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A Remarkable Ene-Like Reaction: Development and Synthetic Applications

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ABSTRACT: A catalytic ene-like reaction of aldehydes with those vinyl ethers that display the oxygen functionality at the central carbon of an allylic system, e.g., 2-methoxypropene, is discussed in detail. The reaction is promoted by 0.05 equiv. of the 1:1 complex of Yb(fod)$_3$ and acetic acid, and it is forms the centerpiece of our synthesis of chlorovulone II, mitomycinoids and phyllanthocin.

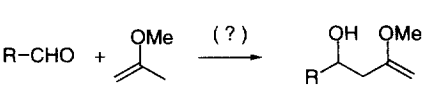
Introduction. The significance of formal ene reactions[2] of aldehydes with olefins has been amply recognized.[3] However, these processes enjoy limited acceptance in preparative work, because of generally limited scope with respect to aldehyde and olefin, frequent need for excess Lewis acid catalysts, poor tolerance of spectator functionality, and consequently modest levels of functionalization available in the ene products.

The insufficient electrophilicity of ordinary aldehydes normally dictates activation with suprastoichiometric amounts of Lewis acid promoters,[4] especially in the bimolecular regime,[5] but then side products are also formed, especially if the aldehyde is enolizable.[6] Intramolecular reactions are more successful than bimolecular ones; however, products of bimolecular processes are generally more useful intermediates. Activated carbonyls (glyoxals, etc.), react more readily and may not require large amounts of catalysts to undergo ene reaction; yet, their use in multistep syntheses is complicated by other technical problems.

Attempts to favor carbonyl-ene processes by the use of nucleophilic olefins such as alkyl- or silyl vinyl ethers have been undermined by the propensity of the former to copolymerize with carbonyl compounds under the influence of Lewis acids,[7] while the latter normally undergo Mukaiyama-type aldolization.[8] In 1993, Mikami[9] and Kuwajima[10] reported formation of ene-type products in reactions of triisopropyl silyl (TIPS) enol ethers. The Mikami reaction is truly catalytic and may be conducted in an enantiocontrolled mode. Nonetheless, the requirement for highly reactive acceptors, glyoxylate esters, persist; furthermore the cost of TIPS ethers is significant. Kuwajima technology works well with ordinary aldehydes; moreover, vinyl thioethers are also successful in this chemistry.[11] However, a slight excess of Me_2AlCl is still required.

The above difficulties clearly conspire against efficiency and practicality of carbonyl-ene reactions. Yet, these transformations enjoy a number of potential advantages over other types of carbonyl additions, especially organometallic ones. For instance, a truly catalytic carbonyl-ene reaction with vinyl ethers such as 2-methoxy propene and congeners that were of simple execution, that worked well with ordinary aliphatic or aromatic aldehydes, and that were not particularly sensitive to moisture or oxygen, would be equivalent to a fully catalytic aldol reaction,[12] yet it would have broader scope, because molecular complexity[13] could be readily increased by electrophilic functionalization of ene adducts (Scheme 1). The reaction would not require strong bases or organometallic reagents to achieve C–C bond formation, minimizing waste and removing the need for rigorous

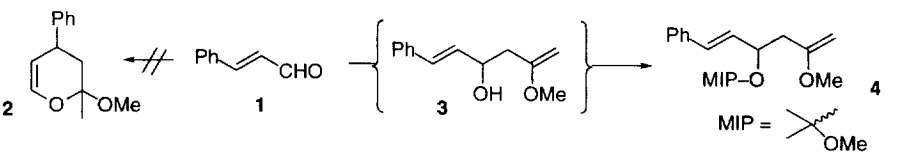
Scheme 1



exclusion of moisture or oxygen. Indeed, the appearance of such a reaction would remove most of the limitations that have prevented the widespread acceptance of carbonyl-ene additions as viable (and valuable) synthetic transformations. In 1991, we discovered a process that fulfills several of these criteria. Herein, we provide an account of how this reaction was found, optimized, and preparatively developed. We also describe applications of the new chemistry to the total synthesis of chlorovulone II, mitomycinoids and phyllanthocin. The structural diversity embodied by these molecules clearly highlights the potential of our ene chemistry in synthetic endeavors.

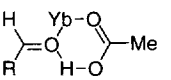
Discussion. Reaction of cinnamaldehyde, **1**, with 2-methoxypropene (2-MP) in the presence of $Yb(fod)_3$ under conditions anticipated to form pyran **2** (5 mol % $Yb(fod)_3$, 1,2-dichloroethane, reflux) gave only the remarkable product **4** in low yield (Scheme 2). This compound may be regarded as originating through an ene-like reaction of the aldehyde with the vinyl ether to give carbinol **3**, an isolable reaction intermediate, which subsequently becomes protected *in situ* by excess vinyl ether. Considerable research was necessary to define optimal conditions for the reaction.[14] These efforts culminated in 1993 with the development of two practical procedures that afforded end products of the type **4** from various aldehydes in high yield and purity.[15]

Scheme 2



Ene products proved to be thermally labile in the presence of the catalyst. Accordingly, conduct of the reaction at room temperature and reduction of the catalyst load to 0.5 mol % greatly improved yields. Furthermore, it was observed that no ene reaction occurred if highly purified aldehydes were used as substrates. It was soon found that carboxylic acid contaminants in the aldehydes were crucial for catalyst activation. Extensive investigations revealed that free carboxylic acids do not induce the reaction without $Yb(fod)_3$, while optimal activity is obtained with a 1:1 molar ratio of carboxylic acid to Yb complex. If excess acid is added, the reaction rate decreases and much polymerization of the vinyl ether occurs. These observations are consistent with the intervention of a ternary complex of $Yb(fod)_3$, aldehyde and acid as the active catalytic species (Scheme 3). In this complex, the aldehyde experiences "double activation" through coordination to the Lewis acidic Yb^{3+} and through hydrogen bonding with the acid proton. These interactions would facilitate nucleophilic attack into the aldehyde. A similar activation scheme has been recently described by Yamamoto as Brønsted acid-assisted Lewis acid catalysis.[16]

Scheme 3

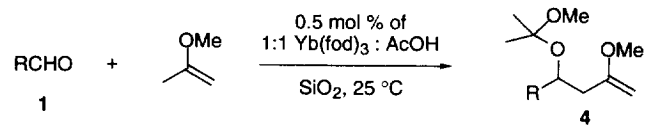


(fod ligands omitted for clarity)

Addition of some silica gel to the reaction mixture was found to have a beneficial effect on rates and product purity; however, SiO_2 is by no means required in the reaction. Its role is not fully understood, but perhaps it serves to remove adventitious moisture and/or to facilitate protection of the primary ene product, which, being an alcohol, could strongly coordinate the Yb, thereby denying the reacting aldehyde access to the catalyst.

Simple, inexpensive vinyl ethers such as 2-MP, a cheap commodity chemical, may be used as solvents for the reaction. This works especially well for aromatic aldehydes. Detailed procedures are provided in the experimental section, but, briefly, typical conditions (Procedure **A**) involve stirring a mixture of aldehyde (1 equivalent), $Yb(fod)_3$ (0.005 equivalents), silica gel (10 times the weight of Yb catalyst) and MP (20 equivalents) at room temperature. Enolizable aldehydes give generally better results when the above protocol is slightly modified (Procedure **B**) by introducing the substrate into the reaction as a 10 % weight/volume solution in CH_2Cl_2. In most cases, the reactions complete in 6 to 48 hours (NMR).[17] The major byproduct of these reactions is a homo-

Table 1: Representative ene reactions with 2-MP



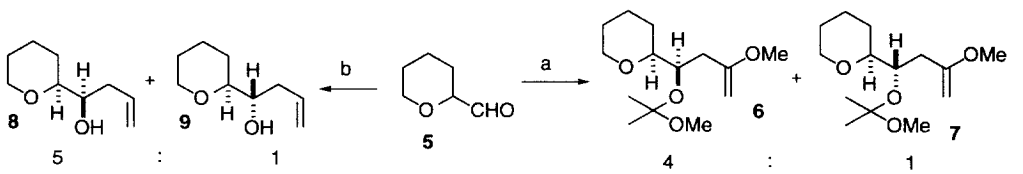
Entry	R	Procedure[a]	Yield[b]
a	Ph–	**A**	100
b	2-NO_2-C_6H_4–	**A**	99
c	2-I-C_6H_4–	**A**	99
d	2-N_3-C_6H_4–	**A**	97
e	4-NO_2-C_6H_4–	**A**	90
f	(*E*)-Ph-CH=CH–	**A**	83
g	*n*-C_3H_7–	**B**	81
h	*cyclo*-C_6H_{11}–	**B**	80
i	MeOOC-CH_2-CH_2–	**B**	98
j	EtOOC-CH=CH–	**B**	82
k	2-I-3-quinolyl–	**A**	99
l	CH_2=CH–	**B**	98

(a) See text for definition of Procedure **A** or **B**.
(b) Crude % yields (see text)

polymer of the starting vinyl ether. This polymer is practically insoluble in methanol, which, in turn, is an excellent solvent for the ene adduct. Therefore, dissolution of the crude ene product in MeOH and filtration of the thick gummy precipitate removes practically all contaminants and affords products of excellent quality (^1H and ^{13}C NMR), removing any need for further purification. Most functional groups that are poor ligands for the Yb catalyst, such as nitro, azide, halogen, olefin, cyano, ester, aryl and heteraryl (quinolines, furans) groups, are well tolerated in our ene reaction, even though several such functionalities probably would not be permissible in several of the ene-type processes described in refs. 3-11. Representative examples appear in Table 1.

Reaction of 2-MP with tetrahydropyran-2-carboxaldehyde proceeded with 4 : 1 selectivity for the Cram-Felkin diastereomer. The stereochemical course of this reaction was ascertained by extensive comparison of the spectra of compounds **6** and **7** and derivatives thereof with those of products **8** and **9** of Sakurai reaction of **5** (Scheme 4). The low level of diastereoselectivity may reflect, at least in part, an intrinsic property of **5**, because even the Sakurai reaction, which is quite Cram-Felkin selective in systems related to **5**,[18] afforded only a modest 5 : 1 Felkin selectivity with this aldehyde. More significantly, the fact that the reaction is Felkin selective, and that

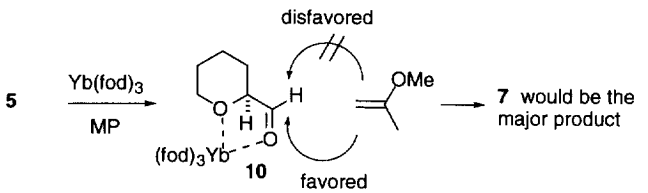
Scheme 4



(a) 2-MP, ene procedure **B**, 96 %; (b) TMS-CH_2-CH=CH_2, BF_3OEt_2, CH_2Cl_2, –20°C

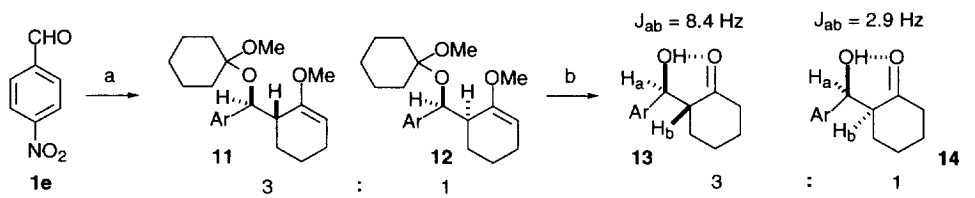
therefore chelation-control[19] is not operative, supports the hypothesis that the catalytic species may be the ternary Yb complex of Scheme 3. Ytterbium(III) favors octacoordination.[20] If six such sites are assumed to be occupied by the diketonate ligands in $Yb(fod)_3$, the availability of two remaining sites for **5** would probably result in formation of a chelate **10** (Scheme 5). Addition to the carbonyl would then occur with anti-Felkin selectivity, in contrast to experiment. The observed diastereoselectivity is most consistent with the availability of only one coordination site for the aldehyde, the other site being probably occupied by the carboxylic acid (cf. Scheme 3).

Scheme 5



While all the above ene reactions use 2-MP, any vinyl ether that incorporates the oxygen functionality at the central carbon of an allylic system will participate in the process.[21] Reaction of 4-nitrobenzaldehyde, **1e**, with 1-methoxycyclohexene yielded a 3:1 ratio of diastereomers **11** (major) and **12** (minor). Their stereochemistry was ascertained after mild acid hydrolysis to a 3:1 mixture of ketols **13** and **14**. The major ketol displayed a coupling constant J_{ab} = 8.4 Hz between protons A and B, suggestive of *anti* relative stereochemistry, while the minor ketol had J_{ab} = 2.9 Hz, consistent with *syn* stereochemistry (Scheme 6).[22]

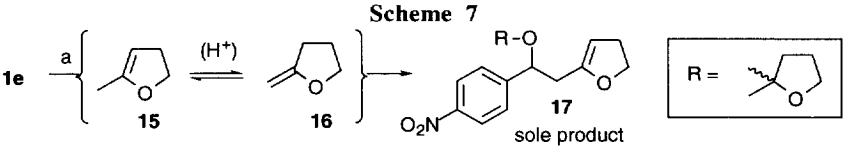
Scheme 6



(a) 1-methoxycyclohexene, ene procedure **B**, 97 %; (b) cat. 0.5 N aq. HCl, CH_2Cl_2, rt, 92 %.

Unsymmetrical ethers may also be used; however, such ethers may undergo prototropic isomerization[23] during the reaction. The least sterically encumbered tautomer normally reacts highly selectively with the aldehyde. For instance, reaction of 4,5-dihydro-2-methyl furan **15** with 4-nitrobenzaldehyde afforded only ene product **17** as a 1.5:1 mixture of unassigned methyl group diastereomers (Scheme 7). So, while the ene reaction is regioselective (it occurs with clean allylic transposition of the vinyl ether), it is not regiospecific (the regiochemistry of the ether does not define that of the products). Far from being a drawback, this property removes the need to make regiochemically defined unsymmetrical ethers as components of ene reactions. Because such ethers are often troublesome to make in pure form, our ene process is one of a few in which non-regiospecificity is actually an advantage. Similar vinyl ether isomerizations are central features of our synthesis of lavendamycin methyl ester.[24]

Scheme 7



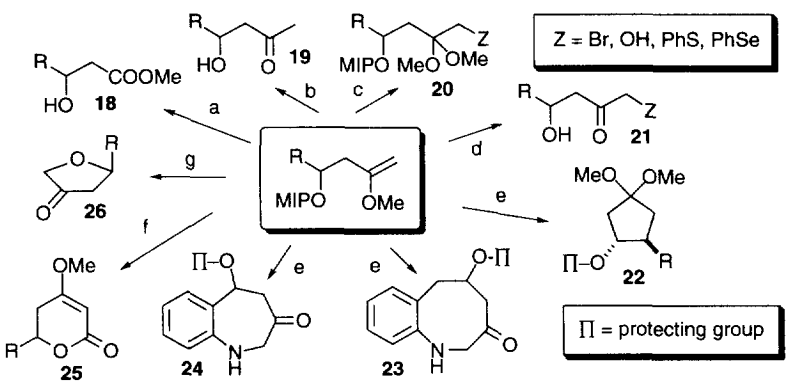
(a) Ene procedure **B**, 96 %

The feasibility of an enantioselective variant of our ene process, at least with 2-methoxypropene, has recently been demonstrated by Carreira.[25] This development greatly increases the preparative potential of the new reaction. We wish to call attention to the major differences between Prof. Carreira's outstanding methodology and ours.

We obtain ene products in protected form; whereas the Carreira catalyst yields hydroxy vinyl ethers of the type shown in Scheme 1. Our catalytic system produces good results with enals, while the Carreira complex may not be ideal for ene reactions of these substrates.[26] It will be seen shortly that both of these properties are useful in the context of the various synthetic projects we have undertaken to demonstrate the usefulness of the ene reaction. Conversely, we have obtained mixed results with ynals, while the Carreira protocol is fully satisfactory with these aldehydes; furthermore, very high enantioselectivity is available under Carreira conditions, while all our compounds described here are racemic. These limitations of our chemistry provide a strong incentive for us to continue our search for a satisfactory lanthanide-based catalyst for enantioselective ene reactions.

The value of the new reaction is clearly a function of how readily and efficiently the ene products could be translated into a diverse array of highly functional building blocks. We have focused our efforts in this area, and even though we have limited ourselves to a study of the adducts of 2-MP, we have already shown the value of the new technology in connection with several synthetic investigations. An outline of especially useful intermediates available from a generic ene product is provided in Scheme 8.

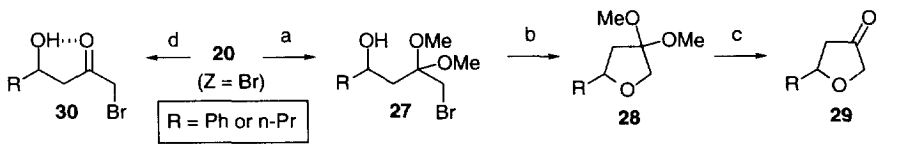
Scheme 8



(a) O_3, CH_2Cl_2, MeOH, cat. K_2CO_3, –78°C, then Me_2S, 90-98%; (b) cat. 0.5 N aq. HCl, CH_2Cl_2, rt, 90-99%; (c) Methanolic NBS (Z = Br; 80-90 %), MCPBA (Z = OH; 70-75 %), PhSCl or PhSeCl (50-70 %), cat. K_2CO_3; (d) Compounds **20**, aq. HCl, 85-95 %; (e) see text; (f) $PdOAc_2$, K_2CO_3, MeOH, CO, 50-60%; (g) compounds **20**, i. CSA, MeOH (- MIP), ii. NaH, iii. aq. HCl, 70-80 %.

Again we stress the equivalence of our reaction to a fully catalytic aldol process, as evident from the conversion of ene adducts into **18** or **19** by ozonolysis or hydrolysis, respectively. The reactive vinyl ether unit is selectively attacked by various electrophiles, even in the presence of other olefinic linkages. In particular, methoxybromination gives α-bromo ketals **20**, which may be subsequently hydrolyzed to α-bromo ketones **21**. Compounds such as **21** are formal aldol products arising from the "wrong" enolate of bromoacetone; therefore we refer to them as "anti-Darzens" ketones. We note that the bromo ketones are quite resilient, e. g. showing no inclination to cyclize to 3-furanones even after prolonged standing at room temperature. Their stability may be attributed to intramolecular hydrogen bonding that locks the molecule in conformation **30** (Scheme 9). However, functionalized 3-furanones, substructures found in a variety of bioactive agents of current interest,[27] may be quickly assembled from **20** (Z = Br) by MIP removal followed by base-promoted cyclization and deprotection. It

Scheme 9

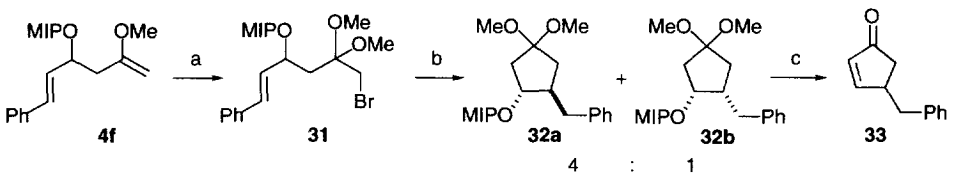


(a) CSA, MeOH, 95-99 %; (b) NaH, THF, rt, 80-85 %; (c) aq. 1N HCl, THF, rt, 90-95 %; (d) aq. 1N HCl, THF, rt. 75-85 %

should be noted that the lack of good synthetic methods for these heterocycles[28] prompted a landmark investigation of their synthesis and chemistry.[29] Various other electrophiles (S and Se halides, $Pd(OAc)_2$, etc.) also react selectively with the vinyl ether of the ene products (Scheme 8).

Bromo ketals incorporating additional olefinic functionality may be converted to cycloalkanes under radical conditions. This is seen, for instance, in the conversion of **31** into a 4:1 mixture of diastereomers **32a** (major) and **32b** (minor, Scheme 10),[30] which furnished cyclopentenone **33** upon acid hydrolysis. Structural similarities between cyclopentanoids **32 / 33** and prostanoid natural products are apparent.

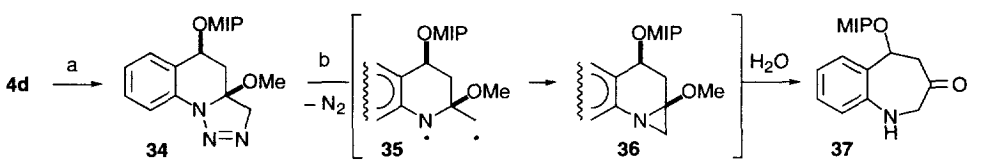
Scheme 10



(a) NBS, MeOH, CH_2Cl_2, 0 °C, 88 %; (b) Bu_3SnH, AIBN, PhH, reflux; (c) Aq. HCl, THF, 63 % b-c.

Ene products of aldehydes which incorporate dipolar functionality may undergo intramolecular reactions leading to synthetically important heterocycles. To illustrate, compound **4d** cyclized in refluxing benzene to give relatively stable triazoline **34** cleanly, quantitatively and stereospecifically. Thermolysis of **34** in xylene (140 °C) promoted Huisgens-type retro-[3 + 2] dipolar loss of diazomethane[31] and aromatization to 3-methoxyquinoline. More interestingly, irradiation of **34** in benzene solution afforded benzazepinone **37** in good yield, probably through the mechanism delineated in Scheme 11.

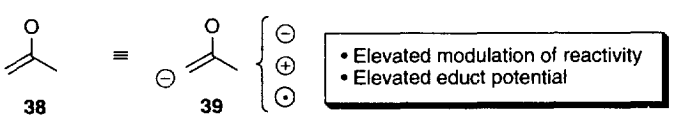
Scheme 11



(a) PhH, refl.; (b) hv (sunlamp), PhH, 48 h 86 % overall;

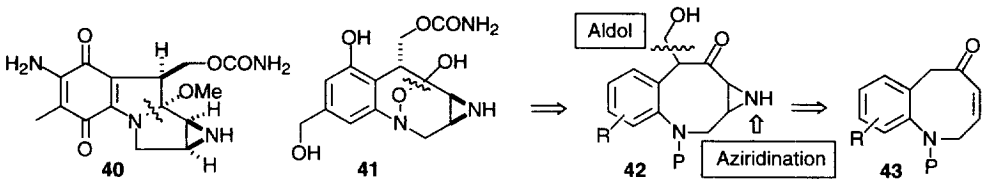
These and other interesting manipulations of ene adducts indicate that, within the boundaries of the new reaction, the allylic system of a generic ether **38** is equivalent to a bifunctional synthon **39.** One end of **39** displays negative polarity (it adds nucleophilically to the aldehyde), while the reactive nature of the other end may be modulated at will (Scheme 12). This imparts elevated educt potential to ene products, and indeed, it permits the use of small, densely functional vinyl ethers as "linchpins" for securing two or more fragments into a larger molecular edifice, or to bridge two regions of a substrate molecule into a more complex structure. It seems best, at this juncture, to illustrate the use of the new chemistry in some synthetic endeavors. Three such exercises will be discussed. It will be seen that in all cases the ene step occurs early in the synthesis, underscoring the fact that unlike other similar transformations, our ene reaction is perfectly suitable for medium- to large-scale work (10-30 g batches of material). Indeed, we find that even less catalyst (0.2 - 0.3 mol %) suffices in large scale work.

Scheme 12



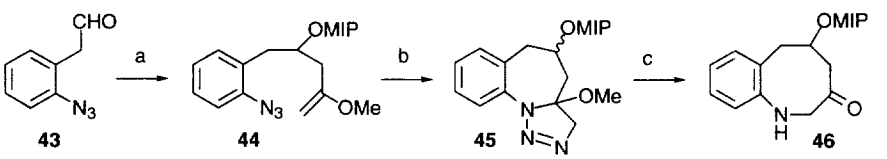
Synthetic Applications. Mitomycinoids[32] e.g., mitomycin C, **40** (clinically used) and FR900482, **41** are antitumor agents for which a good synthesis is still needed. Retrosynthetic dissection of these appealing synthetic

Scheme 13



targets reveals a possible benzazocenone intermediate (Scheme 13) and indeed, some especially successful syntheses of **40** and **41** rest on this general idea.[33] However, methods for the preparation of benzazocenones tend to be lengthy, and only recent advances in methodology[34] have permitted the formulation of shorter routes. Our ene reaction appears to hold good promise in this area, as evident from the concise assembly of model system **46** (Scheme 14), obtained by processing ene adduct **44** in a manner similar to that shown earlier in Scheme 11.[35] Notice that no sensitizer is necessary for the photochemical conversion of triazoline **45** into **46**;[36] furthermore, while compound **34** (Scheme 11) was rather stable, substance **45** eliminated MeOH easily under mild acidic conditions to form the corresponding triazole. Prudence thus advocated the introduction of small amounts of K_2CO_3 in reactions involving this triazoline.

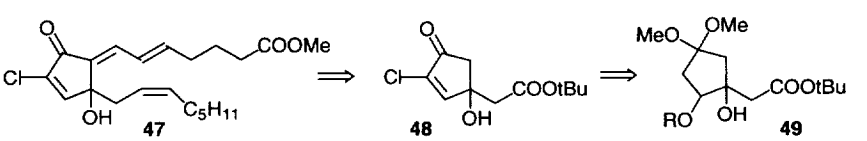
Scheme 14



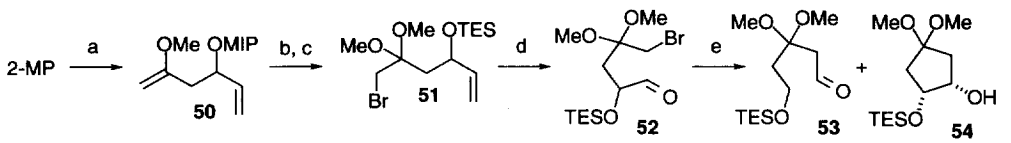
(a) Proced. **A**; (b) PhH, refl., cat. K_2CO_3, 14 h, 51 % chrom. a-b; (c) hv (sunlamp), cat. K_2CO_3, PhH, 32 h 78 %.

Opportunities offered by the ene reaction in the prostanoid area have been explored in a synthesis of (±)-chlorovulone II, **47**.[37] This marine natural product was isolated from a coral as an exceptionally potent cytotoxic agent, with IC_{50} against representative tumors lines equal to about 10 ng/mL. Chlorovulone may be rapidly obtained from intermediate **48** (Scheme 15), which has previously been synthesized in homochiral form from tartaric ester. However, individual antipodes of **47** as well as the racemate display identical biopotency, therefore, enantiopure material does not appear to be necessary for further pharmacological studies. We surmised that (±)-**48** may thus be manufactured from **49**, which clearly reveals its ene roots. Accordingly, the ene adduct **50** of 2-MP with acrolein was converted into aldehyde **52** in preparation for radical-carbonyl cyclization.[38] Unfortunately, this step was inefficient, at least with substrate **52**, providing a modest 31 % yield of **53** as well as 24 % of **54**. Product **53** of formyl transfer was expected; however, the stereoselective formation of only the *cis* diastereomer

Scheme 15



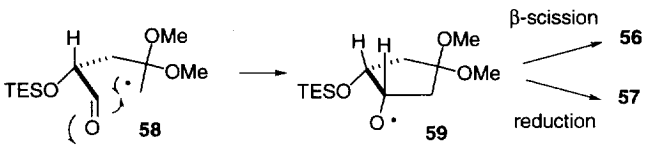
Scheme 16



(a) Acrolein, ene procedure B; (b) NBS, MeOH; (c) Et_3SiCl, Et_3N 55 % a-c; (d) O_3, CH_2Cl_2, MeOH, then Me_2S, 80 %; (e) Bu_3SnH, AIBN, 24 % of **56**, 31 % of **57**.

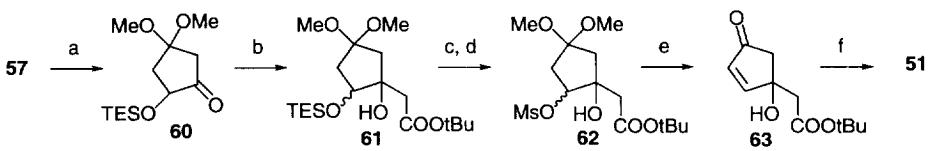
of the desired **57** was not (Scheme 16).[39] The stereochemistry of **57** formally arises through "Felkin-Ahn-like" cyclization of the presumed radical intermediate **58** (Scheme 17). Broader implications of this observation are currently being researched; therefore, no data are yet available regarding the generality of this stereochemical

Scheme 17



outcome. In any event, compound **57** was advanced to intermediate **51** in a conventional fashion (Scheme 18). The present route to **51** is thus shorter that the published alternative, but additional refinements, especially with regard to the radical cyclization step, are clearly needed and are being actively pursued in our laboratory.

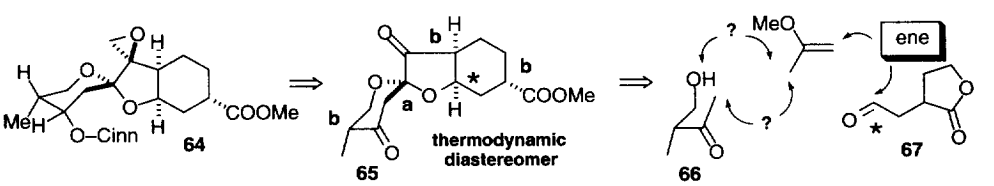
Scheme 18



(a) cat. TPAP, NMO, CH_2Cl_2, 85 %; (b) tBuOAc, LDA, 87 %; (c) TBAF, THF; (d) MsCl, CH_2Cl_2, Et_3N, 84 % c-d; (e) 80 % aq. AcOH, rt, 98 %; (f) Cl_2, CCl_4, then Et_3N, 79 %.

We wish to conclude this panoramic on our ene chemistry with a preview of a stereoconvergent total synthesis of (±) phyllanthocin, **64**. This terpene is the biologically inactive methyl ester of the aglycon of the antitumor agent, phyllanthoside.[40] Outstanding syntheses of both phyllanthocin and phyllanthoside are known,[41] so that an ene-based route to these substances should permit a frank evaluation of the new methodology. Our retrosynthetic hypothesis is summarized in Scheme 19. All but one stereogenic centers in advanced intermediate **65** are epimerizable either with acid or base; furthermore, the relative stereochemistry of **65** corresponds to the thermo-

Scheme 19

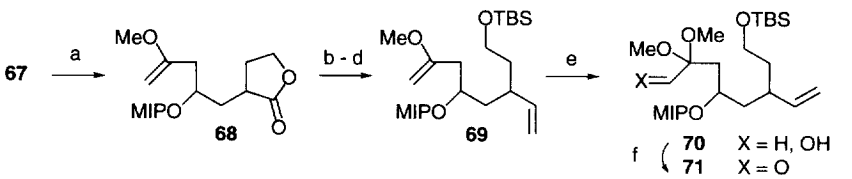


a epimerizable under acidic conditions
b epimerizable under basic conditions

dynamic energy minimum. The only non-epimerizable center, marked with an asterisk, corresponds to the one established through the ene reaction of 2-MP with aldehyde **67**.[42] Thus, the stereochemical outcome of the ene step was anticipated to define both absolute and relative stereochemistry of **65** through epimerization of all stereocenters. This proved to be the case. The synthesis we are about to present is racemic, but recall that absolute stereocontrol is available in the ene step, at least in principle, through Carreira methodology.

The initial phases of our synthesis saw conversion of ene adduct **68** into aldehyde **71** (Scheme 20). It is recognized that the preparation of this reactive material by other methods would be substantially more involved. A key step in this sequence was a chemoselective attack of the vinyl ether with buffered methanolic MCPBA resulting in methoxyhydroxylation of **69** to **70**. The conversion of the lactone carbonyl to an olefin was forced upon us by unanticipated difficulties with a later step of the synthesis.[43]

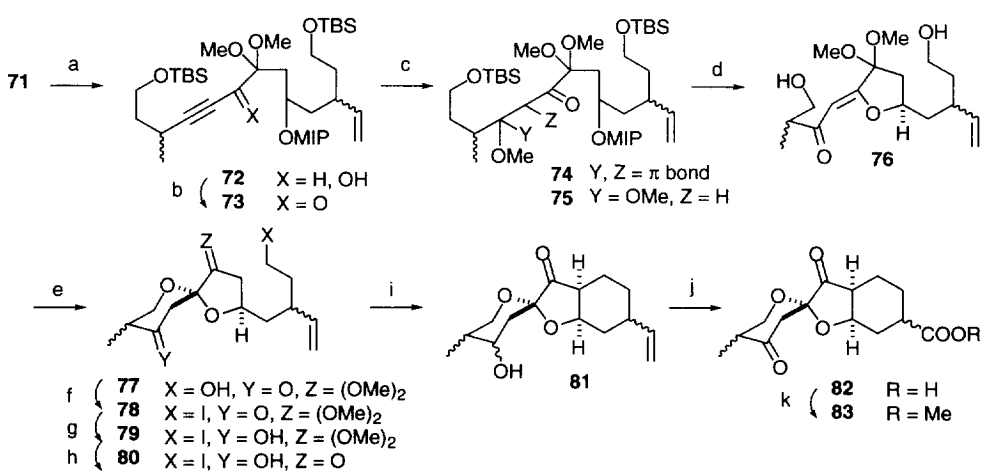
Scheme 20



(a) Ene procedure **B**, 99 %; (b) DIBAL, THF, –78°C; (c) $Ph_3P{=}CH_2$; (d) TBSCl, imidazole, CH_2Cl_2, 55 % b-d; (e) MCPBA, MeOH, 73 %; (f) cat. TPAP, NMO, CH_2Cl_2, 98 %.

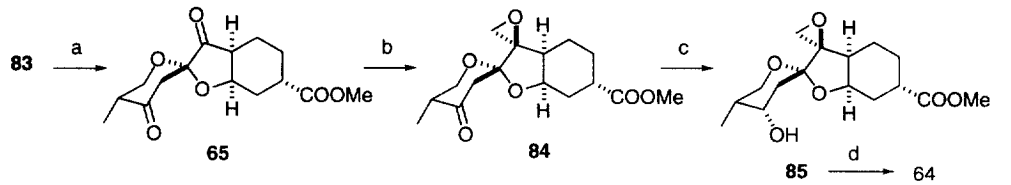
Molecular complexity increased rapidly from **71**. Thus, condensation with the Li acetylide[44] of the TBS ether of 3-methyl-4-pentyn-1-ol[45] furnished carbinol **72**, which was sequentially oxidized to ynone **73** and treated with methanolic Triton B (Scheme 21). A series of acid-catalyzed steps ultimately translated a mixture of Michael-type adducts **74** and **75** into spiroketal **77**, obtained as a mixture of four diastereomers epimeric at the allylic carbon and at the pyran methyl, but of identical, thermodynamic relative configuration of the spirocyclic unit. Intramolecular alkylation installed the 6-membered ring and furnished only the expected *cis* fused perhydrobenzofuran system. A final Sharpless RuO_4 oxidation[46] / esterification afforded a mixture of diastereomers of **83**.

Scheme 21



(a) Li-acetylide (text), –78°C; (b) cat. TPAP, NMO, CH_2Cl_2, 64 % a-b; (c) MeOH, Triton B; (d) Aq. TFA; (e) CSA, CH_2Cl_2, 91 % c-e; (f) MsCl, TEA, then NaI, 95 %; (g) $NaBH_4$, EtOH, –20°C; (h) HCOOH, rt, 96 % g-h; (I) tBuOK, THF, 0°C; (j) cat. $RuCl_3$, KIO_4, 45 % I-j.

Scheme 22



(a) MeI, K_2CO_3, then DBU, 91 %; (b) $Me_2S(O)=CH_2$, THF, –78°C; (c) $NaBH_4$, EtOH, – 20°C, 81 % b-c; (d) Cinnamoyl chloride, DMAP, CH_2Cl_2, 89 %.

It was most pleasing to observe that prolonged exposure of **83** to DBU in THF at room temperature induced convergence of the various diastereomers of the molecule to the thermodynamic stereochemistry (Scheme 22), resulting in great simplification of the its NMR spectra. The sole diastereomer thus remaining, **65**, was efficiently advanced to (±)-phyllanthocin by literature methods. Overall, a 5 % yield of **64** was realized over 20 steps from **67**. The synthesis is longer than the most concise alternatives (Martin, 14 steps; Burke, 15 steps), but the overall yield is almost twice as high; while it is competitive in all respects with other known routes. Furthermore, it may be argued that our building blocks are less costly and more expeditiously made than several components of earlier syntheses. At the same time, opportunity exists for further refinements, and work along these lines continues.

In summary, it appears that the new "ene" chemistry adds a new strategic dimension to the logic of synthetic planning. Of course, much work still lies ahead for us to define the full scope and limitations of the reaction and to engineer a good enantioselective catalyst. Then, just over three years have elapsed since our initial disclosure, during which time we have focused largely on ene adducts of 2-MP. That notwithstanding, we believe that the value of the new reaction in synthetic ventures has been established. We remain hopeful that the manifold aspects of this chemistry currently under development in our laboratories and elsewhere will eventually cause this simple, practical, inexpensive transformation to gain full acceptance among all practitioners of Synthesis.

Acknowledgment. We gratefully thank the National Institutes of Health (CA-55268), the National Science Foundation (CHE 95-26183), the Robert A. Welch Foundation (C-1007), and the Alfred P. Sloan Foundation for support of our research program.

Experimental Section[47]

Ene reaction of a non-enolizable aldehyde (Procedure A). An aldehyde (1 equivalent) was added to a solution of $Yb(fod)_3$ (0.005 equivalents) and glacial acetic acid (0.005 equivalents, introduced as a standard solution in CH_2Cl_2) in 20 molar equivalents of vinyl ether containing suspended silica gel (Merck 60-230 mesh, 10-fold weight amount of $Yb(fod)_3$). The mixture was stirred at room temp., and upon completion (6-72 hrs, TLC and NMR in C_6D_6), it was partitioned between sat. aq. $NaHCO_3$ and CH_2Cl_2. Evaporation yielded the crude product. If contamination from the polymer of the vinyl ether was apparent, the crude material was redissolved in MeOH containing a small amount of K_2CO_3 and the solution was stirred for 30 min. to cause coagulation of the polymer. Filtration (celite) and concentration provided pure ene product, e.g. compound **4e**: R_f (20% EtOAc/hexanes) 0.63. ^1H (C_6D_6) 8.18 (app. d, 2H, J = 8.0 Hz), 7.46 (app. d, 2H, J = 8.0 Hz), 5.01 (dd, 1H, J = 7.4, 6.8 Hz), 3.85 (d, 1H, B part of AB, J = 1.8 Hz), 3.82 (d, 1H, A part of AB, J = 1.8 Hz), 3.10 (s, 3H), 2.90 (s, 3H), 2.61 (dd, 1H, B part of AB, J = 13.6, 6.8 Hz), 2.22 (dd, 1H, A part of AB, J = 13.6, 7.4 Hz), 1.27 (s, 3H), 1.00 (s, 3H). ^{13}C (C_6D_6) 157.7, 150.4, 145.2, 125.1, 121.4, 99.3, 81.9, 68.3, 52.3, 47.0, 43.4, 24.2, 22.9. IR 2997, 2944, 2831, 1662, 1603, 1523, 1450, 1350, 1211, 1144, 1085. MS 295 (M^+), 224, 206, 174, 152, 128, 115, 104, 74, 73 (100%), 72. HRMS(CI) calc. 296.1498 (M^++ H); obs. 296.1479.
Ene reaction of an enolizable aldehyde (Procedure B). Similar to Procedure A, except that only 10 equiv. of vinyl ether was used and the aldehyde was introduced as a 10% solution in CH_2Cl_2. Compound **4h**: ^1H (C_6D_6) 4.09 (ddd, 1H, J = 6.8, 6.4, 2.8 Hz), 4.01 (d, 1H, J = 1.7 Hz), 3.86 (d, 1H, J = 1.7 Hz), 3.28-3.03 (c. m, 1H), 3.19 (s, 3H), 3.14 (s, 3H), 2.61 (dd, 1H, B part of AB, J = 13.8, 6.4 Hz), 2.42 (dd, 1H, A part of AB, J = 13.8, 6.9 Hz), 1.90-1.50 (c. m, 5H), 1.40-1.00 (c. m, 5H), 1.33 (s, 3H), 1.31 (s, 3H). ^{13}C (C_6D_6) 162.5, 100.8, 82.4, 73.5, 54.3, 48.9, 42.3, 38.4, 29.2, 28.0, 27.2, 27.1, 26.0, 25.4, 25.2. IR 2991, 2938, 2851, 1656, 1450, 1377, 1204, 1151, 1072, 1031, 799. MS 225 (M^+– OMe), 209, 162, 155, 115, 89, 73 (100%). HRMS(CI) calc. 257.2117 (M^+ + 1); obs. 257.2117.

Acid hydrolysis of an ene product. A mixture of **4a** (108 mg, 0.43 mmol) and 1N aq. HCl (0.2 mL) in CH_2Cl_2 (4 mL) was stirred at room temp. for 10 min, then it was neutralized (sat. aq. $NaHCO_3$) and extracted with CH_2Cl_2. Evaporation gave 70 mg (98 %) of pure 1-phenyl-1-butanol-3-one, colorless oil, R_f (20% EtOAc/hexanes) 0.20. ^1H 7.23 (c. m, 5H), 5.05 (m, 1H), 3.34 (m, 1H), 2.80 (app. dd, 1H, B part of AB, J = 17.5, 8.7 Hz), 2.68 (ddd, 1H, A part of AB, J = 17.4, 3.6, 1.7 Hz), 2.08 (s, 3H). ^{13}C 208.9, 142.8, 128.4, 127.6, 125.6, 69.8, 51.9, 30.7. IR 3429, 3064, 3030, 2904, 1702, 1364, 1158, 1065, 753, 700. MS 164 (M^+), 146 ($M^+ - H_2O$), 131, 107, 105, 91, 79, 77, 58, 51, 43. HRMS calc. 164.0837; obs. 164.0835

Ozonolysis of an ene product. Ozone was bubbled through a cold (–78°C) solution of **4d** (198 mg, 0.65 mmol) in 4:1 CH_2Cl_2/MeOH (6.5 mL) containing suspended K_2CO_3 (25 mg). When the solution turned blue, excess O_3 was purged (N_2 bubbling), Me_2S (0.2 mL) was added, and the mixture was allowed to warm to room temp. with good stirring. After 1 h, the solution was diluted with more CH_2Cl_2 and sequentially washed with aq. sat. $NaHCO_3$, aq. sat. NaCl and aq. 1N HCl (MIP removal). Filtration through silica gel and concentration yielded 144 mg (96 %) of pure methyl-3-hydroxy-3-(2-azidophenyl)-propionate, colorless oil, R_f (20% EtOAc/hexanes) 0.28. ^1H 7.52 (m, 1H), 7.30 (dt, 1H, J = 7.7, 1.6 Hz), 7.14 (c. m, 2H), 5.29 (dd, 1H, J = 9.3, 2.4 Hz), 3.70 (s, 3H), 2.76 (dd, 1H, B part of AB, J = 16.2 Hz, 3.3 Hz), 2.60 (dd, 1H, A part of AB, J = 16.2, 9.3 Hz). ^{13}C 172.6, 136.0, 133.5, 128.6, 126.8, 125.0, 117.8, 65.7, 51.7, 41.6. IR 3469, 2957, 2134, 1735, 1576, 1490, 1443, 1291, 1204, 1164, 1065, 1032, 759. MS 221 (M^+), 193 (M^+– N2), 161, 144, 133, 120 (100%), 92, 77, 73, 60. HRMS calc. 221.0800; obs. 221.0801.

Methoxybromination of an ene product. A solution of **4a** (304 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added to a cold (0°C), stirred solution of NBS (240 mg, 1.3 mmol) in dry MeOH (1 mL) and CH_2Cl_2 (3 mL) containing suspended K_2CO_3 (ca. 30 mg). Upon completion (30 min, TLC), the mixture was diluted with more CH_2Cl_2 and sequentially washed with 5 % aq. $Na_2S_2O_2$ and sat. aq. $NaHCO_2$. Concentration gave 413 mg (94 %) of 1-phenyl-1-[2-(2-methoxy)-propoxy]-3,3-dimethoxy-4-bromobutane, colorless oil, R_f (20% EtOAc/hexanes) 0.63. ^1H 7.35 (c. m, 5H), 4.76 (t, 1H, J = 6.6 Hz), 3.53 (dd, 1H, B part of AB, J = 11.3, 0.9 Hz), 3.23 (s, 3H), 3.18 (dd, 1H, A part of AB, J = 11.3, 0.7 Hz), 3.07 (s, 3H), 3.02 (s, 3H), 2.39 (ddd, 1H, B part of AB, J = 15.3, 7.0, 0.8 Hz), 2.17 (ddd, 1H, A part of AB, J = 15.3, 6.3, 0.7 Hz), 1.40 (s, 3H), 1.11 (s, 3H). ^{13}C 144.6, 128.0, 127.2, 126.9, 101.2, 100.3, 70.1, 49.3, 48.4, 48.1, 40.1, 32.3, 26.0, 25.0. MS 273 & 271 (M^+–OMIP), 169 & 167, 121, 73 (100%), 43. HRMS calc. 360.0936 (^{79}Br); obs. 360.0899.

Selective MIP release from bromoketals. A solution of 1-bromo-2,2-dimethoxy-4-[2-(2-methoxy)-propoxy]-heptane (308 mg, 0.9 mmol) and anhydrous camphorsulfonic acid (30 mg) in dry MeOH (4 mL) was stirred at room temp.. Upon completion (30 min, TLC), the mixture was diluted with CH_2Cl_2 and washed with sat. aq. $NaHCO_3$. The CH_2Cl_2 extracts were the dried (Na_2SO_4) and evaporated to give 241 mg (99%) of pure free alcohol, colorless oil, R_f (20% EtOAc/hexanes) 0.24. ^1H 3.82 (c. m, 1H), 3.64 (dd, 1H, B part of AB, J = 11.2, 0.9 Hz), 3.44 (d, 1H, A part of AB, J = 11.2 Hz), 3.28 (s, 3H), 3.25 (s, 3H), 2.88 (d, 1H, J = 2.2 Hz), 1.97 (m, 2H), 1.42 (c. m, 4H), 0.93 (br. t, 3H). ^{13}C 101.6, 67.6, 48.8, 48.5, 40.0, 38.8, 32.6, 18.6, 14.0. IR 3428, 2957, 2871, 2831, 1716, 1463, 1423, 1191, 1085, 1045, 925, 812, 686. HRMS calc. 161.1178 (M^+ – CH_2Br); obs. 161.1199.

Complete hydrolysis of bromoketals. A solution of 1-phenyl-1-[2-(2-methoxy)-propoxy]-3,3-dimethoxy-4-bromobutane (145 mg, 0.4 mmol) in THF (3 mL) and 1N aq. HCl (1 mL) was stirred at room temp. for 1h, then extracted with EtOAc. The extracts were washed with sat. aq. NaCl, dried (Na_2SO_4) and concentrated to afford 81 mg (83 %) of 1-bromo-4-hydroxy-4-phenyl-2-butanone of at least 93 % purity (NMR), pale yellow oil, R_f (20% EtOAc/hexanes) 0.28. These sensitive compounds do not survive chromatography. ^1H 7.32-7.18 (c. m, 5H), 5.06 (dd, 1H, J = 9.1, 3.5 Hz), 3.84 (s, 2H), 3.24 (br. s, 1H), 2.98 (dd, 1H, B part of AB, J = 16.8, 9.1 Hz), 2.85 (dd, 1H, A part of AB, J = 16.8, 3.5 Hz). ^{13}C 201.3, 142.4, 128.5, 127.8, 125.5, 70.0, 48.5, 35.0. IR 3437, 3029, 2931, 1721, 1497, 1448, 1391, 1349, 1194, 1068, 1046, 759, 702. MS 163 (M^+ - Br), 107, 105, 88, 86 (100%), 84, 79, 77, 51. HRMS calc. (^{81}Br) 243.9923; obs. 243.9903.

General procedure for 3-furanone dimethyl ketal formation. A solution of 4-bromo-3,3-dimethoxy-1-phenyl-1-butanol (682 mg, 2.4 mmol) in THF (10 mL) was added to a cold (0°C) suspension of NaH (170 mg, 3 eq., initially a 60 % oil dispersion, washed free from oil with hexanes) in THF (40 mL) maintained under Ar. After evolution of H_2 (**CAUTION**) subsided, the mixture was warmed to room temp., stirred until the reaction completed (TLC), then quenched with sat. aq. NH_4Cl (**CAUTION**) and extracted with Et_2O. The extracts were sequentially washed with sat. aq. $NaHCO_3$ and NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue gave 420 mg (85 %) of 2-phenyl-4,4-dimethoxy-tetrahydrofuran, oil, R_f (20% EtOAc/hexanes) 0.54. ^1H 7.40-7.26 (c. m, 5H), 5.03 (dd, 1H, J = 9.7, 6.2 Hz), 4.08 (d, 1H, B part of AB, J = 9.5 Hz), 3.92 (d, 1H, A part of AB, J = 9.5 Hz), 3.31 (s, 3H), 3.28 (s, 3H), 2.51 (dd, 1H, J = 12.5, 6.2 Hz), 2.03 (dd, 1H, J = 12.5, 9.7 Hz). ^{13}C 141.5, 128.4, 127.6, 125.9, 110.5, 80.3, 73.2, 50.4, 49.7, 43.7. IR 3063, 3037, 2944, 2831, 1496, 1457, 1364, 1251, 1144, 1071, 1045, 759, 700. MS 178 ($M^+ - CH_2O$), 177 (M^+ - OMe), 121, 105, 77, 73, 71, 57, 55, 51, 43 (100%), 41. HRMS calc. 178.0994 ($M^+ - CH_2O$); obs. 178.0996.

General procedure for 3-furanone formation. A solution of 2-phenyl-4,4-dimethoxy-tetrahydrofuran (107 mg, 0.5 mmol) in THF (1 mL) and 1N aq. HCl (0.5 mL) was stirred at room temp. until the reaction

completed (TLC). The mixture was diluted with Et_2O, sequentially washed with sat. aq. $NaHCO_3$ and NaCl, dried (Na_2SO_4) and concentrated to give 83 mg (95%) of 4-phenyl-3-tetrahydrofuranone, oil, R_f (20% EtOAc/hexanes) 0.40. ^1H 7.42-7.33 (c. m, 5H), 5.29 (dd, 1H, J = 9.5, 6.3 Hz), 4.25 (br. d, 1H, B part of AB, J = 17.0 Hz), 4.01 (d, 1H, A part of AB, J = 17.0 Hz), 2.88 (dd, 1H, B part of AB, J = 17.9, 6.3 Hz), 2.55 (ddd, 1H, A part of AB, J = 17.9, 9.6, 1.1 Hz). ^{13}C 214.2, 139.9, 128.6, 128.2, 125.8, 79.3, 71.7, 44.6. IR 3509, 3063, 3030, 2918, 1762, 1596, 1496, 1171, 1058, 753, 700. MS 162 (M+), 105, 104 (100%), 78, 77, 51, 28. HRMS calc. 162.0681; obs. 162.0681

Methoxyhydroxylation of an ene product. A solution of freshly purified MCPBA[48] (2.3 g, 13.5 mmol) in CH_2Cl_2 (7 mL) was added to a cold (0°C) solution of compound **69** (3.5 g, 9 mmol, ca. 1.5:1 mixture of 2 unassigned diastereomers) in CH_2Cl_2 (20 mL) and MeOH (5 mL) containing suspended K_2CO_3 (200 mg). After 2 h of vigorous stirring at 0°C, the mixture was diluted with CH_2Cl_2, washed with 1N aq. NaOH, dried (Na_2SO_4) and concentrated. Chromatography of the residue gave hydroxyketal **70** (2.8 g, 73%), colorless oil, mixture of 2 diastereomers, R_f (20% EtOAc/hexanes) 0.25. ^1H 5.50 (m, 1H), 5.05 (m, 2H), 4.12 (m, 1H), 3.90 (dd, 1H, A part of AB, J = 12.0, 9.5 Hz), 3.76 (dd, 1H, B part of AB, J = 12.0, 5.3 Hz), 3.63 (m, 2H) 3.19 (s, 3H), 3.12 (s, 3H), 3.03 (s, 3H), 2.19-1.93 (m, 4H), 1.77-1.38 (m, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 0.99 (s, 9H), 0.07 (s, 6H). ^{13}C 142.1, 114.9, 101.9, 101.3, 68.4, 62.4, 60.6, 49.0, 48.8, 40.0, 38.8, 37.8, 37.5, 31.6, 26.0, 25.4, 18.3, -5.6. IR 3462, 3084, 2957, 2937, 2861, 1638, 1468, 1385, 1257, 1204, 1081, 834. MS 403 (M^+ – MeO), 331, 313, 255, 185, 155, 129, 73.

Benzazepinone formation from ene product 4d. A solution of adduct **4d** (931 mg, 3.2 mmol) in benzene (17 mL) was refluxed for 7 h under Ar atmosphere. The resulting triazoline [R_f (40% EtOAc/hexanes) 0.46. ^1H 7.77 (dd, 1H, J = 8.2, 1.1 Hz), 7.44 (br. d, 1H), 7.29 (compl. t, 1H), 7.07 (dt, 1H, J = 7.6, 1.2 Hz), 5.21 (br. dd, 1H, J = 11.2, 5.8 Hz), 4.53 (d, 1H, B part of AB, J = 18.8 Hz), 3.98 (d, 1H, A part of AB, J = 18.8 Hz), 3.29 (s, 3H), 2.91 (s, 3H), 2.85 (br. dd, 2H, J = 12.4, 5.8 Hz), 1.54 (s, 3H), 1.49 (s, 3H). IR 2991, 2944, 2831, 1726, 1607, 1473, 1371, 1204, 1183, 1086, 1049, 1000, 920, 855. MS 292 (M^+ + 1), 259 (M+ - MeOH), 249, 217, 191, 177, 174, 160, 142, 132, 130, 117, 73 (100%), 43], isolated by simple evaporation of the solvent, began to form the azepinone upon exposure to ambient light. A benzene (12 mL) solution of this triazoline in a common pyrex flask (Ar atm.) was irradiated with a Sylvania 275 W sunlamp until complete conversion to the product occurred. Concentration and chromatography provided 625 mg (78 % overall) of benzazepinone **37**, oil, R_f (40% EtOAc/hexanes) 0.65. ^1H 7.22 (dd, 1H, J = 7.6, 1.5 Hz), 7.13 (dt, 1H, J = 7.5 , 1.5 Hz), 6.82 (dt, 1H, J = 7.4, 0.8 Hz), 6.69 (br. d, 1H, J = 8.1 Hz), 5.04 (d, 1H, J = 7.1 Hz), 4.16 (d, 1H, B part of AB, J = 16.9 Hz), 3.70 (d, 1H, A part of AB, J = 14.7 Hz), 3.24 (d, 1H, B part of AB, J = 14.7 Hz), 3.14 (s, 3H), 2.87 (dd, 1H, A part of AB, J = 14.7, 7.2 Hz), 1.42 (s, 3H), 1.33 (s, 3H). ^{13}C 210.2, 147.2, 132.7, 128.7, 125.8, 119.1, 118.0, 101.2, 68.3, 57.2, 49.7, 47.4, 25.5, 25.3. IR 3389, 2991, 2944, 2831, 2127, 1716, 1603, 1490, 1377, 1317, 1204, 1144, 1065, 1018, 972, 839, 753. MS 249 (M^+), 172, 160, 159, 132, 130, 117, 104, 91, 77, 73 (100%), 43. HRMS calc. 249.1365; obs. 249.1365.

General procedure for cyclopentenone formation. A solution of bromoketal **31** (808 mg, 2.1 mmol), tributyltin hydride (850 mg, 2.9 mmol), and a catalytic amount of AIBN in dry benzene (20 mL) was purged by bubbling with Ar for 15 minutes, then refluxed under Ar atmosphere. Upon completion (7 h, TLC), 10% aq. KF (15 mL) was added to the cooled reaction mixture, which was then stirred overnight. Ether extraction delivered crude **32**, 4:1 mixture of *trans* : *cis* isomers (^1H 7.30-7.16 (c.m, 5H), 3.92 (q, 1H, J = 7.5 Hz), 3.25 (s, 3H), 3.21-3.12 (m, 2H), 3.14 (s, 3H), 3.13 (s, 3H), 2.43-2.24 (c.m, 3H), 1.92-1.78 (c.m, 2H). ^{13}C 140.9, 128.7, 128.2, 125.8, 108.2, 100.4, 74.4, 67.3, 49.0, 48.8, 45.7, 43.1, 39.4, 37.8, 25.8, 25.1. IR 3050, 2990, 2944, 2824, 1496, 1450, 1384, 1211, 1144, 1051, 859, 753, 700. MS 277 (M^+ – OMe), 219, 218, 187 (100%), 155, 116, 91, 73) as a colorless oil. A solution of this material in THF (50 mL) containing aq. 1N HCl (3 mL) was stirred at room temp. until TLC showed complete conversion to **33** (ca. 20 h). The mixture was diluted with CH_2Cl_2, sequentially washed with sat. aq. $NaHCO_3$ and NaCl, dried (Na_2SO_4) and concentrated. Chromatography of the residue provided 314 mg (63 %) of **33**, oil, R_f (20% EtOAc/hexanes) 0.35. ^1H 7.61 (dd, 1H, J = 5.6, 2.5 Hz), 7.40-7.15 (c. m, 5H), 6.20 (dd, 1H, J = 5.6, 2.0 Hz), 3.26 (c. m, 1H), 2.80 (app. d, 2H, J = 7.8 Hz), 2.52 (dd, 1H, B part of AB, J = 18.9, 6.4 Hz), 2.12 (dd, 1H, A part of AB, J = 18.9, 2.2 Hz). ^{13}C 209.8, 167.8, 138.7, 133.9, 128.6, 128.5, 126.4, 42.8, 40.6, 40.5. IR 3090, 3063, 3030, 2924, 2851, 1709, 1589, 1503, 1456, 1410, 1350, 1251, 1184, 700. MS 172 (M^+), 129, 128, 115, 92 (100%), 91 (100%), 65. HRMS calc. 172.0888; obs. 172.0889.

References and Footnotes

1. Fellow of the Alfred P. Sloan Foundation, 1994-1996.
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48. Commercial MCPBA was dissolved in ether and washed with several portions of 1/2 sat. aq. $NaHCO_3$ to remove MCBA. The ether solution was then washed with sat. aq. NaCl, dried (Na_2SO_4) and concentrated. The purified MCPBA so recovered was redissolved in CH_2Cl_2 and any insoluble matter was filtered off. Concentration afforded pure, dry MCPBA.

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