and **15b** are susceptible to ring expansion with diazomethane, the direct conversion of **15b** to the colorless crystalline cyclopentanone **17** (mp 52.5–53 °C; 87%) is a particularly attractive laboratory protocol. The desilylative elimination of **15b** and **17** to produce the labile, synthetically attractive hydroxy ketones **16** and **18** was achieved in excellent yield through use of Bu_4NF or KF in a variety of strictly anhydrous aprotic solvents (Me_2SO, THF, or CH_3CN).

While the above data demonstrate the useful features of **1**, two drawbacks to its application in other contexts have been noted. The ketene, which is a relatively bulky reagent in its own right, is sensitive to the level of steric congestion in its reaction partner. As an illustration, **1** happens to be unreactive toward **19**. Also, although the high level of C_α substitution in cyclobutanones such as **4**, **8**, and **15** does not discourage attack by diazomethane, ring expansion to the corresponding lactones by peracids does not proceed at a rate sufficiently rapid to preclude the incursion of unwanted side reactions.

Nevertheless, the particular juxtaposition of functional groups found in **1** offers an opportunity for achieving simply the annulation of highly unsaturated four- and 5-membered rings under conditions customarily tolerant to a broad range of substituents.[14]

Registry No. **1**, 89121-60-8; **2**, 89121-61-9; **3**, 89121-62-0; **4**, 89121-63-1; **5**, 66977-61-5; **6**, 89121-64-2; **7**, 89121-65-3; **8**, 89121-66-4; **9**, 66977-62-6; **10**, 89121-67-5; **11**, 89121-68-6; **12**, 66031-93-4; **13**, 89144-56-9; **14**, 19980-43-9; **15a**, 89121-69-7; **15b**, 89121-59-5; **16**, 89121-70-0; **17**, 89121-71-1; **18**, 89121-72-2; **19**, 89121-73-3; $(n\text{-}Bu)_4N^+F^-$, 429-41-4; $CH_2{=}C{=}C{=}O$, 61244-93-7; β-(trimethylsilyl)propionic acid, 5683-30-7.

(14) We acknowledge with appreciation the financial support of this research effort by the National Institutes of Health (Grant GM-28468).

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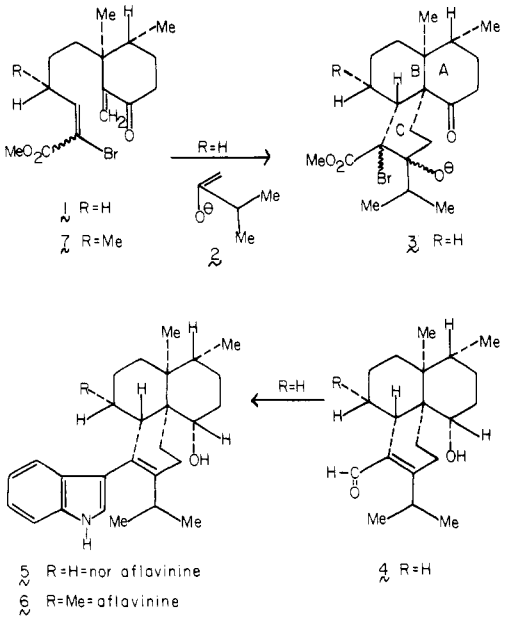
A Notable Stereochemical Variation in the 2 + 2 + 2 Annulation Reaction

Summary: A rapid entry to the epiaflavinine ring system is described.

Sir: Recently a new 2 + 2 + 2 annulation was described.[1] The reaction of compound **1** and lithium enolate **2** in dimethoxyethane gives rise to a group of bromoalkoxides, **3**. Three products, differing only in their configurations at the carbon–bromine and carbon–oxygen bonds, are obtained from **3**. The carbon–carbon backbone stereochemistry is the same in all of these compounds and corresponds to that which pertains in the novel indolic diterpene aflavinine[2] **6**. Indeed, in subsequent experiments, the bromohydrin and the two epoxides derived from **3** have been converted to noraflavinine (**5**) via the hydroxy enal **4**.[3]



It was of interest to study the extendability of this scheme to the methyl homologue **7**. If the pathway followed in the "nor" series would be operative in the case of substrate **7**, a route to aflavinine itself could be developed. In this communication, the realization of the 2 + 2 + 2 annulation with bis electrophile **7** is described. However, the inclusion of the additional methyl group brings about a major change in the stereochemical outcome relative to that observed for the reaction of **1** and **2**. While this divergence complicates the solution to the aflavinine synthesis, *it provides a rare opportunity for insight into the conformations of transients that emerge in this new annulation process.* An account of these findings is given below.

The coupling of subunits of appropriately matched chirality provided a solution to the problem of relating the remotely disposed centers of dissymmetry in structure **7**. Grignard reagent **8a** was prepared from bromide **8**, which was synthesized from (*S*)-citronellol[4] according to Ireland.[5] The preparation of (*R*)-4-methylcyclohex-2-ene-1-one (**9**) from (*R*)-pulegone was recently described from our laboratory.[6] Reaction of **9** with lithium dimethylcuprate (Et_2O, 0 °C) was followed by trapping of the metallo enolate with chlorotrimethylsilane. The resultant silyl enol ether was converted by reaction with palladium acetate into **10** (60% overall), according to the procedure of Saegusa and Ito.[7]

Treatment of Grignard reagent **8a** with enone **10** under the influence of cuprous iodide–dimethyl sulfide complex in ether (0 °C) produced a metallo enolate which was quenched (0 °C) with excess methyl chloroformate to provide a 70% yield of enol carbonate **11** (Scheme I). Reaction of **11** with 3.3 equiv of methyllithium in THF generated the corresponding lithium enolate, which reacted with 4.4 equiv of dimethylmethyleneammonium chloride,[8] to afford crude Mannich base **12**.[9] Ozonolysis of this

(1) Danishefsky, S.; Chackalamannil, S.; Silvestri, M. *J. Org. Chem.* **1983**, *48*, 3615.
(2) Gallagher, R. G.; McCabe, T.; Hirotsu, K.; Clardy, J.; Nicholson, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 243. Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. *J. Agric. Food Chem.* **1981**, *29*, 293.
(3) Danishefsky, S.; Chackalamannil, S., unpublished results, Yale University, 1983.
(4) (*S*)-(−)-Citronellol was obtained from the Fluka Chemical Corp.
(5) Following the procedure by which Ireland prepares the enantiomeric bromide: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
(6) Silvestri, M. G. *J. Org. Chem.* **1983**, *48*, 2419.
(7) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(8) Tietze, L.-F.; Kinast, G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 239.

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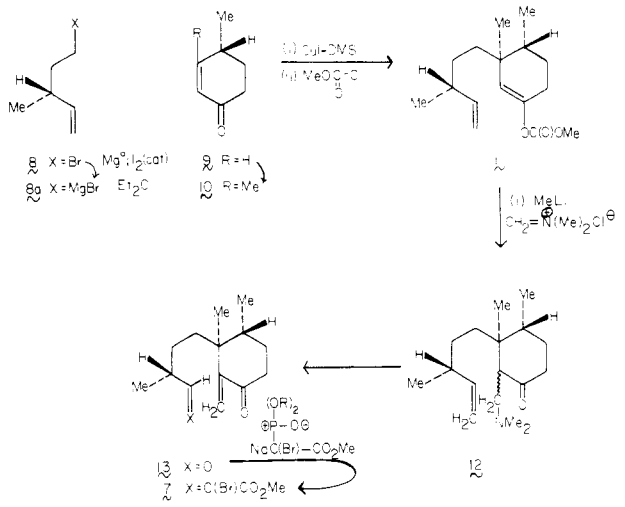
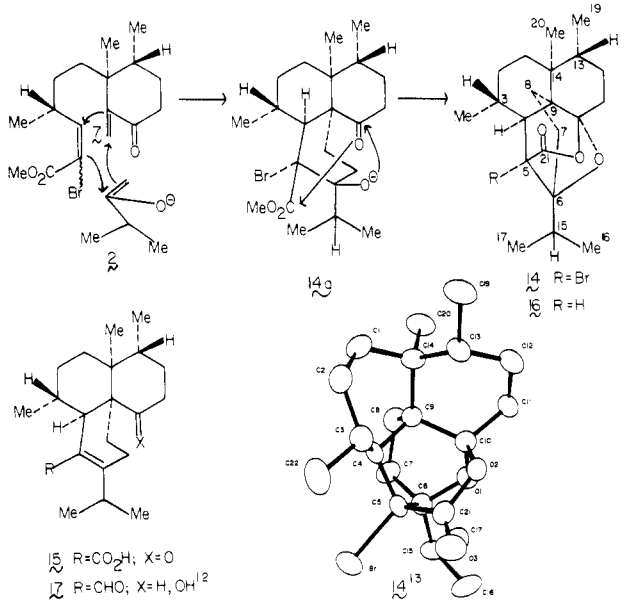
Scheme I



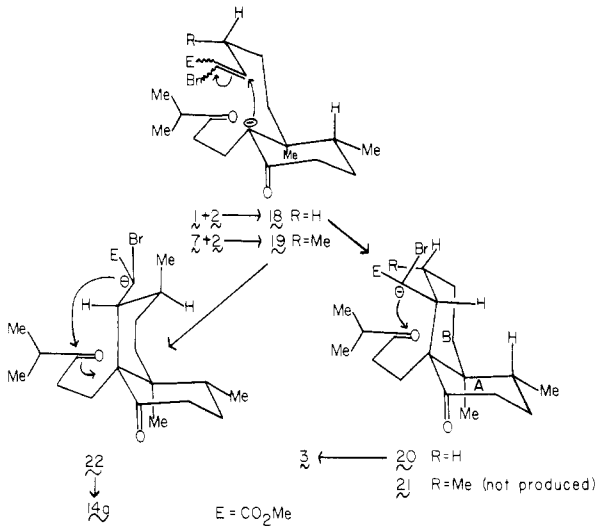
Scheme II



material in methanol–methylene chloride containing sodium bicarbonate was followed by treatment with dimethyl sulfide. This sequence produced a 51% yield (from **11**) of aldehyde enone **13**. Bis electrophile **7** was available in 71% yield upon reaction of **13** with the appropriate Emmons reagent[10] in dimethoxyethane. Compound **7** was employed as ca. a 3:1 mixture of E:Z isomers.

The lithium enolate **2**, generated from the corresponding silyl enol ether by reaction with MeLi,[11] reacted at −78 °C with mixture **7** (Scheme II). . The temperature was allowed to rise to ca. 25 °C. Workup after 24 h afforded a 30% yield of crystalline product, mp 149.5–150.0 °C. The parent ion in its mass spectrum (*m/e* 411) corresponds to a 1:1 adduct **2** + **7**-OMe. Treatment of this compound, formulated as **14**, with zinc and acetic acid, afforded a 65% yield of reductive elimination product **15** as well as a 30% yield of the isomeric product **16**. Esterification of **15** (CH_2N_2) followed by reduction of the derived methyl ester

Scheme III



with lithium aluminum hydride (THF) and then by partial oxidation with $MnO_2(CH_2Cl_2)$ afforded the nicely crystalline hydroxy enal **17**,[12] mp 130–133 °C. The carbon backbone stereochemistry need not be extensively debated, since a single-crystal X-ray determination of the bromo lactone defines its stereochemistry to be that shown in **14**. Compounds **15**–**17** are formulated accordingly.

A dramatic reversal in the stereochemical outcome of the 2 + 2 + 2 annulation has been observed. For the reaction of substrate **1** with enolate **2**, the A:B and B:C fusions both emerge cis. For the corresponding reaction of substrate **7** with the same enolate, the A:B fusion emerges cis but the B:C rings are joined in a trans sense.

This divergence might possibly be rationalized in terms of intermediate **18** (which is the result of addition of **2** to bis electrophile **1**) and its homologue **19** (which arises from the reaction of **2** + **7**) (Scheme III). In the case of **18**, cyclization through a B-ring chair produces **20** in which the α-bromo ester enolate side chain is disposed equatorially. Aldolization of **20** leads to **3** with a cis B:C junction. A corresponding topology in the case of **19** would occasion a severe 1,3-diaxial repulsion of the secondary methyl group at C_3 and the large oxoalkyl side chain (cf. hypothetical structure **21**). This is apparently a higher energy pathway than cyclization through a boat (cf. **19** → **22**) in which serious eclipsing interactions are minimized. Fur-

(9) For the first example of such a reaction, see: Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715. Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *Ibid.* **1977**, *99*, 6066.

(10) Wadsworth, W. S., Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

(11) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464.

(12) The hydroxyl stereochemistry in this compound has not yet been defined.

(13) Crystals suitable for diffraction measurements were obtained by evaporation of hexane at room temperature. The space group is $P2_12_12_1$. Diffraction measurements were made on an Enraf–Nonius CAD-4 fully automated diffractometer using graphite-monochromatized Mo Kα radiation (λ = 0.71073 Å). The unit cell was found by using 25 randomly selected reflections, and cell constants are a = 7.248 (2) Å, b = 12.598 (1) Å, c = 20.971 (3) Å, $\alpha = \beta = \gamma = 90°$. The volume is 1914.9 (9) Å^3 and the calculated density is 1.427 g/cm^3. The crystal was mounted in a sealed capillary tube and 1969 reflections $2\theta \leq 46°$ were collected with 1259 observed ($I \geq 3\sigma I$). The structure was solved by a combination of direct methods and difference Fourier techniques. The bromine atom and ten carbon atoms were located in an electron density map based on the phasing (MULTAN)[1] of 204 reflections ($E_{min} \geq 1.4$). Programs used were the Enraf-Nonius SDP program library (version 18). The enantiomorph was determined from the known configuration at C(14) and C(13). The bromine, carbon, and oxygen atoms were refined anisotropically. Hydrogen atoms were not refined. The function minimized was $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/\sigma(F)^2$, $\sigma(F) = \sigma(F_o^2)/2F_o$; and $\sigma(F_o^2) = [\sigma(I_{raw})^2 + (PF_o^2)^2]^{1/2}/Lp$ to give a final weighted residual of 0.038 and an unweighted residual of 0.038. All intramolecular bond distances and angles are within normal ranges, and there are no abnormally short intermolecular contacts. Figure 1 is a perspective drawing of compound **14**. Tables I–III containing the final X-ray parameters, bond distances and bond angles are provided as supplementary material.

ther cyclization of **22** leads to **14a** and then to **14** (vide supra). However, even in retrospect it is surprising that the boat-like contour implied in **22** with its severe 1,4-interaction would be of lower energy than the chair conformation shown in the hypothetical **21**. Clearly, the level of predictability of the stereochemical outcome of the 2 + 2 + 2 annulation is not yet satisfactory.

Additional explorations of such multiple annulations both from a general methodological sense and for purposes of a total synthesis of aflavinine are in progress.

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Registry No. **2**, 59357-02-7; (*E*)-**7**, 89105-98-6; (*Z*)-**7**, 89163-40-6; **8**, 75420-43-8; **9**, 75337-05-2; **10**, 89162-97-0; **10** TMS enol ether, 89088-84-6; **11**, 89088-85-7; **12**, 89088-86-8; **13**, 89088-87-9; **14**, 89088-88-0; **15**, 89088-89-1; **16**, 89088-90-4; **17**, 89088-91-5; lithium dimethylcuprate, 15681-48-8; dimethyl(methylene)ammonium chloride, 30354-18-8; $ClSiMe_3$, 75-77-4; $ClCO_2Me$, 79-22-1.

Supplementary Material Available: Atomic coordinates, bond angles, and bond lengths for compound **14** (5 pages). Ordering information is given on any current masthead page.

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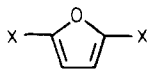
Mechanism of Endoperoxide Formation. 2. Possibility of Exciplexes on the Reaction Coordinates

Summary: The additions of singlet oxygen to phenyl-substituted furans are reported. Different selectivities for the symmetrical and unsymmetrical furans were observed. An exciplex intermediate on the reaction surface is also considered.

Sir: The chemistry of peroxides and the mechanism of their formation have been under investigation for more than 100 years. The rediscovery in the mid 1960s by Foote and Wexler[1] and Corey and Taylor[2] that singlet oxygen was the culprit in many molecular oxidations led to a resurgence in the study of peroxidation. A large number of these studies have focused on the mechanism of the "ene" reaction[3] while the mechanism of endoperoxide formation has been ignored.

We recently[4] reported the rates of additions of singlet oxygen to a series of directly substituted symmetrical (**1**) and unsymmetrical furans (**2**). The selectivity difference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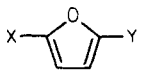
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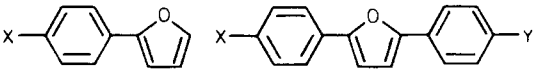
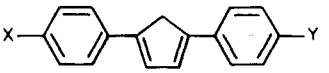
of singlet oxygen for these furans and an examination of that data in terms of the Hammett linear free energy relationship led us to suggest that the electronic properties of the furans influenced the geometry of singlet oxygen approach. In this report we (1) present the rates of additions of singlet oxygen to 20 phenyl- and diphenyl-substituted furans and cyclopentadienes, (2) present additional kinetic data collected for furans **1** and **2** with the Young[5] kinetic technique, and (3) discuss these results and the possibility of an exciplex intermediate.

The rates of singlet oxygen additions to furans (series **3** and **4**) and cyclopentadienes (series **5**) were measured


3 **4**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by the method of Carlsson[6] and are reported in Table I. The rates for the furans (both series **3** and **4**) are also displayed in Figure 1 by utilizing the Hammett LFER formalism.

Examination of these data reveals that the insertion of the phenyl ring between the furan ring and the substituent produces a dramatic attenuation of the effect of substituents on the rates of endoperoxide formations. The rate constant variations for symmetrical furans **1** (a factor of 2800)[4] and unsymmetrical furans **2** (a factor of 10000)[4] are much larger than those that observed for series **3**, **4**, or **5**. The Hammett reaction constant measured for the unsymmetrical series **3** ($\rho = -1.00$), however, is more negative than that obtained for the symmetrical series **4** ($\rho = -0.55$), consistent with the results obtained earlier[4] for the directly substituted furans.

The Carlsson singlet oxygen kinetic method is a dangerous one-point nondifferential technique which responds to total inhibition of the reaction with no internal check to determine if sensitizer quenching is occurring. To rule out the possibility that rubrene quenching is responsible for the different selectivities of single oxygen toward **1** and **2**, we have measured the rates of single oxygen addition to several furans using a different kinetic technique, the Young[5] method, and a different sensitizer, mesoporphyrin IX dimethyl ester. Examination of these data[7] presented in Table II reveals that the symmetrical furans demonstrate a different selectivity ($\rho^+ = -2.02$, $r = 0.999$) than the asymmetrically substituted furans ($\rho = -4.03$, $r = 0.994$) toward singlet oxygen. The experimentally indistinguishable LFER plots generated by the Young and Carlsson techniques and the similar selectivities exhibited by the phenyl and directly substituted furans mitigates against sensitizer quenching as being responsible for the observed selectivity differences.

(1) (a) Foote, C. S.; Wexler, S. *J. Am. Chem. Soc.* **1964**, *86*, 3879. (b) Foote, C. S.; Wexler, S. *Ibid.* **1964**, *86*, 3880.
(2) Corey, E. J.; Taylor, W. C.; *J. Am. Chem. Soc.* **1964**, *86*, 3881.
(3) (a) Foote, C. S. *Acc. Chem. Res.* **1968**, *1*, 104. (b) Gollnick, K. *Adv. Photochem.* **1968**, *6*, 1. (c) Kearns, D. R. *Chem. Rev.* **1971**, *71*, 395. (d) Orfanopoulous, M.; Stephenson, L. M. *J. Am. Chem. Soc.* **1980**, *102*, 1417.
(4) Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 5932.
(5) Young, R. H.; Wehry, R. H.; Martin, R. I. *J. Am. Chem. Soc.* **1971**, *93*, 5774.
(6) Carlsson, D. J.; Suprunchuk, T.; Wiles, D. M. *Can. J. Chem.* **1974**, *52*, 3728.
(7) Furfural, 2-carbomethoxyfuran, and 2,5-dibromofuran all quench diphenylisobenzofuran (DPBF) fluorescence, making their rates unobtainable by using this fluorescence probe. Foote[8] reported similar problems using Young's method with phenols in which the cross-conjugated ketone product quenched diphenylfuran (DPF) fluorescence.
(8) Foote, C. S.; Thomas, M. J. *Photochem. Photobiol.* **1978**, *27*, 683.

0022-3263/84/1949-1321$01.50/0