radical induced addition of propanethiol under neutral conditions and a polar addition under acidic or basic regimes.

Experimental Section

Materials and Methods. Vapor phase chromatography employed one of the following columns: A, 12.5% OV-101, 10 ft × 0.25 in.; B, 25% Carbowax 20M, 10 ft × 0.25 in.; C, 6% SE-30, 10 ft × 0.25 in.; D, 25% QF-1, 10 ft × 0.25 in.; E, 6% QF-1, 10 ft × 0.25 in.; F, 6% Carbowax 20M, 10 ft × 0.25 in. Preparative thin-layer chromatography was carried out on Analtech silica GF chromatography plates. Melting points are corrected. THF was distilled from sodium benzophenone ketyl, Et_2O from $LiAlH_4$, benzene from sodium, CH_2Cl_2 from P_2O_5, and diisopropylamine and pyridine from calcium hydride under a nitrogen atmosphere. Solutions were dried over $MgSO_4$ unless specified otherwise. IR and ^1H NMR spectra were obtained for CCl_4 or $CDCl_3$ solutions. The internal standard was Me_4Si.

General Procedure for the Synthesis of α-Acyloxy Ketones. Isobutyric Ester of 3-Hydroxy-3-methyl-2-butanone (22). To a cold solution (0 °C) of 3.8 mL (36.0 mmol) of 3-hydroxy-3-methyl-2-butanone (75 mL of pyridine) 4.2 mL (40.0 mmol) of isobutyryl chloride was added dropwise. After refluxing for 3 h, the reaction mixture was cooled, poured into ether, and washed with 10% HCl and 5% $NaHCO_3$ solution. Removal of solvents in vacuo yielded 5.66 g. Kugelrohr distillation [bp 50 °C (0.7 torr)] yielded 5.25 g (85%) of **22**: IR 1725 (s), 1470, 1150, 1120, 1030 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.15 (d, J = 7 Hz, 6 H), 1.35 (s, 6 H), 2.0 (s, 3 H), 2.5 (m, 1 H).

Benzoate Ester of 3-Hydroxy-3-methyl-2-butanone (23). Distillation [bp 125–130 °C (3.5 torr)] yielded (74%) **23**: IR 1720 (s), 1601 (w), 1580 (w), 1300, 1150 (br), 1030 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.55 (s, 6 H), 2.0 (s, 3 H), 7.4 (m, 3 H), 8.0 (m, 2 H).

***tert*-Butyrate Ester of 3-Hydroxy-3-methyl-2-butanone (24).** IR 1720 (s), 1470, 1165 (s), 1030, 1020 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.3 (s, 9 H), 1.42 (s, 6 H), 2.0 (s, 3 H).

Acetate Ester of 3-Hydroxy-3-methyl-2-butanone (17). Distillation [bp 62–64 °C (12 torr)] yielded (77%) **17**: IR 1715 (s), 1360, 1260, 1165 (s), 1130 (s), 1020 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.4 (s, 6 H), 2.0 (s, 6 H).

3,3-Dimethylacrylate Ester of 3-Hydroxy-3-methyl-2-butanone (25). To a solution of 4 g of powdered 3-Å molecular sieves and 20 mL (20 mmol) of 3-hydroxy-3-methyl-2-butanone in 40 mL of CCl_4 was added 2.95 g (25 mmol) of 3,3-dimethylacrolyl chloride. The reaction was heated at reflux for 4 days, cooled, and filtered and solvents were removed in vacuo. Kugelrohr distillation [bp 75 °C (0.7 torr)] yielded 3.6 g (97%) of **25**: IR 1710 (s), 1650, 1240, 1145, 1115 (s), 1075 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.40 (s, 6 H), 1.90 (m, 3 H), 2.0 (s, 3 H), 2.12 (m, 3 H), 5.63 (m, 1 H).

Exact Mass Calcd for $C_{10}H_{16}O_3$: 184.1099. Found: 184.1105.

General Procedure for the Synthesis of 3(2*H*)-Furanones from α-Acyloxy Ketones. 2,2-Dimethyl-5-isopropyl-3(2*H*)-furanone (26).[35] To a solution containing 6.0 mmol of sodium hydride (NaH 50% oil dispersion) in 5 mL of dry Me_2SO heated at 80 °C for 0.5 h or until homogeneous was added all at once 650 mg (3.80 mmol) of the isobutyrate ester of 3-hydroxy-3-methyl-2-butanone. Stirring at 80 °C under argon was continued for a period of 1 h after which time the solution was cooled, treated with 3 M H_2SO_4 until acidic, and stirred for an additional 5 min. The solution was extracted into ether and washed with 5% $NaHCO_3$, excess water, and brine. Removal of solvents in vacuo followed by Kugelrohr distillation [bp 50 °C (1.5 torr)] afforded 391 mg (64%) of **26**. An analytical sample was obtained by preparative VPC on column A: IR 2980 (m), 2945 (w), 1705 (s), 1592 (s), 1470 (w), 1365 (w), 1185 (s), 945 cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.29 (s, 6 H), 1.24 (d, J = 7.5 Hz, 6 H), 2.64 (m, 1 H), 5.40 (s, 1 H).

2,2-Dimethyl-5-phenyl-3(2*H*)-furanone (Bullatenone) (27).[16] IR 1700 (s), 1605, 1599, 1560, 1180, 900, 680 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.38 (s, 6 H), 5.88 (s, 1 H), 7.47 (m, 3 H), 7.75 (m, 2 H).

2,2-Dimethyl-5-*tert*-butyl-3(2*H*)-furanone (28). IR 1705 (s), 1665 (w), 1590, 1175, 930, 870 cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.25 (s, 9 H), 1.32 (s, 6 H), 5.28 (s, 1 H).

3,5,5-Trimethyl-2(5*H*)-furanone (18).[51] IR 1755 (s), 1605 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.45 (s, 6 H), 2.03 (d, J = 2 Hz, 3 H), 5.70 (q, J = 2 Hz, 1 H).

3-(1-Methylethenyl)-4,5,5-trimethyl-2(5*H*)-furanone (30). An analytical sample of **30** was obtained by preparative VPC on column A: IR 3100 (w), 2990 (s), 1770 (s), 1300 (m), 1260 (m), 1060 (s), 974 (m), 910 (m) cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.41 (s, 6 H), 1.99 (s, 6 H), 4.98 (s, 1 H), 5.16 (s, 1 H).

Exact Mass Calcd for $C_{10}H_{14}O_2$: 166.0994. Found: 166.0994.

1-(1-Propionyl)-2-cyclopenten-1-ol (32). A solution of 17 mL (130 mmol) of 2-ethyldithiane[52] in 250 mL of THF was cooled to −30 °C and 59 mL of 2.2 M *n*-butyllithium was added over 10 min. The solution was stirred at −50 to −25 °C for 3 h, and 10 mL (120 mmol) of freshly distilled 2-cyclopentenone was added neat over 5 min at −10 to 0 °C.[52] The mixture was stored at 0 °C for 24 h. After solvents were removed in vacuo, 75 mL of water was added. The mixture was extracted with ether and the organic layer washed with H_2O. Removal of solvents in vacuo and Kugelrohr distillation [90 °C (1 torr)] to remove excess dithiane reagent afforded 22 g of dithiane adduct.

A solution of 10 g of the dithiane in 200 mL of aqueous 80% acetonitrile was added to a suspension of 39 g of mercuric chloride and 50 g of calcium carbonate in 400 mL of 80% acetonitrile,[53] and the resultant mixture was heated at reflux under N_2 for 5 h. The reaction mixture was allowed to cool to room temperature over 3 h and filtered, and the filter cake was washed with 1:1 methylene chloride–pentane. After removal of the organic solvent in vacuo, the aqueous mixture was extracted with methylene chloride; the organic layer washed with 5 M ammonium acetate, water, and brine and dried over sodium sulfate and decolorizing charcoal. Removal of solvent in vacuo and distillation [80–82 °C (8 torr)] yielded 2.84 g (37%) of **32**: IR 3500 (s), 3065 (m), 1710 (s), 1125 (s), 1085 (s), 1040 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.10 (t, J = 7 Hz, 3 H), 1.65–2.8 (complex, 6 H), 3.95 (br s, 1 H), 5.50 (m, 1 H), 6.10 (m, 1 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.31; H, 8.76.

2,3-Dimethyl-1-oxaspiro[4.4]nona-2,6-dien-4-one (33). A solution at 0 °C of 3 equiv of LDA was generated from 1 mL of diisopropylamine and 2.7 mL 2.2 M *n*-butyllithium in hexane, and the hexane was removed in vacuo. THF (20 mL) was added and the solution cooled to −78 °C, and 0.280 g (2.0 mmol) of **32** in 5 mL of THF was added over 5 min. The reaction was stirred at −78 °C for 45 min, and 660 mg (6.0 mmol) of *N*-acetylimidazole[17] in 8 mL of THF was added. The mixture was stirred at −78 °C for 1 h and allowed to warm to room temperature over 45 min. The mixture was poured into 2 N HCl, and extracted with ether, and the combined organic layers were washed with water and brine. Removal of solvents in vacuo afforded 276 mg of a mixture (37:63 by NMR) of product and starting material. An analytical sample of **33** was obtained by preparative VPC on column F: IR 1705 (s), 1640 (m), 1120

(50) See, for example, K. Griesbaum, *Angew. Chem., Int. Ed. Engl.*, **9**, 273 (1970), and references within.

(51) T. C. McMorris, *J. Org. Chem.*, **35**, 458 (1970).

(52) E. J. Corey and D. Seebach, *J. Org. Chem.*, **40**, 231 (1975).

(53) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971).

(s), 1040 (m), 840 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.60 (s, 3 H), 2.12 (s, 3 H), 2.2–2.8 (m, 4 H), 5.35 (m, 1 H), 6.20 (m, 1 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.15; H, 7.50.

2,2,5-Trimethyl-3(2*H*)-furanone (19).[34] To a solution of 2.4 equiv of LDA generated from 1.1 mL of diisopropylamine and 3.1 mL of 2.2 M *n*-butyllithium in 20 mL of THF at −78 °C, 315 μL (3.0 mmol) of 3-hydroxy-3-methyl-2-butanone in 5 mL of THF was added dropwise over 5 min. After 30 min at −78 °C, 440 mg (4.0 mmol) of *N*-acetylimidazole[17] in 10 mL of THF was added over 4 min. The reaction was stirred at −78 °C for 1 h and allowed to warm to room temperature over 1 h. The solution was poured into 50 mL of 2 N HCl and extracted with ether. The organic phase was washed with water and brine. Removal of solvent in vacuo and Kugelrohr distillation [100 °C (45 torr)] yielded 0.163 g of a mixture (3.4:1 by NMR) of **19** and starting material. Preparative VPC on column F yielded pure **19**: IR 1705 (s), 1605 (s), 1190 (s), 940, 860 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.25 (s, 6 H), 2.16 (s, 3 H), 5.20 (s, 1 H).

3-Methyl-3-(trimethylsiloxy)-2-butanone (35).[54] A solution of 4.2 mL (40.0 mmol) of 3-hydroxy-3-methyl-2-butanone, 22.4 mL (160 mmol) of triethylamine, and 10.2 mL (80 mmol) of chlorotrimethylsilane in 120 mL of DMF was stirred at room temperature under N_2 for 24 h. The reaction mixture was poured into 1:1 (v/v) ether–pentane and washed with saturated $NaHCO_3$, water, and brine. Removal of solvents in vacuo afforded 7.45 g of crude **35**. Distillation [bp 65–70 °C (19 torr)] yielded 6.36 g (91%) of pure **35**: IR 1710 (s), 1250 (s), 1200 (s), 1030 (s), 840 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 1.27 (s, 6 H), 2.08 (s, 3 H).

General Procedure for the Synthesis of 3(2*H*)-Furanones. 3-Hydroxy-6-methyl-6-(trimethylsiloxy)-1-hepten-5-one (34a). To a magnetically stirred solution of 1.2 equiv of LDA generated from 0.50 mL of diisopropylamine and 1.71 mL of *n*-BuLi (2.1 M) in 28 mL of THF at −78 °C, 0.523 g (3.01 mmol) of 3-methyl-3-(trimethylsiloxy)-2-butanone in 3 mL of THF was added dropwise over 5 min. After 45 min at −78 °C, 0.22 mL (3.29 mmol) of acrolein in 3 mL of THF was added and the mixture stirred 5 min at −78 °C followed by addition of saturated ammonium chloride solution. The reaction mixture was poured into ether and washed with brine. Removal of solvents in vacuo yielded 0.6149 g (89%) of **34a**: IR 3500, 3075, 1702 (s), 1648 (sm), 1200, 1040, 845 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 1.35 (s, 6 H), 2.80 (d, J = 6 Hz, 2 H), 3.15 (br s, 1 H), 4.58 (t, J = 6 Hz, 1 H), 5.2 (m, 1 H), 5.42 (m, 1 H), 5.7–6.2 (m, 1 H).[55]

6-Methyl-6-(trimethylsiloxy)-1-heptene-3,5-dione (31a). A solution of Collins reagent[21b] (6.2 equiv) was generated from 1.65 g (16.5 mmol) of CrO_3 and 2.67 mL (33.0 mmol) of pyridine in 134 mL of CH_2Cl_2. After the solution was stirred for 30 min at room temperature under N_2, 0.614 g (2.67 mmol) of **34a** in 8 mL of CH_2Cl_2 was added and the mixture was stirred 20 min at room temperature under N_2. The reaction mixture was poured into CH_2Cl_2 and washed with 5% NaOH, 10% HCl, saturated $NaHCO_3$, and brine. Removal of solvents in vacuo yielded 0.344 g (57%) of **31a**. An analytical sample was obtained by Kugelrohr distillation [55 °C (0.25 torr)]: IR 1705 (s), 1640, 1560, 1200, 1040, 845 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 1.33 (s, 6 H), 5.2–6.2, (m, s, m, 3 H), 6.23 (s, 1H).

Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.87; H, 8.77. Found: C, 58.25; H, 8.91.

2,2-Dimethyl-5-ethenyl-3(2*H*)-furanone (9). A solution of 9.3438 g (1.51 mmol) of **31a**, 78 mL of 50% aqueous THF, and 43 mL of 5% HCl was stirred at room temperature under N_2 for 4.5 h. The mixture was poured into brine and extracted with Et_2O, and the combined organic materials were washed with saturated $NaHCO_3$. Removal of solvents in vacuo afforded 0.179 g of **9**. Kugelrohr distillation [bp 35–50 °C (0.08 torr)] yielded 0.105 g (50 %) of **9**: IR 1700 (s), 1655 (sm), 1640, 1180, 950, 930 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.30 (s, 6 H), 5.43 (s, 1 H), 5.6–6.67 (m, 3 H).

Exact Mass Calcd for $C_8H_{10}O_2$: 138.068. Found: 138.0675.

2,6-Dimethyl-3-hydroxy-6-(trimethylsiloxy)-1-hepten-5-one (34b). IR 3500, 3075, 1720, 1660, 1200, 1050, 850, 680 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.01 (s, 9 H), 1.48 (s, 6 H), 1.75 (br s, 3 H), 2.77 (d, J = 6 Hz, 2 H), 3.00 (br s, 1 H), 4.37 (t, J = 6 Hz, 1 H), 4.77 (br s, 1 H), 4.93 (br s, 1 H).

2,6-Dimethyl-6-(trimethylsiloxy)-1-heptene-3,5-dione (31b). Kugelrohr distillation [70 °C (0.20 torr)] provided an analytical sample of **31b**: IR 3500 (sm) 1690 (s), 1610, 1590, 905, 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.01 (s, 9 H), 1.30 (s, 6 H), 1.83 (br s, 3 H), 5.28 (br s, 1 H), 5.87 (br s, 1 H), 6.10 (s, 1 H).[55]

Anal. Calcd for $C_{12}H_{22}O_3Si$: C, 59.48; H, 9.09. Found: C, 59.24; H, 9.19.

2,2-Dimethyl-5-(1-methylethenyl)3(2*H*)-furanone (10). Kugelrohr distillation [28 °C, (0.05 torr)] yielded (60%) **10**: IR 1705 (s), 1640 (s), 1550, 1175, 850 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.48 (s, 6 H), 2.00 (m, 3 H), 5.33 (m, 1 H), 5.47 (s, 1 H), 5.88 (m, 1 H).

2-[(*tert*-Butyldimethylsiloxy)methyl]-3-hydroxy-6-methyl-6-(trimethylsiloxy)-1-hepten-5-one (34). IR 3500 (br), 1705 (br, sm), 1100 (br), 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10, 0.17 (s, s, 15 H), 0.93 (s, 9 H), 1.35 (s, 6 H), 2.88 (d, J = 6 Hz, 2 H), 3.33 (br s, 1 H), 4.22 (br s, 1 H), 4.53 (t, J = 6 Hz, 1 H), 5.08 (br s, 2 H).

2-[(*tert*-Butyldimethylsiloxy)metyl]-6-(trimethylsiloxy)-1-heptene-3,5-dione (31c). Preparative thin-layer chormatography (1:2 Et_2O–CH_2Cl_2, R_f 0.81) yielded an analytical sample of **31c**: IR 1720 (s), 1700 (sm), 1575, 1100 (br), 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 6 H), 0.17 (s, 9 H), 0.92 (s, 9 H), 1.40 (s, 6 H), 4.35 (br s, 2 H), 5.75 (br s, 1 H), 6.05 (br s, 1 H), 6.17 (s, 1 H).[55]

Anal. Calcd for $C_{18}H_{36}O_4Si_2$: C, 58.07; H, 9.68. Found: C, 58.19; H, 9.61.

2,2-Dimethyl-5-[1-(hydroxymethyl)ethenyl]-3(2*H*)-furanone (11). A solution of 0.656 g (1.74 mmol) of **31c**, 86 mL of 50% aqueous THF, and 47 mL of 5% HCl was stirred at room temperature under N_2 for 4 h. The mixture was poured into brine and thoroughly extracted with Et_2O, and the combined organic material was washed with saturated $NaHCO_3$. Removal of solvents in vacuo afforded 0.4756 g of a yellow-orange oil which by IR [1700 (br), 1650 (w)] was shown to possess the furanone ring. This oil was then dissolved in a mixture of 8 mL of THF, 8 mL of H_2O, and 24 mL of glacial acetic acid, and the solution was stirred for 18 h at room temperature. Removal of solvents in vacuo followed by preparative thin-layer chromatography (Et_2O, R_f 0.30) afforded 0.1250 g (43%) of **11**: IR 3420, 1702 (s), 1644, 1601, 1175 cm^{-1}; NMR ($CDCl_3$, 220 MHz) δ 1.37 (s, 6 H), 3.17 (br s, 1 H), 4.38 (m, 2 H), 5.63 (s, 1 H), 5.78 (m, 1 H), 6.12 (m, 1 H).

Exact Mass Calcd for $C_9H_{12}O_3$: 168.0786. Found: 168.0788.

1-Hydroxy-4-methyl-1-phenyl-4-(trimethylsiloxy)-3-pentanone (34d). An analytical sample was prepared by preparative thin-layer chromatography [1:1 (v:v) ether–methylene chloride, R_f 0.89]: IR 3500 (s), 1705 (s), 1210, 1050, 850 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.01 (s, 9 H), 1.33 (s, 6 H), 2.83 (d, J = 6.5 Hz, 2 H), 3.28 (br s, 1 H), 4.90 (t, J = 6.5 Hz, 1 H), 7.1 (br s, 5 H).

Anal. Calcd for $C_{15}H_{24}O_3Si$: C, 64.26; H, 8.57. Found: C, 64.17; H, 8.36.

4-Methyl-1-phenyl-4-(trimethylsiloxy)-1,3-pentanedione (31d). Preparative thin-layer chromatography (1:8 ether–pentane, R_f 0.69) yielded an analytical sample of **31d**: IR 1601 (br), 1560 (br), 1200, 1044, 900, 840, 685 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 1.45 (s, 6 H), 6.43 (s, 1 H), 7.27 (br s, 3 H), 7.67 (br s, 2 H).[55]

Anal. Calcd for $C_{15}H_{22}O_3Si$: C, 64.72; H, 7.91. Found: C, 64.64; H, 7.94.

2,2-Dimethyl-5-phenyl-3(2*H*)-furanone (Bullatenone) (27).[16] Preparative thin-layer chromatography (1:2 Et_2O–CH_2Cl_2, R_f 0.69) yielded 0.091 g (78%) of a white solid (mp 64–65 °C), identical in all respects with bullatenone prepared previously above.

5-Hydroxy-2-methyl-2-(trimethylsiloxy)-3-heptanone (34e). IR 3550, 1705 (s), 1200, 1040, 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.01 (s, 9 h), 0.8–1.5 (m, s, 11 H), 2.50 (d, J = 4 Hz, 2 H), 2.85 (br s, 1 H), 3.75 (m, 1 H).[55]

Anal. Calcd for $C_{11}H_{24}O_3Si$: C, 56.85; H, 10.41. Found: C, 56.58; H, 10.33.

2-Methyl-2-(trimethylsiloxy)-3,5-heptanedione (31e). IR 3500 (sm), 1700 (s), 1600, 1200, 1040, 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 1.13 (t, J = 7 Hz, 3 H), 1.40 (s, 6 H), 2.30 (q, J = 7 Hz, 2 H), 5.90 (s, 1 H).

Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.37; H, 9.56. Found: C, 57.51; H, 9.84.

2,2-Dimethyl-5-ethyl-3(2*H*)-furanone (37). Kugelrohr distillation [bp 100 °C (31 torr)] yielded (66%) of **37**: IR 1710 (s), 1600 (s), 1180, 920 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.29 (s, 3 H), 1.30 (t, J = 7.5 Hz, 3 H, 2.27–2.67 (q, J = 7.5 Hz, 2 H), 5.23 (s, 1 H).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.59; H, 8.63. Found: C, 68.43; H, 8.40.

General Aldol Procedure Used in Synthesis of Furanones 38–40. 5-Hydroxy-2-methyl-2-(trimethylsiloxy)-3-nonanone (34f). To a magnetically stirred solution of 1.2 equiv of LDA generated from 0.35 mL of diisopropylamine and 1.1 mL of 2.2 M *n*-BuLi in 16 mL of THF at −78 °C, 0.3360 g (1.93 mmol) of 3-methyl-3-(trimethylsiloxy)-2-butanone in 4 mL of THF was added dropwise over 5 min. After 45 min at −78

(54) D. J. Costa, N. E. Boutin, and J. G. Riess, *Tetrahedron*, **30**, 3793 (1977).

(55) The enolic proton of 1,3-diketones is very broad and thereby not readily observed.

°C, 2.75 mL (0.955 mmol) of saturated (0.35 M) zinc chloride/THF solution[19] was added and the reaction stirred 5 min; then 0.1896 g (2.20 mmol) of valeraldehyde in 6 mL of THF was added and the mixture was stirred 5 min at −78 °C, followed by addition of saturated ammonium chloride solution. The reaction mixture was poured into ether and washed with brine. Removal of solvents in vacuo yielded 0.386 g (77 %) of **34f**: IR 3500 (br), 1710 (s), 1200 (s), 1040 (s), 840 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 0.95 (t, J = 6 Hz, 3 H), 1.35 (br s, m, 10 H), 2.60 (d, J = 4 Hz, 1 H), 2.66 (s, 1 H), 3.2 (br s, 1 H), 3.83 (m, 1 H).

2-Methyl-2-(trimethylsiloxy)-3,5-nonanedione (31f). An analytical sample of **31f** was obtained by Kugelrohr distillation [80 °C (0.20 torr)]: IR 1705 (m), 1690 (s), 1200 (s), 840 cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 0.90 (br t, J = 6 Hz, 3 H), 1.40–1.8 (s, m, 10 H), 2.20 (t, J = 6 Hz, 2 H), 5.75 (s, 1 H).[55]

Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.44; H, 10.07. Found: C, 60.58; H, 10.23.

2,2-Dimethyl-5-*n*-butyl-3(2*H*)-furanone (38). Preparative thin-layer chromatography (Et_2O, R_f 0.70) yielded (45%) of **38**: IR 1705 (s), 1600 (s), 1180 (m), 950 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.00 (t, J = 6 Hz, 3 H), 1.33 (s, 6 H), 1.60 (m, 4 H), 2.17 (t, J = 7 Hz, 2 H), 5.25 (s, 1 H).

Exact Mass Calcd for $C_{10}H_{16}O_2$: 168.1150. Found: 168.1150.

5-Hydroxy-2-methyl-2-(trimethylsiloxy)-3-undecanone (34g). IR 3500 (br, m), 1715 (s), 1200 (br), 1040 (s), 940 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 0.95 (t, J = 5 Hz, 3 H), 1.33 (br s, 16 H), 2.63 (d, J = 4 Hz, 1 H), 2.73 (s, 1 H), 3.25 (br s, 1 H), 3.80 (m, 1 H).

2-Methyl-2(trimethylsiloxy)-3,5-undecanedione (31g). An analytical sample of **31g** was obtained by Kugelrohr distillation [100 °C (0.20 torr)]: IR 1700 (w), 1600 (br s), 1200 (s), 1640 (s), 840 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 0.95 (t, J = 5 Hz, 3 H), 1.33 (br s, 14 H), 2.17 (t, J = 6 Hz, 2 H), 5.75 (s, 1 H).[55]

Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.92; H, 10.49. Found: C, 62.87; H, 10.70.

2,2-Dimethyl-5-hexyl-3(2*H*)-furanone (39). Kugelrohr distillation [bp 50–60 °C (0.06 torr)] yielded (62%) of **39**: IR 1700 (s), 1600 (s), 1180 (s), 940 (w) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.93 (t, J = 5 Hz, 3 H), 1.33 (s, m, 14 H), 2.50 (t, J = 7 Hz, 2 H), 5.27 (s, 1 H).

Exact Mass Calcd for $C_{12}H_{28}O_2$: 196.1463. Found: 196.1457.

2-Hydroxy-5-methyl-1-phenyl-5-(trimethylsiloxy)-4-heptanone (34h). IR 3500 (br), 1705 (s), 1380 (m), 1200 (s), 1040 (s), 840 (s), 700 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.01 (s, 9 H), 1.27 (s, 6 H), 2.67 (d, J = 7 Hz, 2 H), 3.60 (d, J = 6 Hz, 2 H), 4.17 (m, 1 H), 7.31 (br s, 5 H).

5-Methyl-1-phenyl-5-(trimethylsiloxy)-2,4-heptanedione (31h). Preparative thin-layer chromatography (1:1 ether–pentane, R_f 0.74) yielded an analytical sample: IR 1700 (w), 1600 (br s), 1200 (m), 1040 (m), 840 (m), 700 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.10 (s, 9 H), 1.28 (s, 6 H), 3.50 (s, 2 H), 5.67 (s, 1 H), 7.17 (br s, 5 H).[55]

Anal. Calcd for $C_{16}H_{24}O_3Si$: C, 65.73; H, 8.22. Found: C, 65.56; H, 8.45.

2,2-Dimethyl-5-benzyl-3(2*H*)-furanone (40). Preparative thin-layer chromatography (Et_2O, R_f 0.62) yielded (50%) of **40**: IR 1700 (s), 1600 (s), 1380 (m), 1180 (s), 940 (w), 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.30 (s, 6 H), 3.67 (s, 2 H), 5.08 (s, 1H), 7.20 (s, 5 H).

Exact Mass Calcd for $C_{13}H_{14}O_2$: 202.0994. Found: 202.0988.

2-Methyl-2-(trimethylsiloxy)-3-pentanone (41).[56] To a stirred solution of 1.2 equiv of LDA generated from 0.36 mL of diisopropylamine and 1.15 mL of 2.2 M *n*-BuLi in 16 mL of THF at −78 °C, 0.355 g (2.04 mmol) of 3-methyl-3-(trimethylsiloxy)-2-butanone in 3 mL of THF was added dropwise over 5 min. After 50 min at −78 °C, 140 μL (2.25 mmol) of methyl iodide in 3 mL of THF was added. The reaction mixture was stirred at room temperature for 30 min, poured into ether, and washed with brine. Removal of solvent in vacuo yielded 0.271 g. Kugelrohr distillation [bp 100–110 °C, (30 torr)] yielded 0.227 g (60%) of **41**: IR 1710 (s), 1250 (s), 1200 (s), 1030 (s), 840 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 1.00 (t, J = 7 Hz, 3 H), 1.30 (s, 6 H), 2.60 (q, J = 7 Hz, 2 H).

3,5-Dimethyl-2-hydroxy-1-phenyl-5-(trimethylsiloxy)-4-heptanone (34i). IR 3500 (m), 1710 (s), 1040 (s), 845 (s), 700 (s); NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 1.27 (br s, 9 H), 2.63 (m, 3 H), 3.57 (m, 2 H), 7.17 (br s, 5 H).

3,5-Dimethyl-1-phenyl-5-(trimethylsiloxy)-2,4-heptanedione (31i). An analtyical sample of **31i** was obtained by preparative thin-layer chromatography (1:1 ether–pentane, R_f 0.71): IR 1710 (s), 1705 (s), 1255 (s), 1630 (s), 880 (s), 835 (s), 690 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 0.17 (s, 9 H), 1.10 (d, J = 7 Hz, 3 H), 1.33 (s, s, 6 H), 3.60 (s, 2 H), 4.17 (q, J = 7 Hz, 1 H), 7.13 (br s, 5 H).[55]

5-Benzyl-2,2,4-trimethyl-3(2*H*)-furanone (42). Preparative thin-layer chromatography (1:1) ether–pentane, R_f 0.42) yielded (18%) **42**: IR 1705 (s), 1628 (s), 1090 (s), 700 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.27 (s, 6 H), 1.65 (s, 3 H), 3.73 (s, 2 H), 7.20 (s, 5 H).

Exact Mass Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.1148.

α-Bromoacrolein.[24] A suspension of 11.22 g (0.20 mol) of acrolein in 100 mL of H_2O was cooled to 0 °C. Bromine (32 g, 0.205 mol) was added dropwise over a 2.5-h period. After the solution was stirred an additional 30 min the product was steam-distilled from the reaction mixture. The organic layer was redistilled through a Vigreux column [39 °C (17 torr)], yielding 14.98 g (56%) of α-bromoacrolein: IR 1700 (s), 1599, 900 cm^{-1}; NMR (CCl_4, 60 MHz) δ 6.83 (q, J = 3.5 Hz, 2 H), 9.25 (s, 1 H).

1,1-Diethoxy-2-bromo-2-propene (43).[25] To 14.98 g (0.11 mol) of α-bromoacrolein were added 20.35 g (0.1375 mol) of ethyl orthoformate, 6 mL of absolute ethanol, and 0.45 g of ammonium nitrate. The soltuion was refluxed for 1.5 h to a dark red color, cooled, and filtered and volatile solvents were removed in vacuo. The remaining red oil was fractionally distilled through a Vigreux column at 21 torr; the forerun before 70 °C was discarded, affording 16.64 g (77%) (bp 73–75 °C) of **43**: IR 1640, 1100 (br) 910 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.17 (t, J = 7 Hz, 6 H), 3.5 (dq, J = 7 Hz, 2 Hz, 4 H), 4.78 (s, 1 H), 5.63 (m, 1 H), 6.05 (m, 1 H).

1,1-Diethoxy-2-(hydroxymethyl)-2-propene (44).[23] A solution of 0.500 g (2.39 mmol) of 1,1-diethoxy-2-bromo-2-propene and several crystals of 2,2′-dipyridyl indicator in 15 mL of THF was cooled to −78 °C under N_2. *n*-BuLi (2.30 M; 1.25 mL, 2.868 mmol) was added. The reaction was stirred 1 h at −78 °C; then gaseous formaldehyde was bubbled in rapidly while the reaction temperature was maintained between −78 and −72 °C. Once the indicator color had changed from red to yellow, the reaction was continued for 15 min, and then quenched with 5 mL of saturated ammonium chloride solution. The reaction mixture was poured into ether and washed with brine. Removal of solvents in vacuo yielded 0.340 g. Kugelrohr distillation [bp 48–50 °C (0.25 torr)] yielded 0.275 g (72%) of **44**: IR 3400, 1665 (sm, br), 1250 (br), 925 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.15 (t, J = 7 Hz, 3 H), 2.8 (br s, 1 H), 3.48 (dq, J = 7 Hz, 3 Hz, 4 H), 4.0 (br s, 2 H), 4.83 (s, 1 H), 5.17 (br s, 2 H).

1,1-Diethoxy-2-[(*tert*-butyldimethylsiloxy)methyl]-2-propene. A solution of 1.10 g (6.92 mmol) of **44**, 1.05 g (15.22 mmol) of imidazole, and 1.15 g (7.61 mmol) of *tert*-butyldimethylsilyl chloride in 70 mL of distilled DMF was stirred at room temperature under N_2 for 36 h.[26] The solution was poured into 1:1 ether–pentane and washed with brine. Removal of solvents in vacuo yielded 1.823 g. Kugelrohr distillation [bp 60 °C (0.20 torr)] yielded 1.718 g (91%) of the silyl compound: IR 1665 (sm, br), 1080 (br), 850 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.03 (s, 6 H), 0.88 (s, 9 H), 1.15 (t, J = 7 Hz, 3 H), 3.45 (dq, J = 7 Hz, 3 Hz, 4 H), 4.07 (br s, 1 H), 4.73 (s, 1 H), 5.17 (m, 2 H).

Anal. Calcd for $C_{14}H_{30}O_3Si$: C, 61.31; H, 10.95. Found: C, 61.36; H, 10.83.

2-[(*tert*-Butyldimethylsiloxy)methyl]acrolein (36c). A solution of 0.500 g (1.83 mmol) of 1,1-diethoxy-2-[(*tert*-butyldimethylsiloxy)-methyl]-2-propene and 100 mg of oxalic acid in 20 mL of 9:1 (v:v) CH_2Cl_2–H_2O was gently refluxed for 72 h. The solution was cooled and anhydrous sodium carbonate was added until no further CO_2 evolution was observed; the mixture was then stirred 15 min, poured into CH_2Cl_2, and washed once with 50% saturated sodium bicarbonate solution. Removal of solvents in vacuo yielded 0.430 g. Kugelrohr distillation [bp 30 °C (0.25 torr)] yielded 0.318 g (87%) of **36c**: IR 1690 (s), 1120, 840 (br) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 4.22 (m, 2 H), 6.08 (m, 1 H), 6.50 (m, 1 H), 9.58 (s, 1 H).

Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 60.00; H, 10.00. Found: C, 60.00; H, 10.15.

General Procedure for the γ-Alkylation of 3(2*H*)-Furanones. 2,2-Dimethyl-5-*tert*-butyl-3(2*H*)-furanone (28). To a solution containing 10 mL of THF, 0.295 mL (2.10 mmol) of diisopropylamine, and 0.395 mL (2.2 mmol) of HMPA cooled under argon at 0 °C was added, with stirring, 1.0 mL of 2.2 M *n*-BuLi. After the addition was complete the solution was cooled to −78 °C and stirred for 30 min, followed by slow addition of 324 mg (2.07 mmol) of 2,2-dimethyl-5-isopropyl-3(2*H*)-furanone in 5 mL of THF. After the addition the solution was stirred for 45 min at −78 °C and quenched with 0.284 g (2.0 mmol) of MeI. The reaction was allowed to warm to room temperature over 30 min, quenched with 10% HCl (5 mL), and extracted into ether. The organic layer was washed with 10% HCl, water, and brine. Removal of solvent in vacuo afforded 336.4 mg (93%) of a solid (mp 62 °C). An analytical sample of **28**, obtained from preparative VPC on column A, was identical in all respects with that prepared above.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.58; H, 9.45.

(56) C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8109 (1977).

2,2,5-Trimethyl-3(2*H*)-furanone (19).[34] Kugelrohr distillation [bp 100 °C (45 torr)] yielded **19** in 85% yield, identical in all respects with that prepared above.

2,5-Dimethyl-2-(1-pentenyl)-3(2*H*)-furanone (54). Kugelrohr distillation [bp 80 °C (1 torr)] yielded (87%) **54**. An analytical sample was obtained by preparative VPC on column A: IR 3090 (sm), 1710, 1655 (sm), 1100 (br), 920 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.20 (s, 3 H), 1.30–2.10 (m, 6 H), 2.11 (s, 3 H), 4.70–5.15 (complex m, 2 H), 5.20 (br s, 1 H), 5.58 (m, 1 H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.46; H, 9.10.

2-(2-Butynyl)-2,5-dimethyl-3(2*H*)-furanone (46). Kugelrohr distillation [bp 110 °C (15 torr)] yielded (71%) **46**: IR 1700 (s), 1599 (s), 1105 (m), 910 (s) cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.28 (s, 3 H), 1.73 (t, J = 1.0 Hz, 3 H) 2.16 (s, 3 H), 2.35 (m, 2 H), 5.23 (s, 1 H).

Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.13; H, 7.40.

2,2-Dimethyl-5-ethyl-3(2*H*)-furanone (37). Kugelrohr distillation [bp 100 °C (31 torr)] yielded (85%) **37** identical in all respects with that prepared above.

2,2-Dimethyl-5-hexyl-3(2*H*)-furanone (39). Kugelrohr distillation [bp 90 °C (0.5 torr)] yielded (84%) **39**. An analytical sample, obtained by preparative VPC on column A, was identical in all respects with that prepared above.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.24; H, 10.45.

2,2-Dimethyl-5-(1,1-dimethyl-3-butenyl)-3(2*H*)-furanone (55). An analytical sample of **55** was obtained by preparative VPC on column A: IR 3110 (w), 3000 (m), 1702 (s), 1580 (s), 1350 (m), 1185 (s), 1080 (m), 1000 (w), 925 (m) cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.20 (s, 6 H), 1.29 (s, 6 H), 1.29 (s, 6 H), 2.28 (d, J = 7 Hz, 2 H), 4.96 (m, 1 H), 5.61 (m, 1 H).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 73.12; H, 9.45. Found: C, 73.18; H, 9.34.

2,2-Dimethyl-5-(1,1-dimethylhexyl)-3(2*H*)-furanone (56). Kugelrohr distillation [bp 100 °C (0.5 torr)] yielded (83%) **56**. An analytical sample was obtained by preparative VPC on column A: IR 2960 (s), 2865 (s), 1701 (s), 1580 (s), 1190 (s), 1130 (m), 1088, 940 cm^{-1}; NMR (CCl_4, 220 MHz) δ 0.88 (t, J = 7.5 Hz, 3 H), 1.19 (s, 6 H), 1.27 (s, 6 H), 1.25–1.70 (m, 8 H), 5.18 (s, 1 H).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.10; H, 10.83.

2,2-Dimethyl-5-[1-methyl-1-(phenylseleno)ethyl]-3(2*H*)-furanone (57). Preparative TLC (Et_2O, R_f 0.70) yielded (75%) **57** as a yellow oil: IR 3080, (s), 1705 (s), 1580 (s), 1070 (s), 940 (m), 685 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.25 (s, 6 H), 1.54 (s, 6 H), 4.94 (s, 1 H), 7.15, 7.61 (m, 5 H).

2-(2-Butynyl)-5-ethyl-2-methyl-3(2*H*)-furanone (47). An analytical sample of **47** was obtained by preparative VPC on column B: IR 2985 (m), 1700 (s), 1695 (s), 1380 (m), 1117 (s), 992 (w), 921 (w) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.21 (t, J = 9.4 Hz, 3 H), 1.42 (s, 3 H), 1.77 (t, J = 3 Hz, 3 H), 2.54 (m, 2 H), 5.41 (s, 1 H).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.00; H, 7.89.

2-(2-Butynyl)-2-methyl-5-[1-(phenylseleno)ethyl]-3(2*H*)-furanone (58). IR 1702 (s), 1600 (s), 960 (s), 680 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.35 (s, 3 H), 1.80 (m, 2 H), 2.0 (m, 3 H), 2.5 (d, J = 5 Hz, 3 H), 5.3 (q, J = 5 Hz, 1 H), 5.80 (s, 1 H), 7.2–7.7 (m, 5 H).

2-Ethyl-6-methyl-4*H*-pyran-4-one (59).[57] An analytical sample of **59** was obtained by preparative TLC (Et_2O, R_f 0.32): IR 1670, 1620 (br), 915, 855 cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.28 (t, J = 7 Hz, 3 H), 2.20 (s, 3 H), 2.51 (q, J = 7 Hz, 2 H), 6.00 (br s, 2 H).

3-Ethoxy-2,6,6-trimethyl-2-cyclohexenone (60).[36] An analytical sample of **60** was obtained by preparative VPC on column C: NMR (CCl_4, 60 MHz) δ 1.15 (s, 6 H), 1.32 (t, J = 6 Hz, 3 H), 1.58 (t, J = 1.5 Hz, 3 H), 1.75 (t, J = 6 Hz, 2 H), 2.50 (br t, J = 6 Hz, 2 H), 3.99 (q, J = 6 Hz, 2 H).

2-(Carbomethoxy)-1-methylenetetrahydrofuran (61) and 2-(Carbomethoxy)-1-ethyl-4,5-dihydrofuran (62). The mixture was separated by preparative VPC on column A.

VPC I (**61**): NMR (CCl_4, 220 MHz) δ 1.43 (s, 3 H), 1.84 (m, 1 H), 2.59 (m, 1 H), 3.68 (s, 3 H), 3.84 (s, 1 H), 4.09 (m, 2 H), 4.16 (s, 1 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.82; H, 7.36.

VPC II (**62**): IR 1710 (s), 1650, 1230, 1085, 910 cm^{-1}; NMR (CCl_4, 220 MHz) δ 1.11 (t, J = 7.0 Hz, 3 H), 2.62 (q, J = 7.0 Hz, 2 H), 2.84 (t, J = 10.0 Hz, 2 H), 3.63 (s, 3 H), 4.36 (t, J = 10 Hz, 2 H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.34; H, 7.73.

1-(Carboethoxy)-2-ethoxy-1-methyl-2-cyclopentene (63). An analytical sample of **63** was obtained by preparative VPC on column D: IR 2990 (m), 1735 (s), 1650 (s), 1250 (s), 1185 (s), 1100 (s), 1032 (m) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.21 (t, J = 7.5 Hz, 3 H), 1.25 (t, J = 7.5 Hz, 3 H), 1.30 (s, 3 H), 1.60–2.51 (comp, 4 H), 3.78 (q, J = 7.5 Hz, 2 H), 4.11 (q, J = 7.5 Hz, 2 H), 4.50 (t, J = 2 Hz, 1 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.39; H, 9.00. Found: C, 66.63; H, 9.15.

5,6-Dehydro-5-pentyl-2,2,6-trimethyl-1,3-dioxan-4-one (64) and 5,6-Dehydro-2,2-dimethyl-6-hexyl-1,3-dioxan-4-one (65). The mixture was separated by preparative TLC (8:2 pentane–ether).

R_f 0.57 (**64**): IR 2960 (m), 2940 (m), 1730 (s), 1647 (s), 1400 (s), 1275 (s), 1248 (m), 1164 (m), 910 (w) cm^{-1}; NMR (CCl_4, 220 MHz) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.22–1.56 (m, 6 H), 1.65 (s, 6 H), 2.00 (s, 3 H), 2.25 (t, J = 7.5 Hz, 2 H).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.57.

R_f 0.38 (**65**): IR 2965 (s), 2940 (s), 1732 (s), 1640 (s), 1390 (s), 1282 (s), 1218 (s), 1020 (s), 905 (m) cm^{-1}; NMR (CCl_4, 220 MHz) δ 0.90 (t, J = 7.5 Hz, 3 H), 1.25–1.63 (m, 8 H), 1.70 (s, 6 H), 2.22 (t, J = 7.5 Hz, 2 H), 5.25 (s, 1 H).

Anal. Calcd for $C_{12}H_2O_3$: C, 67.89; H, 9.50. Found: C, 68.02; H, 9.67.

3-(Carboethoxy)-2-ethoxy-2-octene (66). An analytical sample of **66** was obtained by preparative VPC on column E: IR 2950 (s), 1699 (s), 1620 (s), 1280 (m), 1068 (m), 982 (w) cm^{-1}; NMR (CCl_4, 220 MHz) δ 0.89 (t, J = 7 Hz, 3 H), 1.31 (m, 12 H), 2.25 (m, 5 H), 3.93 (q, J = 7 Hz, 2 H), 4.09 (q, J = 7 Hz, 2 H).

Anal. Calcd for $C_{13}H_{24}O_3$: C, 67.13; H, 10.59. Found: C, 66.77; H, 10.25.

2,2-Dimethyl-5-(1-methylethenyl)-3(2*H*)-furanone (11). A solution of 2.0 g (6.0 mmol) of **57** in 18 mL of THF cooled to 0 °C was treated with 2.05 mL of 30% H_2O_2 (18.0 mmol) dropwise. The solution was stirred an additional 30 min at 0 °C and then at room temperature for 30 min. The product was isolated by extraction into ether and washing with 5% bicarbonate solution. Removal of solvent in vacuo and Kugelrohr distillation [bp 80 °C (0.5 torr)] yielded 577 mg of crystalline **11** (mp 60.5–61.0 °C), identical in all respects with that prepared above.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.89. Found: C, 71.23; H, 7.77.

2-(2-Butynyl)-2-methyl-5-(1-ethenyl)-3(2*H*)-furanone (67). A solution of 0.207 g (0.620 mmol) of **58** in 3 mL of THF was cooled to 0 °C and 0.32 mL of 30% H_2O_2 was added dropwise. The reaction was stirred at 0 °C for 20 min, and then at room temperature for 30 min. The solution was extracted into Et_2O and washed with 10% HCl and brine. Removal of solvents in vacuo and Kugelrohr distillation [bp 102 °C (1.5 torr)] yielded 76.6 mg (70%) of **67**. An analytical sample was obtained by preparative thin-layer chromatography (ether, R_f 0.64): IR 2990 (w), 1701 (s), 1645 (m), 1595 (m), 1380 (m), 1122 (s), 1035 (m) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.44 (s, 3 H), 1.75 (s, 3 H), 2.54 (q, J = 14.4 Hz, 2 H), 5.54 (s, 1 H), 5.72 (d, J = 13.0 Hz, 1 H), 6.25 (d, J = 16.6 Hz, 1 H), 6.54 (m, 1 H).

Exact Mass Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0841.

2,2,5-Trimethyltetrahydro-3-furanone (68). To a slurry of 9.73 mg (5.11 mmol) of purified copper(I) iodide in 6.0 mL of dry ether cooled to 0 °C was added 8.0 mL (10.4 mmol; 1.3 M) of methyllithium. After the resulting clear solution was stirred for 5 min, 188 mg (1.68 mmol) of 2,2-dimethyl-3(2*H*)-furanone in 1.0 mL of ether was added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by pouring into a vigourously stirred saturated ammonium chloride solution. The organic material was then extracted into ether, washed with saturated ammonium chloride and brine, and dried over $MgSO_4$. Removal of the ether on a steam bath and purification by VPC on column B afforded 72% of **68**: IR 2860–2950 (s, br), 1755 (s), 1460 (s), 1380 (s), 1185 (s, br), 1145 (s), 1115 (s), 1040 (w), 975 (m), 915 (w), 875 (w) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.15 (s, 3 H), 1.2 (s, 3 H), 1.35 (d, J = 6.0 Hz, 3 H), 2.19 (dd, J = 18 and 5.4 Hz, 1 H), 2.59 (dd, J = 18 and 10.3 Hz, 1 H), 4.0–4.4 (m, 1 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.48; H, 9.58.

2,2-Dimethyl-5-butyltetrahydro-3-furanone (69). To a slurry of 223 mg (1.17 mmol) of purified copper(I) iodide in 7.0 mL of dry ether cooled to 0 °C was added 1.2 mL (2.7 mmol; 2.25 M) of *n*-butyllithium. After the mixture was stirred for 5 min, 108 mg (0.97 mmol) of 2,2-dimethyl-3(2*H*)-furanone in 1.0 mL of ether was added dropwise and the mixture was stirred at 0 °C for 1 h. The reaction was quenched by pouring into ether–50% aqueous NH_4OH and the organic layer was washed with 50% aqueous NH_4OH and brine. Removal of the solvent

(57) K. S. Banerjee and S. S. Deshapande, *J. Indian Chem. Soc.*, **52**, 41 (1975).

in vacuo afforded 159 mg (97.5%) of **69**, which was shown by VPC calibration on column B to be 95% pure: IR 2850–2910 (s, br), 2860 (s), 1750 (s), 1460 (s), 1375 (s), 1180 (s, br), 1115 (s, br), 1000–1020 (w, br), 880 (w) cm^{-1}; NMR (CCl_4, 220 MHz) δ 0.94–0.97 (t, J = 6 Hz, 3 H), 1.13 (s, 3 H), 1.2 (s, 3 H), 1.27–1.63 (m, 6 H), 2.09 (dd, J = 18 and 10 Hz, 1 H), 2.44 (dd, J = 18 and 5.0 Hz, 1 H), 4.0–4.4 (m, 1 H).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.48; H, 10.54.

2,2-Dimethyl-5-phenyltetrahydro-3-furanone (70).[58] To a solution of 100 mg (0.49 mmol) of CuBr in 0.5 mL of $(CH_3)_2S$ and 0.7 mL of dry ether cooled to −23 °C was added 0.6 mL (1.05 mmol; 1.75 M) of phenyllithium dropwise. After the mixture was stirred for 20 min, 47 mg (0.42 mmol) of 2,2-dimethyl-3(2*H*)-furanone in 1.0 mL of ether was added slowly and the mixture was stirred for 1 h while the temperature was maintained between −38 and −25 °C. The mixture was then brought to room temperature and stirred for an additional hour. Workup consisted of pouring into NH_4Cl–Et_2O, and washing with 10% aqueous NH_4OH and brine. Removal of the solvent in vacuo and purification by VPC on column A afforded 79% of **70**: IR 2980 (w), 1760 (s), 1650 (w), 1460 (w), 1180 (s), 1120 (s), 700 (s), cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.2 (s, 3 H), 1.3 (s, 3 H), 2.36 and 2.67 (AB of ABX, J_{AB} = 18 Hz, J_{AX} = 10 Hz, J_{BX} = 6 Hz, 2 H), 5.06 (dd, X of ABX, J_{AX} = 10 Hz, J_{BX} = 6 Hz, 1 H).

2,2-Dimethyl-5-phenyl-3(2*H*)-furanone (Bullatenone) (27).[16] A mixture of 77 mg (7 mmol) of selenium dioxide and 19.7 mg (0.1 mmol) of 2,2-dimethyl-5-phenyltetrahydro-3-furanone in 6.0 mL of *tert*-butyl alcohol was refluxed 48 h. Elemental selenium was removed by stirring for 3 h with a methanolic slurry of deactivated Raney nickel followed by filtration. After removal of the solvent in vacuo, the residue was dissolved in ether and washed with 10% aqueous acetic acid and brine. Purification by preparative layer chromatography [3:1 (v/v) ether–hexane] afforded 13.7 mg (70%) of bullatenone identical with that prepared previously.

2,2-Dimethyl-5-(1-methylhexyl)-3(2*H*)-furanone (71). To a solution containing 22.3 mg (0.117 mmol) of CuI in 7.0 mL of ether cooled to 0 °C was added 125 μL of 0.275 mmol) 2.2 M *n*-BuLi. The resultant green-black solution, stirred for 5 min at 0 °C, was treated with 140 mg (0.95 mmol) of furadienone **10** in 1.0 mL of ether dropwise. The reaction mixture was stirred at 0 °C for 1 h, quenched with 50% aqueous NH_4OH, extracted into ether, and washed with 50% NH_4OH and brine. Removal of solvent in vacuo and Kugelrohr distillation afforded 185 mg of furanone **71** (86%). An analytical sample of **71** was obtained by preparative VPC on column A: IR 2980 (m), 2940 (s), 1700 (s), 1590 (s), 1470 (w), 1385 (m), 1190 (s), 942 cm^{-1}; NMR ($CDCl_3$, 220 MHz) δ 0.89 (t, J = 6.0 Hz, 3 H), 1.20 (d, 7.0 Hz, 3 H), 1.29 (br s, 8 H), 1.36 (s, 6 H), 2.59 (q, J = 7.0 Hz, 1 H), 5.34 (s, 1 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.55. Found: C, 74.13; H, 10.60.

2,2-Dimethyl-5-[1-(acetoxymethyl)ethenyl]-3(2*H*)-furanone (72). A solution of 36.7 mg (0.218 mmol) of **11**, 200 μL of pyridine, and 75 μL (0.795 mmol) of acetic anhydride was cooled at −10 °C overnight. Removal of solvents in vacuo yielded 68.0 mg. Preparative thin-layer chromatography (Et_2O, R_f 0.56) yielded 36.2 mg (79%) of **72**: IR 1735 (s), 1690, 1645, 1550, 1180 (s) cm^{-1}; NMR (CCl_4, 60 MHz) δ 1.43 (s, 6 H), 2.12 (s, 3 H), 4.83 (br s, 2 H), 5.63 (s, 1 H), 5.77 (m, 1 H), 6.22 (m, 1 H).

Exact Mass Calcd for $C_{11}H_{14}O_4$: 210.0892. Found: 210.0899.

2,2-Dimethyl-5-(1-pentylhexyl)-3(2*H*)-furanone (73). To a suspension containing 93.2 mg (0.49 mmol) of CuI in 3 mL of ether cooled to 0 °C was added 0.45 mL (0.99 mmol) of 2.2 M *n*-BuLi. The resultant black solution was stirred at 0 °C for 10 min; then 17.5 mg (0.083 mmol) of **72** in 3 mL of ether was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, poured into 5 mL of saturated NH_4Cl, and extracted into ether. Removal of solvent in vacuo yielded 12.6 mg. Preparative thin-layer crhomatography (1:1 ether–pentane, R_f 0.60) provided 8.7 mg (40%) of **73**: IR 1705 (s), 1600 (s), 1180 (m), 950 (m); NMR (CCl_4, 60 MHz) δ 0.90 (br t, J = 7 Hz, 6 H), 1.17–1.75 (br s, m, 22 H), 2.50 (m, 1 H), 5.43 (s, 1 H).

Exact Mass Calcd for $C_{17}H_{30}O_2$: 266.2246. Found: 266.2236.

Reaction of 3(2*H*)-Furanone 13 with *n*-Propanethiol under Basic Conditions. A solution of 56.0 mg (0.50 mmol) of **13**, 2 drops of diisopropylamine, and 120 μL of *n*-propanethiol in 2 mL of benzene was stirred at room temperature for 13 days. Removal of solvent in vacuo yielded 50.3 mg (54%) of crude **74** [NMR (CCl_4, 60 MHz) δ 1.0 (t, J = 7 Hz, 3 H), 1.40 (s, 6 H), 1.75 (m, 2 H), 2.6–3.0 (m, 4 H), 5.50 (dd, J = 10 Hz and 5 Hz, 1 H)], which could not be purified by distillation or chromatography due to its instability.[2]

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Reaction of 3(2*H*)-Furanone 13 with *n*-Propanethiol under Acidic Conditions. A solution of 50.5 mg (0.451 mmol) of **13**, 5 mg of *p*-toluenesulfonic acid, and 120 μL of *n*-propanethiol in 2 mL of benzene was stirred at room temperature for 13 days. Removal of solvent in vacuo yielded 40.8 mg (48.%) of crude **74**.

Reaction of 3(2*H*)-Furanone 10 with *n*-Propanethiol under Basic Conditions. A solution of 47.1 mg (0.310 mmol) **10**, 90 μL of *n*-propanethiol, and 2 drops of diisopropylamine in 3 mL of benzene was sitrred at room temperature for 48 h. Removal of solvents in vacuo yielded 70 mg. Preparative thin-layer chromatography (Et_2O, R_f 0.64) yielded 29.7 mg (42%) of **75**: IR 1715 (s), 1600, 1075 (s), 935 (m) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.0 (t, J = 7 Hz, 3 H), 1.33 (d, J = 7 Hz, 3 H), 1.38 (s, 6 H), 1.40 (m, 2 H), 2.52 (t, J = Hz, 2 H), 3.66 (m, 1 H), 3.82 (m, 2 H), 5.40 (s, 1 H).

Anal. Calcd for $C_{12}H_{20}O_2S$: C, 63.17; H, 8.77. Found: C, 62.81; H, 8.78.

Reaction of 3(2*H*)-Furanone 10 with *n*-Propanethiol under Acidic Conditions. A solution of 50.0 mg (0.329 mmol) of **10**, 90 μL of *n*-propanethiol, and 5 mg of *p*-toluene sulfonic acid in 3 mL of benzene was stirred at room temperature for 49 h. Removal of solvents in vacuo yielded 76.9 mg; preparative thin-layer chromatography (Et_2O, R_f 0.64) yielded 52.6 mg (70%) of **75**.

Reaction of 3(2*H*)-Furanone 11 with *n*-Propanethiol under Basic Conditions. A solution of 66.3 mg (0.395 mmol) of **11**, 180 μL of *n*-propanethiol, and 3 drops of triethylamine in 4.3 mL of benzene was stirred at room temperature for 18 h. Removal of solvents in vacuo yielded 96 mg; preparative thin-layer chromatography (Et_2O, R_f 0.38) yielded 62.7 mg (65%) of **76**: IR 3450 (m), 1702 (s), 1585, 1120 (s) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.92 (t, J = 7.2 Hz, 3 H), 1.32 (s, 6 H), 1.55 (m, 2 H), 2.90 (m, 1 H), 2.46 (t, J = 7.2 Hz, 2 H), 2.78 (dd, J = 7.0 Hz, 3.6 Hz, 2 H), 2.90 (br s, 1 H), 3.80 (m, 2 H), 5.40 (s, 1 H).

Exact Mass Calcd for $C_{12}H_{20}O_3S$: 244.1133. Found: 244.1142.

A solution of 20.5 mg (0.122 mmol) of **11**, 57 μL of *n*-propanethiol, and 0.90 mL of borate buffer (pH 9) in 1.4 mL of benzene was stirred at room temperature for 72 h. The mixture was poured into ether and the aqueous layer was removed and washed with ether. Removal of solvents in vacuo yielded 34.8 mg. Preparative thin-layer chromatography (Et_2O, R_f 0.38) yielded 17.0 mg (57%) of **76**.

Reaction of 3(2*H*)-Furanone 11 with *n*-Propanethiol under Neutral Conditions. A soltuion of 47.5 mg (0.283 mmol) of **11** and 130 μL of *n*-propanethiol in 3 mL of benzene was stirred at room temperature for 68 h. Removal of solvent in vacuo yielded 102.5 mg. The mixture was separated by preparative thin-layer chromatography (1:4 (v/v) Et_2O–CH_2Cl_2).

R_f 0.68 (77): 27.0 mg (32%); IR 1695 (s), 1595 (m), 1080 (m) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.98 (t, J = 7.2 Hz, 6 H), 1.38 (s, 6 H), 1.60 (m, 4 H), 2.48 (t, J = 7.2 Hz, 4 H), 2.84 (dd, J = 14.4 Hz, 7.2 Hz, 4 H), 2.97 (m, 1 H), 5.46 (s, 1 H).

Exact Mass Calcd for $C_{15}H_{26}O_2S_2$: 302.1374. Found 302.1355.

R_f 0.58 (**78**): 20.0 mg (22%); IR 1690 (s), 1590, 1075 (s) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.98 (t, J = 7.2 Hz, 6 H), 1.40 (s, 6 H), 1.60 (m, 4 H), 2.50 (m, 1 H), 2.58 (t, J = 7 Hz, 4 H), 2.88 (d, J = 14.4 Hz, 2 H), 3.06 (d, J = 14.4 Hz, 2 H), 5.76 (s, 1 H).

Exact Mass Calcd for $C_{15}H_{26}O_3S_2$: 318.1323. Found: 318.1335.

Reaction of 3(2*H*)-Furanone 11 with *n*-Propanethiol under Acidic Conditions. A solution of 45.0 mg (0.268 mmol) of **11**, 125 μL of *n*-propanethiol, and 5 mg of *p*-toluenesulfonic acid in 3 mL of benzene was stirred at room temperature for 67 h. Removal of solvents in vacuo yielded 77.7 mg. Preparative thin-layer chromatography (1:4 Et_2O–CH_2Cl_2, R_f 0.68) yielded 48.1 mg (60%) of 77.

Reaction of 3(2*H*)-Furanone 72 with *n*-Propanethiol under Neutral Conditions. A solution of 30.4 mg (0.45 mmol) of **72** and 67 μL of *n*-propanethiol in 2 mL of benzene was stirred at room temperature for 68 h. Removal of solvents in vacuo yielded 56 mg. Preparative thin-layer chromatography (1:1 (v/v) ether–pentane, R_f 0.23) yielded 11.9 mg (32%) of **79**: IR 1750 (s), 1704 (s), 1600 (m), 1235 (s), 1178 (s) cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.0 (t, J = 7 Hz, 3 H), 1.38 (s, 6 H), 1.64 (m, 2 H), 1.98 (s, 3 H), 2.56 (t, J = 7 Hz, 2 H), 2.82 (t, J = 7 H, 2 H), 4.40 (m, 2 H), 5.50 (s, 1 H).

Exact Mass Calcd for $C_{14}H_{22}O_4S$: 286.1239. Found: 286.1246.

Reaction of 3(2*H*)-Furanone 72 with *n*-Propanethiol under Basic Conditions. A solution of 31.9 mg (0.152 mmol) of **72**, 3 drops of triethylamine, and 75 μL of *n*-propanethiol in 3 mL of benzene was stirred at room temperature for 72 h. Removal of solvents in vacuo yielded 24.7 mg. Preparative thin-layer chromatography (Et_2O, R_f 0.62) yielded 13.4 mg (30%) of 77.

Reaction of 3(2*H*)-Furanone 72 with *n*-Propanethiol under Acidic Conditions . A solution of 36.2 mg (0.172 mmol) of **72**, 75 μL of *n*-propanethiol, and 5 mg of *p*-toluenesulfonic acid in 3 mL of benzene was stirred at room temperature for 68 h. Removal of solvents in vacuo

yielded 48 mg. Preparative thin-layer chromatography (Et_2O, R_f 0.64) yielded 30.0 mg (58%) of 77.

Reaction of Geiparvarin with *n*-Propanethiol under Acidic Conditions. A solution of 28.0 mg (0.0705 mmol) of geiparvarin, 20 μL of *n*-propanethiol, and 1 mg of *p*-toluenesulfonic acid in 1.0 mL of benzene was stirred at room temperature for 115 h. Removal of solvent in vacuo yielded 34 mg. Preparative thin-layer chromatography [1:1 (v/v) Et_2O–CH_2Cl_2, R_f 0.50] yielded 14 mg (47%) of **80**. A second chromatography provided an analytical sample: IR 1695 (s), 1605 (s), 1595 (s), 1270 (m) cm^{-1}; NMR ($CDCl_3$, 250 MHz) δ 1.02 (t, t, J = 7.3 Hz, 3 H), 1.42 (s, s, 6 H), 1.66 (m, 2 H), 2.64 (m, 2 H), 3.30 (m, 1 H), 3.48 (m, 1 H), 4.20 (m, 2 H), 5.46, 5.54 (s, s, 1 H), 6.31 (d, J = 10 Hz, 1 H), 6.90 (m, 2 H), 7.44 (m, 1 H), 7.70 (d, J = 10 Hz, 1 H).

Anal. Calcd for $C_{22}H_{26}O_5S$: C, 65.63; H, 6.52. Found: C, 65.10; H, 6.49.

Reaction of Geiparvarin with *n*-Propanethiol under Basic Conditions. A solution of 9.9 mg (0.0303 mmol) of geiparvarin, 20 μL of *n*-propanethiol, and 1 drop of diisopropylamine in 1.0 mL benzene was stirred at room temperature for 70 h. Removal of solvents in vacuo yielded 11.1 mg. Preparative thin-layer chromatography (1:1 CH_2Cl_2–Et_2O, R_f 0.50) yielded 4.9 mg (40%) of **80**.

Hydroquinone Inhibition. A solution of 45.9 mg (0.273 mmol) of **11**, 130 μL of *n*-propanethiol, and 10 mg of 2,5-di-*tert*-butylhydroquinone in 3 mL of benzene was stirred at room temperature under N_2 for 67 h. Removal of solvents in vacuo yielded 60.0 mg of starting material.

A solution of 27.0 mg (0.1297 mmol) of **72**, 65 μL of *n*-propanethiol, and 10 mg of 2,5-di-*tert*-butylhydroquinone in 2 mL of benzene was stirred at room temperature under N_2 for 68 h. Removal of solvents in vacuo yielded 36.3 mg of starting material.

A solution of 130 mg (0.077 mmol) of **11**, 75 μL of *n*-propanethiol, 3 mg of *p*-toluenesulfonic acid, and 5 mg of 2,5-di-*tert*-butylhydroquinone in 1.4 mL of benzene was stirred at room temperature for 72 h. Removal of solvents in vacuo and thin-layer chromatography (Et_2O, R_f 0.38) yielded 7.3 mg (52%) of **76**.

A solution of 8.9 mg (0.0424 mmol) of **72**, 75 μL of *n*-propanethiol, 1.0 mg of *p*-toluenesulfonic acid, and 5 mg of 2,5-di-*tert*-butylhydroquinone in 1.4 mL of benzene was stirred at room temperature for 73 h. Removal of solvents in vacuo and preparative thin-layer chromatography (Et_2O, R_f 0.62) yielded 10.6 mg (82%) of 77.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health through Grant No. CA-22807. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalysis and the Middle Atlantic Regional NMR Facility (NIH No. 542) at The University of Pennsylvania, where the 220- and 360-MHz NMR spectra were recorded.

Aromatic Substitution in the Gas Phase. Alkylation of Arenes by Gaseous $C_4H_9^+$ Cations

Fulvio Cacace,* Giovanna Ciranni, and Pierluigi Giacomello

Contribution from the Istituto di Chimica Farmaceutica e Tossicologica, Università di Roma, 00100 Rome, Italy. *Received June 17, 1980*

Abstract: Butyl cations, obtained in the dilute gas state from the radiolysis of butane in the pressure range from 70 to 750 torr, have been allowed to react with benzene, toluene, and their mixtures or with trace amounts of *o*-xylene in the gaseous system. The gas-phase butylation yields invariably *sec*-butylarenes, remarkably free of isomeric byproducts, namely *n*- and *tert*-butylarenes. Other alkylation experiments, where gaseous butyl cations from the reaction of butane with radiolytically formed H_3^+ ions were used as reagent, confirmed the exclusive formation of *sec*-butylarenes. The butylation process displays the positional and substrate selectivity and the dependence of orientation on the pressure of the system, typical of other gas-phase ionic substitutions. At high pressures, ortho–para orientation predominates in the sec-butylation of toluene, with a ortho:meta:para ratio of 43:30:27 at 715 torr. As the pressure is reduced, a gradual shift in favor of the thermodynamically most stable meta-substituted arenium ion is observed, leading to a ortho:meta:para ratio of 31:48:21 at 70 torr.

Introduction

The study of gas-phase aromatic substitution by charged reagents generated in the dilute gas state with specifically designed radiolytic techniques has provided direct information on the intrinsic reactivity, selectivity, and steric requirements of free, unsolvated carbenium ions.[1-6]

This paper reports the extension of the study to aromatic alkylation by gaseous butyl ions, obtained directly from the γ radiolysis of butane in the pressure range from 70 to 750 torr or from the reaction of gaseous H_3^+ ions with butane and pentane, strongly diluted in H_2 gas. The interest of the investigation is twofold. In the first place, the mechanistic features of the gas-phase aromatic butylation can be directly evaluated and compared to those of related alkylation processes that occur both in the gas phase and in solution.

In the second place, the reaction with the aromatic substrate and the nature of the products formed represent a useful probe to sample the isomeric composition of the gaseous butyl ions and to gather additional information on the rate of interconversion of the $C_4H_9^+$ isomers.

Experimental Section

Materials. *n*-C_4H_{10} and H_2 were research grade gases obtained from Matheson Co., with a stated purity greater than 99.9 mol %, and were used without further purification. The aromatic substrates and pentane were GLC standards obtained from C.Erba Co., whose purity exceeded 99.8 mol %. The isomeric alkylarenes required as reference compounds for identification purposes in GLC were obtained from commercial sources (Aldrich Chemical Co. and C.Erba Co.) or prepared according to established procedures, their identity being confirmed by NMR and IR spectroscopy.

Procedure. The techniques used for the preparation of the samples and their irradiation have been described.[3,4] The dose, ranging from 2.0 to 4.0 Mrad, was delivered at the rate of 0.5 Mrad h^{-1} in a 220 Gammacell from Nuclear Canada Ltd., at the temperature of 24 °C. A small mole fraction (typically a few torr) of O_2 was used in all experiments as a thermal radical scavenger. The analysis of the products was carried out by GLC, using a Sigma 1 chromatograph equipped with a FID unit, on the following columns: (i) 10% EDO-1 on 100–120 mesh Chromosorb P-AW, 20 ft × $^1/_8$ in. o.d., operated at 0 °C for the analysis of the gases; (ii) 5% SP-1200 + 1.75% Bentone 34 on 100–120 mesh Supelcoport, 6

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