[2 + 2] Photocycloadditions in the Synthesis of Chiral Molecules

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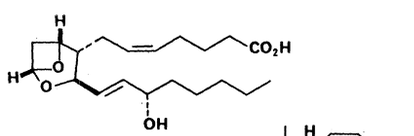
Summary. A strategy for the synthesis of chiral molecules that receives growing popularity among organic chemists employs the photochemically mediated [2 + 2] cycloaddition reaction. These reactions can be performed on a multigram scale and often proceed with high yield and with stereocontrol. These features, in combination with the useful properties of the four-membered ring photoproducts in subsequent chemical transformations, make them attractive options in the early stage of a synthesis design. Various combinations of unsaturated functional groups can participate in this reaction process. Accordingly, these chemical reactions can be economical solutions to problems relating to the synthesis of a variety of target molecules.

At the turn of the century several reports appeared on the use of light as a reagent in organic synthesis. Ciamician's research efforts resulted in the discovery of the photochemically mediated [2 + 2] cycloaddition of an enone and an alkene to afford a cyclobutane (*1*). His colleague Paternò followed this report with a description of the first [2 + 2] photocycloaddition of an aldehyde to an alkene to provide an oxetane (*2*). During the ensuing 80 years organic chemists have come to recognize and routinely employ the photochemical method for effecting this cycloaddition reaction in complex syntheses of chiral molecules. The four-membered ring products are found to occur in such compounds as thromboxane A_2 (**1**) (*3*), the arachidonic acid metabolite that plays an important role in platelet aggregation and muscle constriction in humans, and the sesquiterpene essential oil caryophyllene (**2**) (*4*).



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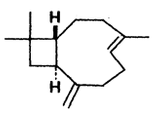

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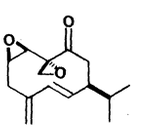
A feature of these photoproducts with far-reaching implications is that they serve as vehicles for subsequent chemical manipulations. It is this property that has imparted great significance to these chemical reactions in the field of organic synthesis. Evidence for this comes from the recent literature where one can find several reviews on the application of these reactions in organic synthesis (*5–7*).

The purpose of this article is to report some developments from our laboratories that have employed the photochemical [2 + 2] cycloaddition reaction as a springboard for the synthesis of naturally occurring substances with significant physiological properties. Through chemical synthesis, samples of these important and often scarce molecules can be prepared, which may facilitate subsequent studies of their biological properties. Modification of their structure through synthesis can lead to new materials with altered properties. In this process of creating new substances we learn about the nature of chemical reactivity.

Synthesis of a Sex Pheromone of the American Cockroach

Isolation of periplanones A and B. In 1952 an important result in pheromonal research was reported by Roth and Willis. These workers were studying the reproductive behavior of the three most common species of cockroaches (*germanics, orientalis*, and *americana*) and found that the female of *Periplaneta americana* was able to sexually stimulate the male by olfactory communication (*8*). Many years of intensive investigations of the active component produced by the female American cockroach led to refinement of the techniques used for the isolation of the pheromone and of the bioassay to determine activity. Employing optimal conditions for pheromone biosynthesis and executing a direct extraction on mass scale, Persoons and coworkers were able to isolate and determine the structures of two active components termed periplanone A (pA) and periplanone B (pB) (*9–11*). In this work, the alimentary tracts of 35,000 insects were dissected and the midguts were extracted. Another 20,000 insects were kept in a cage suitable for routine recovery of feces, which were extracted and added to the material isolated from the midguts. Silica gel chromatography separated the active compounds pB (200 μg) and pA (20 μg). Through a combination of spectroscopic analyses, primarily nuclear magnetic resonance spectroscopy (NMR), the structure of pB was established as that depicted in **3**. A tentative assignment of structure for pA based largely on mass spectral analysis was suggested and is shown as **4**.



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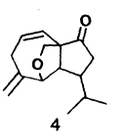

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In 1979 W. C. Still reported his landmark studies that culminated in the synthesis of pB (*12, 13*). Through conformational analysis of germacranoid intermediates, Still established the relative stereochemistry of pB and laid the groundwork for a powerful method of stereocontrol in organic synthesis based on conformational analysis of medium and large ring systems (macrocyclic stereocontrol).

With samples of pB made available through synthesis, breakthroughs in neurobiological studies of the pB olfactory response have been reported. For example, Sass (*14*) and Nishino and Manabe (*15*) have employed electrophysiological techniques to show that two separate receptors for pA and pB exist in the antennae of the male cockroach. Thus, a two-component attractant system has been developed by the American cockroach. These studies complement earlier work by M. Burrows and his co-workers, which resulted in the discovery of two sets of interneurons in the deutocerebrum of the male American cockroach brain that respond separately to either pA or pB (*16*). From the standpoint of the cockroach, pA and pB are not the same and both are important. The cockroach has developed two distinct systems to detect these pheromones and process the information they impart by

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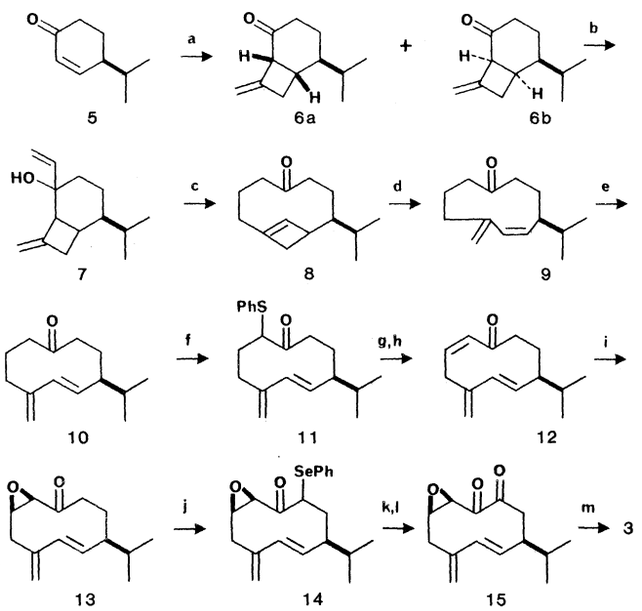


Scheme 1. The conditions and yields represented by the letters a to m are: (a) CH_2=C=CH_2, diethyl ether, *hν* (450-watt Hanovia lamp equipped with a Pyrex filter), −30°C, 72 percent yield (6a:6b = 2:1); (b) CH_2=CHMgBr, diethyl ether, −78°C, 63 percent yield; (c) KH (5 equivalents), 18-Crown-6, tetrahydrofuran, 60°C, 25 minutes, 100 percent yield; (d) toluene, 175°C, 20 hours, 77 percent yield; (e) benzene, *hν* (450-watt Hanovia lamp equipped with a Vycor filter), 82 percent yield; (f) tetrahydrofuran, $LiN(Si(CH_3)_3)_2$, −78°C, $C_6H_5SSO_2C_6H_5$, regioselectivity = 16:1; (g) aqueous methanol, $NaIO_4$, 71 percent yield from **7**; (h) toluene, 110°C, 45 percent yield; (i) tetrahydrofuran, $(CH_3)_3COOH$, KH, 0°C, 83 percent yield (four to one mixture of β and α epoxides); (j) tetrahydrofuran, $Li[N(i\text{-}C_3H_7)_2]$, −78°C, C_6H_5SeBr, 83 percent yield; (k) 30 percent H_2O_2, tetrahydrofuran, 97 percent yield; (l) tetrahydrofuran, acetic anhydride, CH_3CO_2Na, and then methanol, H_2O, K_2CO_3, 60 percent yield; (m) dimethyl sulfoxide, tetrahydrofuran, $[(CH_3)_3S]I$, $(CH_3SOCH_2)Na$, 62 percent yield.

separate paths. The reasons for this and the mechanism by which this is achieved remain a mystery.

Recent entomological studies have shown that pB exhibits sex attractant properties in addition to its previously recognized sex excitant properties (*17, 18*). The synthesis of the sex pheromones pA and pB and the design and synthesis of analogs could lead to further neurobiological studies and an understanding of the chemical basis for olfaction. A flexible synthesis might be modified to provide radioactively labeled pheromones or affinity-column analogs that could be employed in the isolation of the bioreceptor molecules. A greater understanding of the two-component attractant system might also lead to an optimal procedure for use of the sex pheromones as lures in baited traps.

[2 + 2] *Allene photocycloadditions.* Our studies of the synthesis of sex pheromones pA and pB have employed an allene photocycloaddition to a cyclohexenone as an entry point in each synthesis. These [2 + 2] photocycloaddition reactions illustrate the ability of this method to rapidly construct the carbon skeletons of both molecules. In this section an efficient synthesis of pB, which contains a ten-membered ring, will be detailed (*19, 20*).

The virtues of early and rapid skeletal construction in a synthesis have been appreciated by organic chemists for some time. In the periplanone B problem we recognized that regioselective photocycloaddition of an allene to a substituted cyclohexenone would set the stage for a rearrangement to form a ketone (called an oxy-Cope rearrangement) followed by a ring-opening rearrangement of the cyclobutene ring (scheme 1). The resultant product contains many structural similarities to the target system.

The ten-membered-ring ketone containing the *trans*-butadiene present in pB was constructed in five steps from the enone **5**. Four of the five steps employ light or heat as the reagent to mediate the transformations. The synthesis commenced with a [2 + 2] photocycloaddition of enone **5** and allene on a multigram scale. The regiochemical outcome of this reaction was anticipated on the basis of the pioneering studies of [2 + 2] photocycloadditions in the laboratories of Corey (*21, 22*). The reaction affords two stereoisomers (**6a** and **6b**) that need not be separated since the stereocenters at the ring-fusion carbons are returned to achiral trigonal centers in subsequent transformations and thus converge on the same end product. A Grignard addition of vinyl bromide to the ketone produced a divinylcyclohexanol **7**. Marvell and Whalley had first shown that compounds of this type serve as substrates for thermally induced oxy-Cope ([3.3] sigmatropic) rearrangements to provide ring expanded cyclodecenones (*23*). Presumably due to poor overlap of the orbitals in the 1,5-diene, **7** failed to undergo the desired transformation under thermolysis or metal-catalyzed (palladium acetate, mercuric trifluoroacetate) conditions. However, when the conditions of Evans and Golob were used for the anion-accelerated oxy-Cope rearrangement (*24*) a smooth transformation of **7** to the cyclobutene bridgehead olefin **8** took place. The product of this reaction is now a candidate for another thermally allowed rearrangement, the electrocyclic ring opening of a cyclobutene. Heating **8** at 175°C for 24 hours provided a 2:1 mixture of the *cis* and *trans* 1,3-diene isomers **9** and **10**, which could be photoisomerized to a 15:1 mixture favoring the desired *trans* diene **10**.

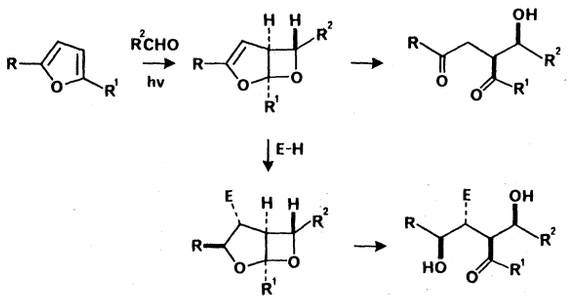
The photocycloaddition reaction that initiated the synthesis provided in one step a β,γ-unsaturated ketone that served as an ideal precursor to the divinylcyclohexanol required for ring expansion. The anion-accelerated oxy-Cope rearrangement produced the ten-membered ring with concomitant shift of the olefin into the four-membered ring. Here, the olefin was properly positioned for the electrocyclic ring opening that produced the required diene moiety. The cyclodecenone **10** was prepared in multigram quantities in five steps and converted to pB by a procedure that required eight additional steps. Interestingly, an electroantennagram bioassay indicated **10** was capable of initiating an electrical signal from a severed antenna of a male (but not female) American cockroach (*25*).

A solution to the problem of converting cyclodecenone **10** to pB was uncovered after we noted that enolization of the ketone and sulfenylative trapping of the resultant enolate could be made to proceed with regio- and stereocontrol. We believe the regiocontrol that is operating in the enolization reaction is a manifestation of what Still has termed macrocyclic stereocontrol (*26*). The formation of the enolate removes a serious transannular interaction between the methylene group adjacent to the ketone and an olefinic carbon of the diene.

The introduction of the phenylsulfenyl group provided a route to the *cis* enone **12** by pyrolytic sulfoxide elimination. Bis epoxidation of the *cis* enone occurred in a stereoselective manner analogous to that in the Still synthesis of pB (*12*). To complete the synthesis, the introduction of the requisite ketone functionality was achieved by means of a selena-Pummerer rearrangement.

Our studies of the chemistry and neurobiology of the American cockroach sex pheromones continue (*25*). We have prepared analogs of pB and are evaluat-

ing their activity. With these compounds in hand, the search for the pB receptor is under way. Studies in support of the synthesis of pA and isolation of the pA receptor are also in progress.



Scheme 2.

A Photochemical Equivalent to *Threo*-Selective Aldol Condensation

The Paternò-Büchi photocycloaddition (*7*) of aldehydes to furan heterocycles was examined in detail by Sakurai and his co-workers and was shown to give rise to *exo*-substituted photoadducts with a high degree of regio- and stereocontrol (*27, 28*). We recognized that in this reaction the furan can be considered an equivalent to a *Z*-enolate and that the photoadduct serves as a type of protected aldol (*29*). Accordingly, the furan-carbonyl photocycloaddition is related to the stereoselective aldol condensation, a reaction of considerable importance in organic synthesis (*30–34*). Hydrolytic unmasking of the photoadduct yields aldol products with the *threo* configuration. A special feature of the photoadduct is that its cup-shaped geometry lends itself to a variety of reactions wherein electrophilic reagents add to the enol ether from the convex face. The resulting product can then be hydrolytically unmasked to afford an acyclic chain with a variety of substitution patterns. The identity of the substituents on the chain is determined by the selection of R groups on the furan and aldehyde and by the reaction conditions (scheme 2).

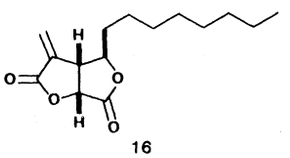
We have learned how to oxidize or reduce the dihydrofuran with stereocontrol, and we have been able to form carbon-carbon bonds at either the alpha or beta positions of the enol ethers. Having gained confidence in our ability to produce a variety of structural types, we have embarked on new studies with the objective of illustrating how this strategy can be applied to the synthesis of naturally occurring systems. Our approach to the synthesis of various target molecules using the photoaldol reaction was simplified by the information we received from other workers' studies of the application of the aldol reaction (or equivalent processes) to syntheses of chiral molecules (*30–34*). The following sections provide several illustrations.

Antibiotics, antifungals, and mycotoxins. The growth of a mold colony from spores present in the air is not an uncommon occurrence. These molds, usually *Aspergillus* or *Penicillium* species, synthesize a variety of secondary metabolites that provide an effective means of fending off potential competitors from their food source. These metabolites have been classified by observing the type of organisms that respond to them in a deleterious manner. To drive away bacteria or other fungi the molds produce antibacterials or antifungals, and these compounds (when available from fermentation or synthesis) have been used by man to combat bacterial or fungal infections. These fungi are also capable of producing metabolic products, termed mycotoxins, which are toxic to mammals. As mycotoxin-producing molds tend to grow rapidly and aggressively, they can cause epidemic mycotoxicoses, several of which have had a massive impact on human communities (*35, 36*).

These compounds have for a long time attracted the attention of organic chemists. In some cases they may have important therapeutic value. A study of the relation between their structure and activity may contribute significantly to a mechanistic understanding of their mode of action. In the case of mycotoxins, this understanding might lead to a means of protection against their toxic effects.

In the following sections we discuss our studies of the furan-carbonyl photocycloaddition reaction as a method for stereocontrolled synthesis of two metabolites produced by *Aspergillus* species. Five-membered-ring heterocycles are a structural feature these two compounds share. A stereochemical feature they share is a *threo*-aldol embedded in their structures (or in the structures of logical synthetic precursors).

Avenaciolide: An antifungal metabolite from Aspergillus avenaceus. When grown in aqueous media *Aspergillus avenaceus* G. Smith produces a metabolite (avenaciolide, **16**) which possesses antifungal properties (*37–39*). At *p*H 3.5,



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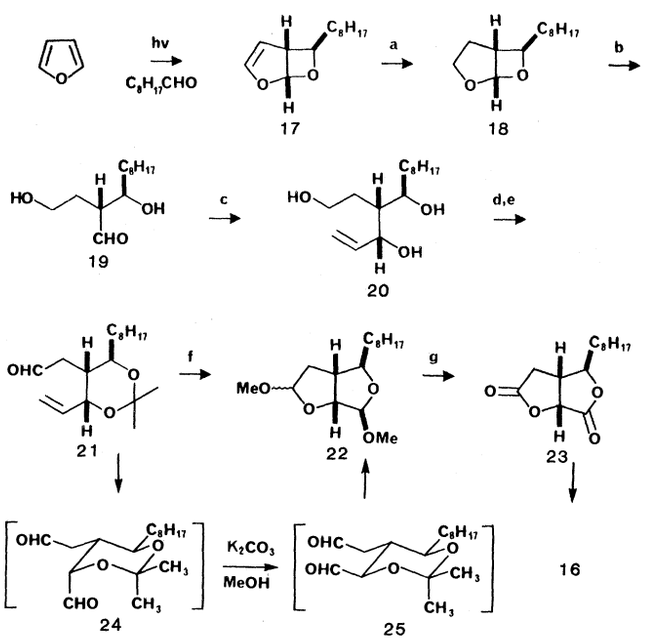
avenaciolide inhibits germination of spores of a wide range of fungi (for example, *Botrytis allii* and *Penicillium gladioli*) at concentrations of 1 to 10 μg/ml. This unusual bis-lactone is also weakly antibacterial.



Scheme 3. The conditions and yields represented by the letters a to g are: (a) H_2, Rh-Al_2O_3, ethyl acetate, 97 percent yield; (b) 0.1*N* HCl and tetrahydrofuran (1:4), 96 percent yield: (c) CH_2=$CHMgBr$, tetrahydrofuran, room temperature, 80 percent yield; (d) acetone, $CuSO_4$, *p*-toluenesulfonic acid; (e) pyridinium chlorochromate, CH_3CO_2Na, CH_2Cl_2, 91 percent yield; (f) ozone, methanol, −78°C, and then $(CH_3)_2S$, room temperature, and then K_2CO_3, and then HCl, 31 percent yield; (g) *m* - chloroperbenzoic acid, $BF_3 \cdot O(C_2H_5)_2$, CH_2Cl_2, 80 percent yield.

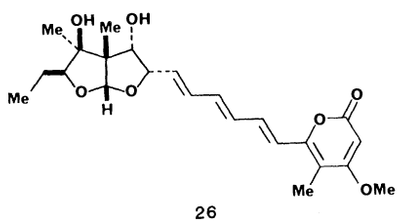
Avenaciolide was first synthesized by Johnson in 1969 and has since been prepared by alternative routes by several research teams (*40–48*). We felt an efficient synthesis of avenaciolide would serve to illustrate an important feature of the furan-carbonyl photocycloaddition strategy (*49*): the photoaddition reaction can be easily carried out on a multigram scale with a high degree of stereocontrol so that its use as the first step in a synthesis can be recommended (scheme 3).

The photocycloaddition of nonanal to furan afforded a single photoadduct **17** in near quantitative yield on a 50-g scale. In this manner, two readily available starting materials were joined and two of the stereocenters in the target system were created. At this stage we required a method for the insertion of carbon monoxide into the acetal bond of the oxetane. Methods for such a transformation are known, especially those mediated by organometallic compounds of transition metals; however, we chose a slightly more circuitous but stereospecific method, as follows. Hydrogenation of **17** yielded **18**, and then hydrolysis provided the *threo*-aldol **19**, which exists as the corresponding butyrolactol. Comparison of **19** and **16** reveals the *threo*-aldol substructure of avenaciolide. The addition of vinyl magnesium bromide proceeded with 5:1 stereoselection to yield **20** and the corresponding allylic epimer, respectively. Although the stereochemistry at the allylic carbinol site of the major diastereomer is opposite to that required for the avenaciolide synthesis, we recognized this could be corrected at a later stage.

We were able to engage the two secondary hydroxyls in the formation of an acetonide, leaving free the remaining primary (less hindered) hydroxyl. Oxidation to the aldehyde **21** set the stage for final skeletal construction and correction of the offending stereocenter. In a one-pot operation **21** was converted to the bismethoxy lactols labeled **22** (a 2:1 mixture of methoxy anomers) with complete inversion of configuration at the carbon bearing the allylic ether in **21**. Ozonolysis and reduction of **21** gave rise to the axial aldehyde **24**, which in a chair conformation suffers a severe 1,3-diaxial interaction with the axial methyl at the ketal carbon center. Due to the presence of the carbonyl group, this compound can transform into the all equatorially substituted isomer **25** upon base-catalyzed epimerization. Addition of potassium carbonate effected the desired transformation, and after equilibration was complete the mixture was acidified. These conditions resulted in the cleavage of the acetonide and formation of the skeleton of avenaciolide. This method of 1,3-stereochemical control was introduced by Stork and co-workers as part of their studies directed toward the synthesis of erythronolide A and was termed "ancillary stereocontrol" (*50*). A feature of this method is that the stereochemical outcome of the Grignard addition is inconsequential to the avenaciolide synthesis. Accordingly, the 5:1 mixture of stereoisomers produced in this step could be used, allowing greater material throughput.

Direct oxidation of **22** afforded the lactone **23** (15-g scale) which served as the penultimate compound in the Johnson synthesis of avenaciolide (*41*). Using Johnson's conditions for introduction of the α-methylene group in the A-ring butyrolactone, we were able to complete the synthesis (*49*).

Asteltoxin: A mycotoxin isolated from Aspergillus stellatus. Investigations of toxic maize cultures of *Aspergillus stellatus* resulted in the isolation and structural determination of a mycotoxin that was named asteltoxin, **26** (*51*). This mycotoxin is a member of a class of compounds distinguished by the presence of an α-pyronylpolyene side chain. Related compounds such as the aurovertins and citreoviridin have been used extensively as inhibitors of oxidative phosphorylation. Recent studies have indicated that



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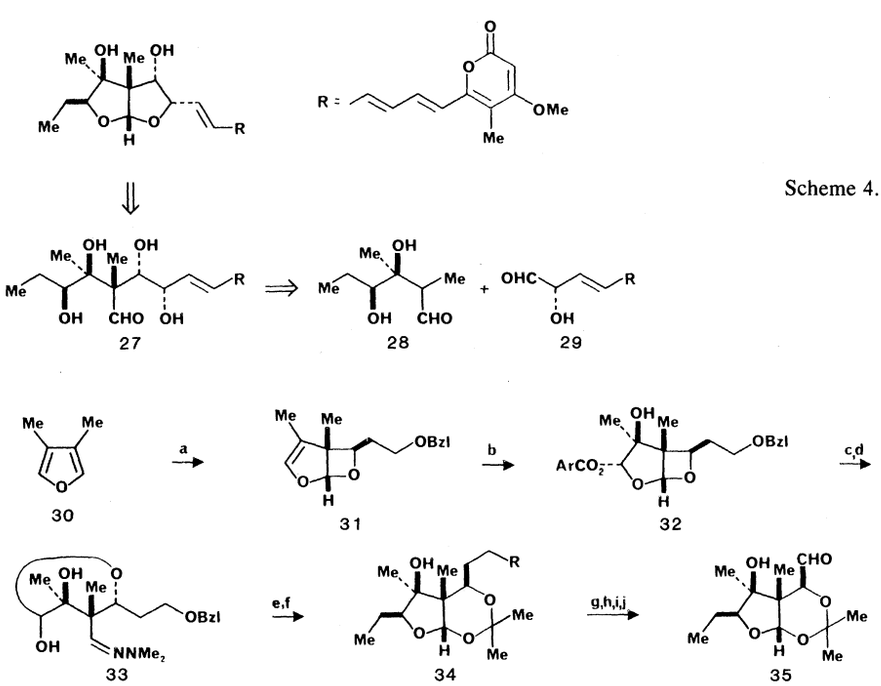
asteltoxin has a similar inhibitory effect on the adenosinetriphosphatase activity of *Escherichia coli* BF_1 (*52*). Extensive studies have been reported on the biological activity and biosynthesis of members of this class; however, before we initiated our studies we found no reports on the chemical synthesis of any of the members of this important class of compounds.

An analysis of the B-ring tetrahydrofuran of asteltoxin revealed the presence of a β-hydroxy acetal moiety. The corresponding aldehyde **27**, from an imagined hydrolysis of the bis(tetrahydrofuran), can be recognized as the product of a *threo*-aldol condensation of **28** and **29** or their equivalents in the indicated manner (scheme 4). Accordingly, our strategy was to carry out a first step *threo*-selective Paternò-Büchi photocycloaddition reaction and to use the cup-shaped geometry of the resultant molecule to fa-

Scheme 4.



Scheme 5. The conditions and yields represented by the letters a to j are: (a) β-benzyloxypropanal, benzene, diethyl ether, *hν* (Vycor lamp), 6 hours, 63 percent yield; (b) *m*-chloroperbenzoic acid, $NaHCO_3$, CH_2Cl_2, 80 percent yield; (c) 3 *N* HCl and tetrahydrofuran (1:3); (d) $(CH_3)_2NNH_2$, CH_2Cl_2, $MgSO_4$, 72 percent yield; (e) C_2H_5MgBr, tetrahydrofuran, room temperature, 48 hours; (f) acetone, $CuSO_4$, camphorsulfonic acid, 55 percent yield; (g) Li, NH_3, diethyl ether, 98 percent yield; (h) o-$NO_2C_6H_4SeCN$, $(n$-$C_4H_9)_3P$, tetrahydrofuran; (i) H_2O_2, tetrahydrofuran, 81 percent yield; (j) ozone, CH_2Cl_2, methanol, dimethyl sulfide, 92 percent yield.

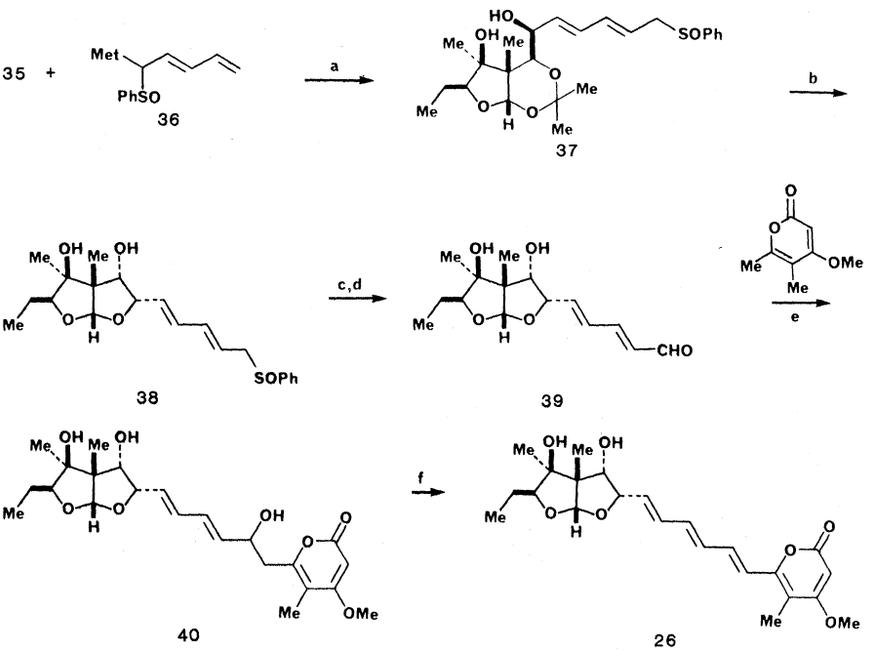
cilitate introduction of the remaining peripheral stereocenters (*53, 54*).

Our synthesis began with a Paternò-Büchi photocycloaddition of 3,4-dimethylfuran and β-benzyloxypropanal on a 10-g scale (scheme 5). The *exo*-substituted photoadduct **31** was oxidized with *m*-chloroperbenzoic acid (MCPBA) to yield the β-hydroxytetrahydrofuran **32**. Hydrolysis afforded the desired *threo*-aldol, which exists as the monocyclic lactol. Protection of the more reactive free aldehyde produced the hydrazone **33**. Then, we were able to use the α-hydroxyl substituent to direct introduction of the ethyl side chain to the hemiacetal carbon. Chelation-controlled addition of ethyl magnesium bromide provided, after hydrolysis and internal protection, the acetonide **34**. Degradation of the β-benzyloxyethyl side chain to an aldehyde set the stage for final introduction of the pyronyltriene side chain.

Completion of the synthesis required the stereoselective addition of a 4-formyl-1,3-butadiene anion equivalent and a final crossed-aldol condensation-dehydration reaction with a suitable α-pyrone. These objectives were achieved by a process that is outlined in scheme 6. Corey's anion **36** (*55*) reacted smoothly with the aldehyde **35** to provide a 3:1 mixture of primary addition products. When the products stood at room temperature for several hours, a double [2.3] sigmatropic rearrangement took place, resulting in the formation of the pentadienyl sulfoxide **37** as the major stereoisomer. A Pummerer rearrangement and hydrolysis produced the dienal **39**, which could be coupled with the indicated pyrone by the crossed-aldol reaction to give **40**. Selective dehydration of the secondary hydroxyl on the side chain in the presence of the more hindered, unprotected secondary and tertiary hydroxyls on the ring system completed the synthesis of asteltoxin, **26**.

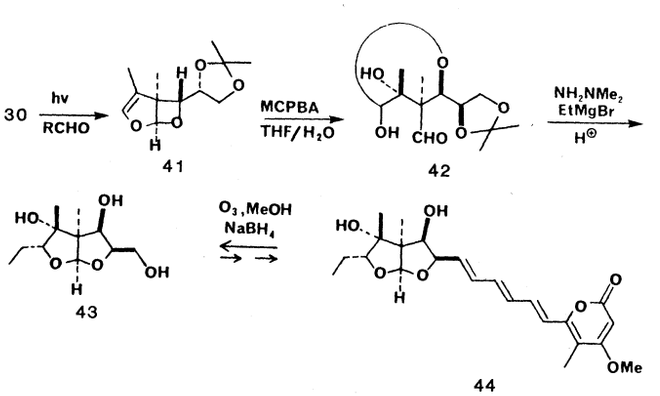
When compared to an authentic sample of natural asteltoxin, our synthetic material exhibits identical spectroscopic and chromatographic properties. Our material differs from natural asteltoxin in that it exists as a racemic mixture. We are presently studying a new synthetic route to asteltoxin that would result in the nonracemic natural product. However, the absolute configuration of asteltoxin, which had not been determined, was a problem that had to be dealt with in the early part of these studies. Our experiments that relate to this point are outlined in scheme 7.

Whereas the furan-carbonyl photocycloaddition results in a highly diastereoselective *threo*-aldol addition, the reaction proceeds with lack of facial selectivity for the chiral aldehydes that we have examined. For example, irradiation of D-glyceraldehyde acetal (readily available from D-mannitol) in the presence of 3,4-dimethylfuran afforded a nearly 1:1 mixture of **41** and the *threo* adduct resulting from opposite facial selectivity. These two compounds can be separated by silica gel chromatography. When **41** was treated with MCPBA in aqueous tetrahydrofuran, oxidation and ring opening ensued and the lactol **42** was isolated. Protection of the free aldehyde and chelation-controlled addition of ethyl magnesium bromide to the lactol proceeded with the same stereocontrol observed in the racemic synthesis. Treatment with acid effected the removal of the acetonide and caused cyclization to the bis(tetrahydrofuran) **43**. Ozonolytic degradation of natural asteltoxin and subsequent reduction with sodium borohydride afforded the same triol **43**. Comparison of the optical rotation values of our synthetic substance with the degradation product showed that these substances have the same absolute configuration (*56*). These results indicate the absolute configuration of asteltoxin is as shown in scheme 7.

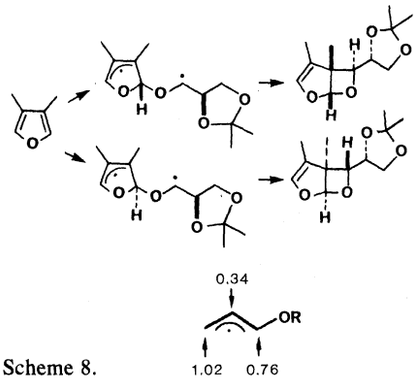


Scheme 6. The conditions and yields represented by the letters a to f are: (a) **36**, *n*-butyl lithium, −78°C, and then **35**, NH_4Cl in water, room temperature, 3 hours, 89 percent yield; (b) camphorsulfonic acid, CH_2Cl_2, 77 percent yield; (c) $CF_3CO_2COCH_3$, acetic anhydride, 2,6-lutidine; (d) $HgCl_2$, $CaCO_3$, CH_3CN and water (4:1), 60 percent yield; (e) pyrone, Li[N(*i*-$C_3H_7)_2$], hexamethylphosphoramide, tetrahydrofuran, −78°C, and then **39**, −78°C, 80 percent yield; (f) *p*-toluenesulfonyl chloride, dimethylaminopyridine, $(C_2H_5)_3N$, CH_2Cl_2, 82 percent yield.

Mechanism of the furan-carbonyl photocycloaddition reaction. The lack of fa-



Scheme 7.



Scheme 8.

cial selectivity in the addition of the furan to an excited state of a chiral aldehyde is in contrast to the normal aldol reaction (*30–34*). This feature of the photoreaction suggests the operation of a mechanism that is insensitive to the substitution pattern of the chiral aldehyde. One such mechanism is depicted in scheme 8. Reaction between an excited aldehyde (singlet or triplet state) and the furan proceeds with initial carbon-oxygen bond formation to produce either of the two diradical species shown. A stereocenter adjacent to the carbonyl is now in a 1,4-relationship to the newly formed stereocenter at the acetal carbon and is expected to exert little influence as a stereocontrol device. Two stereocenters are present in these intermediates, but the stereocenter at the acetal carbon is expected to completely dictate the stereochemical outcome of the diradical bond formation. In each case ring closure will produce a *cis* ring fusion with an *exo*-substituted side chain, as in the reaction of achiral aldehydes. The stereocenter on the side chain is inconsequential to the outcome of diradical closure and has minimal influence, stereochemically, on the initial acetal formation.

The regiochemical alternative of diradical ring closure would provide the product of a [4 + 2] cycloaddition. From our proposed diradical intermediate there might appear to be little impediment to such a process since the product, as well as the corresponding transition state, is expected to contain less total strain energy. We believe ring closure in the observed sense (to provide the [2 + 2] adduct) is favored by virtue of the greater free valency at C_3 of the 1-oxyallyl radical. For example, a simple Hückel molecular orbital calculation of 1-methoxyallyl radical **44** provides the values of free valence index at the three carbon centers indicated in scheme 8 (*57*). This calculation indicates that bond formation with a carbon radical would be favored at the C_3 position, since bonding at C_1 would involve a greater loss of the π-bonding character present in the oxyallyl radical intermediate.

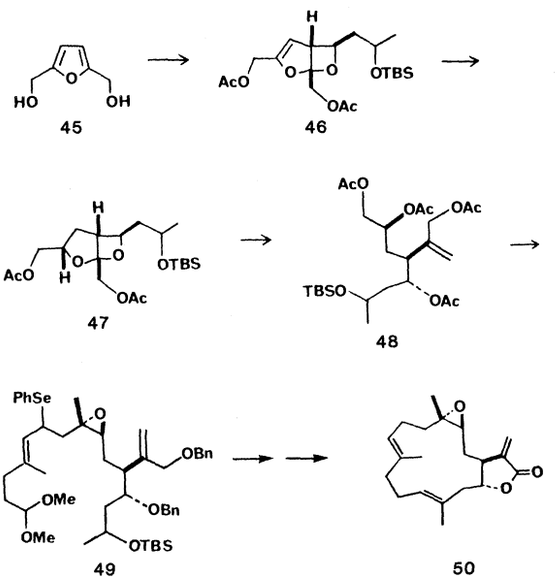
Our hypothesis for the mechanism of this reaction should be considered tentative. Nevertheless, it serves as a working model. The mechanism can be tested by examining the effect of furan substituents on the mode of selectivity (whether [2 + 2] or [4 + 2] addition is favored) and by examining the relative efficiency of various intramolecular cycloadditions. These experiments are ongoing in our laboratories.

Current Studies

The previous two examples illustrate the application of the Paternò-Büchi photocycloaddition of a furan and an aldehyde to the synthesis of compounds that contain five-membered-ring oxygen heterocycles. We are currently involved in several studies that employ this reaction as an entry point for the synthesis of other types of compounds. For example, significant progress has been made in our studies directed towards the synthesis of members of the cembranolide class of diterpenes, which contain 14-membered rings. These compounds are represented by the structures of the antileukemic substances crassin acetate and isolobophytolide (*58*). A brief description of our studies in this area is given in scheme 9.

The acyclic chain **48** can be prepared in six steps from 2,5-bis(hydroxymethyl)furan, **45**. A photocycloaddition of this furan and β-*t*-butyldimethylsiloxybutanal on a 25-g scale provided, after acetylation, the photoadduct **46**. Hydrogenation from the convex face proceeded with complete stereocontrol to produce **47**. Hydrolysis, acetylation, and Wittig methylenation afforded **48**, which contains three of the four stereocenters present in the target molecule, isolobophytolide. The *seco* derivative **49**, which contains all the carbons and stereocenters present in isolobophytolide, **50**, has been prepared in 14 steps from **48** (*59*). We are currently investigating methods for closure of the 14-membered ring and completion of the cembranolide synthesis.

In this brief account of photochemically mediated [2 + 2] cycloadditions in chiral molecule synthesis one strategy has been revealed that receives growing popularity. These reactions provide four-membered ring adducts that can be transformed in a controlled manner to advanced synthetic intermediates with skeletal and stereochemical complexities. As entry points in challenging syntheses, these reactions present the possibility for concise and efficient solutions to a variety of synthesis problems.



Scheme 9.

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Gas-Phase Ion Chemistry

Paul B. Comita and John I. Brauman

Summary. Progress has been made in the understanding of potential energy surfaces for unimolecular ion dissociations and ion-molecule reactions. With recent advances in instrumentation, many new techniques have been developed to generate and study ions, ion-molecule complexes, and large ionic clusters. Developments in ion spectroscopy have enabled considerable advances to be made in the determination of ion structures.

The study of the chemistry of ions in the gas phase has advanced rapidly in the last decade due to developments in ion trapping technology, light source technology, and ion detection methods. As is the case in many areas of chemistry, new technology has opened the door to new experiments and insights.

Perhaps the single most important motivation for studying ions in the gas phase is that the data obtained from such species will reflect the intrinsic properties of the ion. That is, the structure and reactivity are unperturbed by neighboring molecules or ions in the solid phase or solvent molecules and counterions in the liquid phase. The intrinsic properties of a molecular ion can be analyzed and interpreted in a straightforward manner and perhaps be related to a fundamental property of the ion itself rather than to its surrounding environment. The critical effects of solvation can thus be clarified by an understanding of intrinsic molecular properties. In addition, verification and elucidation of solvation effects has become possible with the ability to generate and study large ionic clusters that are composed of many neutral molecules loosely bound to an ion.

Among the challenging experimental aspects of gas-phase ion chemistry today are the quest for an understanding of geometrical structures and bonding and the quest for a detailed understanding of the intrinsic reactivities and potential energy surfaces for ion-molecule reactions with a view towards evaluating theories of the dynamics of chemical reactions.

Reaction Dynamics

Most early studies of ionic reactions in the gas phase focused on unimolecular fragmentations and rearrangements recorded in electron-impact mass spectra. Through the use of new technology and techniques, particularly ion cyclotron resonance (ICR), flowing afterglow, ion beams, and high-pressure mass spectrometry, significant progress has been made in understanding the dynamics and mechanisms of ionic reactions, not only in unimolecular fragmentations but also in reactions of higher order. With the development of new ion trapping technology and detection devices, such as pulsed (and now Fourier transform) ICR and selected ion flow tubes, it has become possible to examine both negative and positive ions with a wide variety of structural features. The dependence of ionic reactions on both temperature and translational energy has been investigated, and with the use of laser sources, the vibrational energy of the ion can be specifically varied to measure its effect on reaction dynamics.

Unimolecular reactions. Unimolecular fragmentation of gas-phase ions can

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