[2 + 2] Photocycloaddition/Fragmentation Strategies for the Synthesis of Natural and Unnatural Products†

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Contents

I. Introduction

The pioneering efforts of Pattenden[1] and Oppolzer[2] have established the utility of the intramolecular version of the de Mayo reaction,[3] the photoaddition/retroaldol fragmentation of β-diketones and alkenes, in organic synthesis (Scheme 1).

This general strategy of photoaddition/retroaldol fragmentation has subsequently been extended to a variety of other chromophores. This review will focus on the application of the intramolecular photocycloaddition/fragmentation of dioxinones and vinylogous amides to the stereoselective synthesis of a variety of complex ring systems.

The photocycloaddition/fragmentation outlined in Scheme 2 provides an efficient approach to the synthesis of bridged bicyclic ring systems, such as the bicyclo[5.3.1]undecane moiety that constitutes the AB rings of the naturally occurring antitumor agent taxol (**5**). We reasoned that fragmentation of a bicyclo[4.2.0]octane moiety would provide a general solution to the formation of the eight-membered taxane B ring (Scheme 2). The requisite bicyclooctane could be prepared by an intramolecular [2 + 2] photocycloaddition, a reaction that has been used to considerable advantage in synthesis and that has been the subject of excellent reviews by Crimmins and others.[4]

Due in large measure to its promising biological activity and unique mechanism of action, the synthesis of the structurally complex naturally occurring antitumor agent taxol (**5**) has attracted the attention of synthetic chemists around the world for over two decades. These prodigious efforts have recently culminated in the first two reported total syntheses of taxol by Holton and Nicolaou.[5] However, the development of novel strategies and tactics in organic synthesis, inspired by the unique structure of taxol yet applicable to diverse structural motifs, is perhaps an even more enduring legacy of these synthetic studies.[6] It is in this context that our efforts in this area are summarized herein. Starting with this intriguing structure, we have developed photochemical methodology which, while it has not led to the synthesis of taxol *per se*, has resulted in the application of [2 + 2] photocycloaddition/fragmentation reactions to the preparation of materials which cannot be otherwise prepared and to the solution of a broad range of challenging problems in organic synthesis.

† Dedicated to our friend and colleague Professor Ralph Hirschmann on the occasion of the inauguration of the Hirschmann–Makineni Chair of Bioorganic Chemistry at the University of Pennsylvania.

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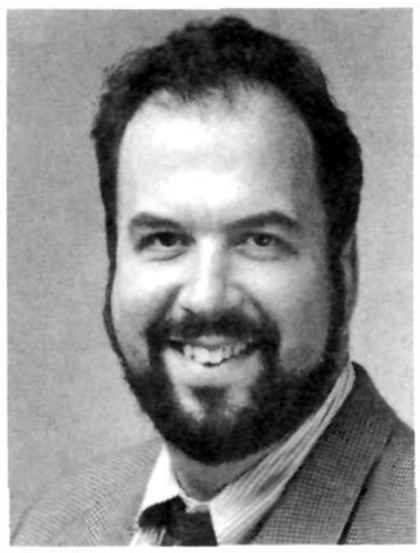
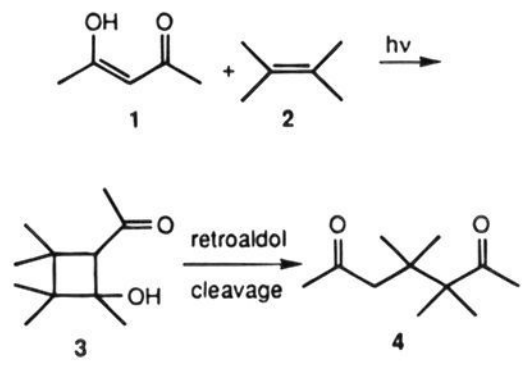


Jeffrey D. Winkler was born in 1956 in Chicago, IL. As an undergraduate at Harvard College, where he graduated *cum laude* in Chemistry in 1977, he participated actively in the chemical research programs of Professor James Wuest, Dr. Larry Blaszczak, and Professor E. J. Corey. At Columbia University, he worked with Professor Gilbert Stork on the stereochemistry of the intramolecular Michael addition and the application of this methodology to the synthesis of adrenosterone. Upon receiving his Ph.D. degree in 1981, he joined the laboratories of Professor Ronald C. D. Breslow as an American Cancer Society Postdoctoral Fellow, where he pursued projects involving the synthesis of transamination mimics and organic ferromagnets. In 1983, he joined the Chemistry Department at the University of Chicago as an Assistant Professor. He moved to the University of Pennsylvania in 1990, where he is currently Associate Professor of Chemistry and a Member of the University of Pennsylvania Cancer Center. In his independent career first at Chicago and now at Penn, he has established an active research laboratory engaged in both synthetic organic and bioorganic chemistry. A theme common to most of the synthetic program in Professor Winkler's laboratory, which forms the subject of this review, is the application of the [2 + 2] photocycloaddition of dioxenone and vinylogous amide chromophores to the stereoselective construction of structurally complex carbon skeleta. He is the co-author of over 40 publications in refereed journals and has delivered over 70 invited lectures at academic and industrial research laboratories. His honors and awards include the first American Cyanamid Young Faculty Award (1989–1992), the H. Martin Friedmann Lectureship at Rutgers University (1993), the National Institutes of Health Career Development Award (1988–1993), and a Merck Foundation Award for Faculty Development (1985). He was also a Fellow of the Alfred P. Sloan Foundation (1987–1989) and he currently serves as Chairman of the Philadelphia Organic Chemists' Club. Professor Winkler lives in suburban Philadelphia with his wife, Beverly D. Eskreis, M.D., a dermatologist, and their three children, Sarah, 11, Lauren, 9 and Jonathan, 5.

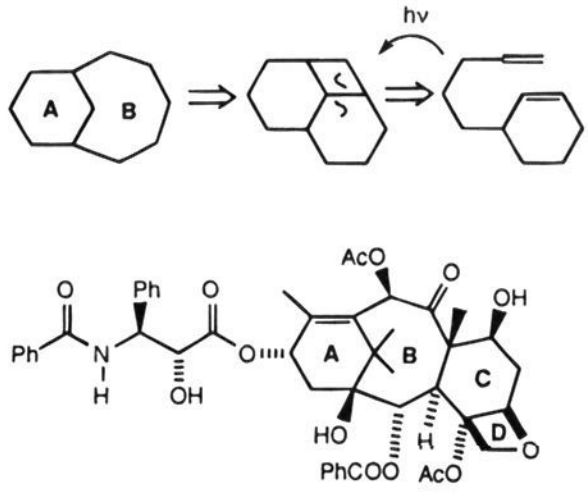
Corinne Mazur Bowen was born in 1969 in Cheektowaga, NY. She is currently a graduate student in Professor Winkler's group at the University of Pennsylvania. She received her B.S. degree from Saint Joseph's University in Philadelphia, PA, in 1991 and then her M.S. in organic chemistry at the University of Illinois at Urbana—Champaign under the direction of Professor John A. Katzellenbogen. Her research interests lie in the areas of natural product synthesis and the development of spectroscopic probes for biochemical systems.

Fina Liotta, born in Camporeale, Italy (1963), received her B.A. and Ph.D. degrees from Rutgers University, studying under the direction of Professor Stan S. Hall. During her graduate work she was a visiting student at the Royal Institute of Technology, Stockholm, working under the direction of Professor Torbjörn Norin. In 1993 she joined the laboratory of Professor Jeffrey D. Winkler where she is currently a postdoctoral associate. Her research interests include the total synthesis of natural products and synthetic methodology.

Scheme 1



Scheme 2



5, taxol

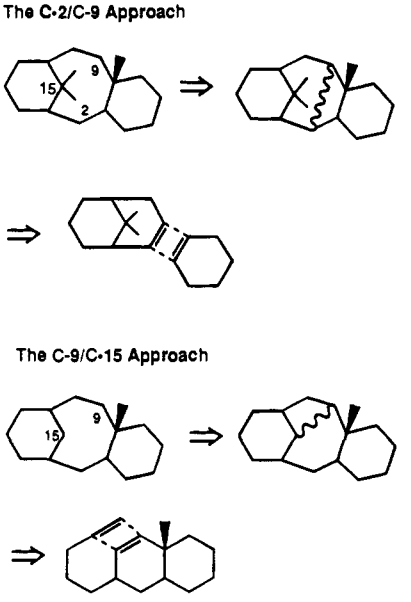
The total synthesis of taxol must involve the assembly of four dissimilar rings with both fused and bridged ring connectivities. While there is a great deal of methodology available for the synthesis of fused bicyclic ring systems sharing a single carbon–carbon bond (BC[7] and CD[8] rings), much less is available for the construction of bridged bicyclic ring systems, i.e., sharing two carbon–carbon bonds (AB rings[9]). And while the repertoire of reactions of the synthetic organic chemist is generally well-equipped to address issues of six-membered ring formation, the efficient synthesis of eight-membered rings remains a more daunting challenge in synthesis.[10] At the start of our synthetic studies in 1983, we therefore focused our efforts on the development of methodology for the construction of the bicyclo[5.3.1]undecene moiety that constitutes the AB ring system of taxol,

simultaneously addressing the issues of eight-membered ring synthesis and the construction of bridged, bicyclic ring systems.

A. de Mayo Approaches to the Synthesis of Taxol

The application of the photoaddition/fragmentation strategy to the synthesis of tricyclic taxane skeleta can involve the fragmentation of either the C-2/C-9 bond or the C-9/C-15 bond (taxane numbering, Scheme 3) and has been examined by several research groups.

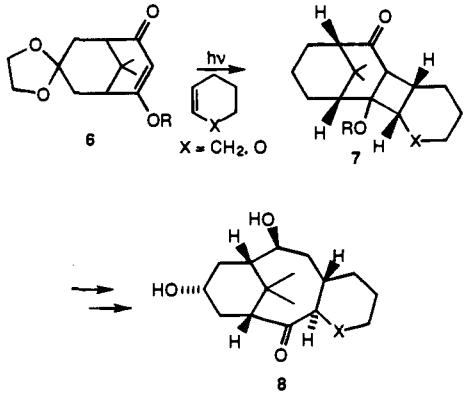
Scheme 3



1. The C-2/C-9 Approach

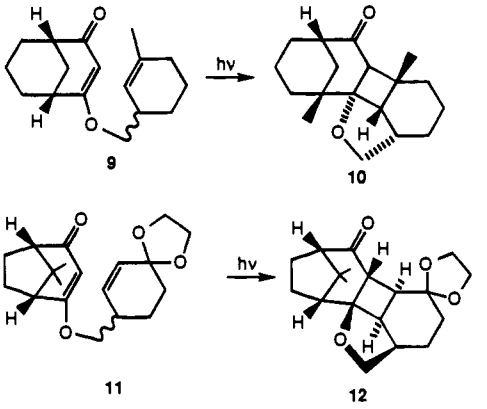
The C-2/C-9 approach has the advantage of being compatible with the direct incorporation of the C-15 geminal dimethyl group. However, it leads, in the retrosynthetic sense, to an intermolecular photocycloaddition of a bridged photosubstrate (Scheme 3) which may be accompanied by regio- and stereoselectivity problems. In fact, both intermolecular and intramolecular versions of this sequence have been examined. Blechert has reported the preparation of a tricyclic taxane **8** via photocycloaddition of **6** with cyclohexene or dihydropyran as shown in Scheme 4.[11] Fetizon has applied a similar approach to the synthesis of both AB[12] and BC[13] bicyclic ring systems. Swindell has taken advantage of the C-2/C-9 disconnection to access the BC rings of the taxane skeleton using a vinylogous imide photocycloaddition (see section VI.B).[14]

Scheme 4



The development of intramolecular versions of this reaction has been reported independently by Inouye[15] and Berkowitz,[16] using photosubstrates **9** and **11** to obtain **10** and **12**, respectively (Scheme 5).

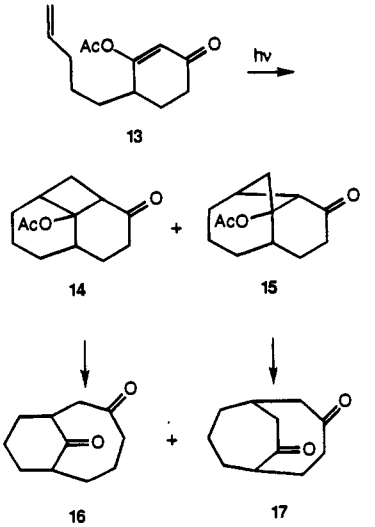
Scheme 5



2. The C-9/C-15 Approach

We reasoned that fragmentation of the C-9/C-15 bond (Scheme 3) would lead to the more useful retrosynthetic disconnection, since this analysis leads to a fused and not a bridged bicyclic precursor and a photocycloaddition reaction that would necessarily be intramolecular. The earlier studies of Pattenden, however, gave some cause for concern. Irradiation of enol acetate photosubstrate **13** was reported to lead to formation of both the "head-to-head" and "head-to-tail" products, **14** and **15** respectively, in a 2:1 molar ratio (Scheme 6). These photoadducts were then fragmented to bicyclic diones **16** and **17**. No regiochemical preference was observed in the photocycloaddition, i.e., both photoadducts were formed.[1]

Scheme 6



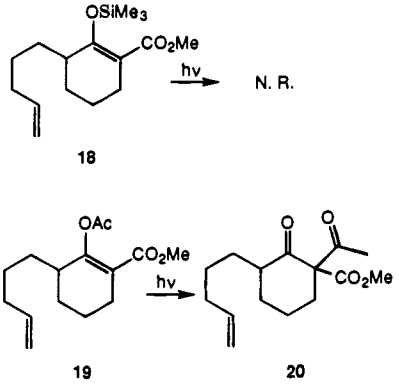
B. The Dioxinone Photocycloaddition Reaction

1. The de Mayo Reaction

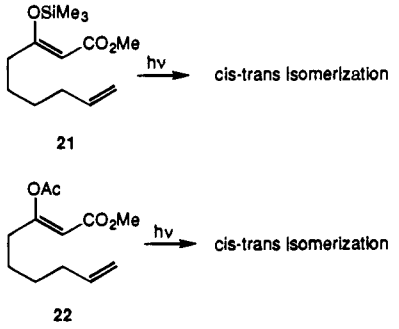
While the work of de Mayo and others amply demonstrated the utility of the photoaddition/retroaldol fragmentation of β-diketone enols, regiochemi-

cal complications surrounding the selective alkylation and enolization of the starting β-diketones have somewhat limited the generality of this methodology in synthesis. On the other hand, both the selective enolization and alkylation of β-keto ester is well known,[17] so the analogous reaction of β-keto esters would address both of these regiochemical ambiguities. However, the photochemical reactivity of β-keto esters is not the same as that of the corresponding β-diketones. Irradiation of a β-keto ester in the presence of an alkene leads not to cyclobutane formation from the enol of the keto ester, but instead to oxetane formation via the ketone carbonyl.[18] It therefore appeared to be necessary to covalently "lock" the keto esters as the enol tautomers. Toward this end, we examined the irradiation of enol silyl ethers, **18** and **21**, and enol acetates, **19** and **22**, of both cyclic and acyclic β-keto esters (Schemes 7 and 8). The only new products observed in these reactions resulted from photo-Fries rearrangement of the cyclic enol acetate (Scheme 7) and cis–trans isomerization of both acyclic substrates (Scheme 8). None of the desired cyclobutane photoadducts were observed.[19]

Scheme 7



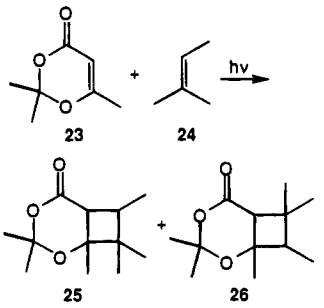
Scheme 8



2. Baldwin's Modification of the de Mayo Reaction

In 1980, Baldwin reported a solution to this problem using dioxinone heterocycles as covalently locked enol tautomers of β-keto esters (Scheme 9).[20] Intermolecular cycloaddition of dioxinones, such as **23**, occurs in good yield using stoichiometric quantities of a variety of alkenes. However, the regiochemical outcome of the cycloaddition with unsymmetrical alkenes proved to be difficult to predict on the basis of exisiting models for enone photocycloaddition.[4c,e] We reasoned that the intramolecular version of the dioxinone photocycloaddition reaction could provide greater regiochemical control[21] and that it might also

Scheme 9

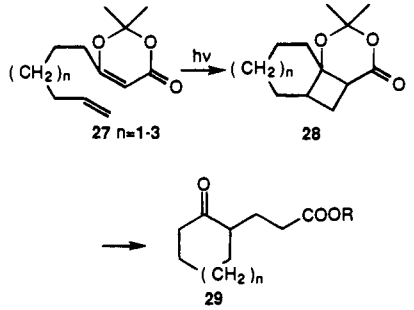


be useful for the construction of bridged ring systems that are not accessible using standard de Mayo methodology.[1]

3. Applications of the Dioxinone Photocycloaddition Reaction

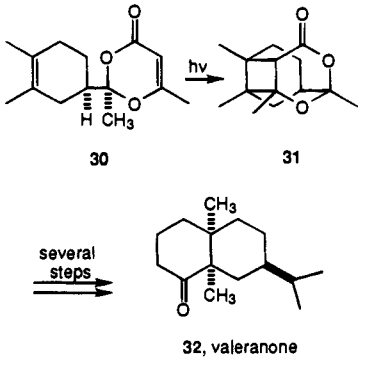
We were delighted to find that the intramolecular version of this reaction led to the formation of six-, seven-, and eight-membered ring keto esters, **29**, in excellent yield with exceedingly high (>50:1) levels of regiochemical control (Scheme 10).[22]

Scheme 10



Dioxinone photocycloaddition methodology has been investigated by several research groups.[23a,b] The total synthesis of (+)-elemol was accomplished by Baldwin and Nunn using dioxinone photocycloaddition as a key step.[23c] An intramolecular dioxinone photocycloaddition was used by Takeshita and coworkers for the stereoselective synthesis of (+)-valeranone (**32**, Scheme 11).[24]

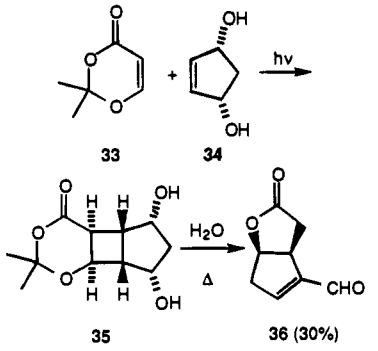
Scheme 11



Sato and co-workers developed an efficient synthesis of lactone **36**, a useful prostaglandin intermediate, via photocycloaddition of **33** and **34** (Scheme 12).[25]

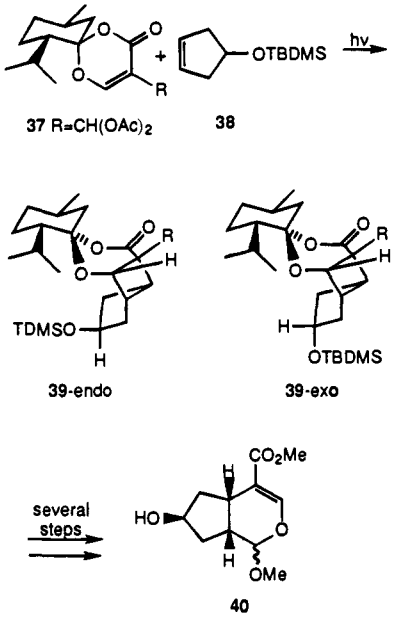
The dioxinone photocycloaddition reaction has also been applied to the control of absolute stereochemistry using homochiral dioxinones. For example, Sato

Scheme 12



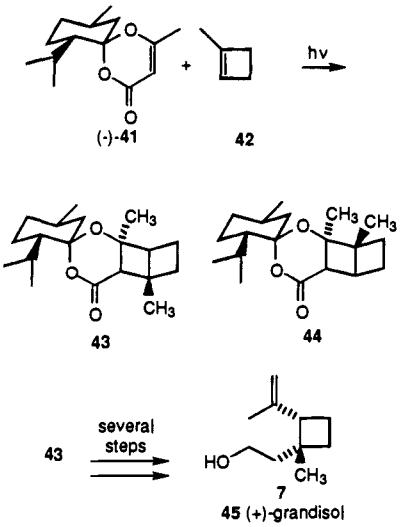
has also achieved the asymmetric synthesis of iridoid **40** starting from **37**, which is derived from menthone (Scheme 13).[26]

Scheme 13



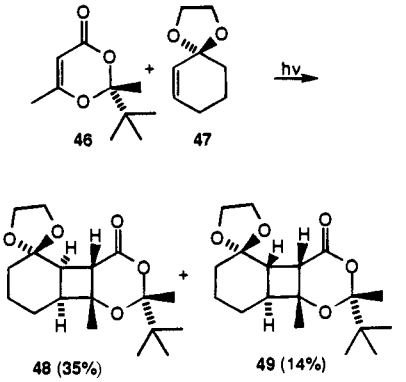
Demuth and co-workers have used asymmetric photocycloadditions of homochiral, spirocyclic dioxinones in the synthesis of both enantiomers of grandisol **45** (Scheme 14).[27] (−)-Grandisol may be obtained from the enantiomer of **41**.

Scheme 14



In an effort to demonstrate asymmetric induction in intermolecular dioxinone photocycloadditions, Lange and Organ have investigated the facial selectivity in photocycloadditions of homochiral 2,2-disubstituted dioxinones such as **46** (Scheme 15).[28]

Scheme 15

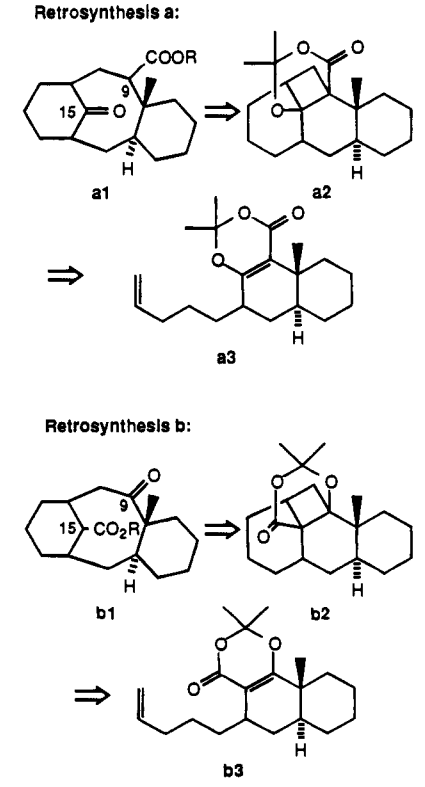


II. The Dioxinone Approach to the Synthesis of Taxol

A. Retrosynthetic Strategy

The isomeric δ-keto ester (**a1** and **b1**) retrons, shown in Scheme 16, could be easily obtained from an intramolecular dioxinone photocycloaddition/fragmentation sequence. The application of the intramolecular dioxinone photocycloaddition/fragmentation sequence to the synthesis of these isomeric δ-keto ester skeleta of taxol leads to two complementary disconnections, retrosyntheses **a** and **b**, shown in Scheme 16.

Scheme 16



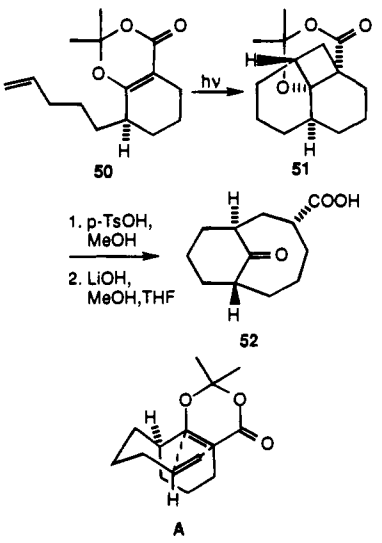
These retrosyntheses necessarily differ in the orientation of the dioxinone chromophore in photo-

substrates **a3** and **b3**. In the case of **a3**, photocycloaddition/fragmentation could result in taxane model system **a1**, in which the ketone functionality is at C-15 and the ester functionality is an appendage at C-9. On the other hand, the dioxinone chromophore is transposed in photosubstrate **b3**. Photocycloaddition/fragmentation, in this case, could result in taxane model system **b1**. In **b1**, the ketone functionality is at C-9 and the ester appendage is at C-15.

B. Bicyclic Taxane Model System

The first model system that was examined, lacking the C ring shown in retrosynthesis **a** (Scheme 16), is shown in Scheme 17. It was found that irradiation of dioxinone **50** led to the exclusive formation of a unique photoadduct, **51**, which on fragmentation resulted in the formation of *trans*-bicyclo[5.3.1]-undecan-11-on-3-carboxylic acid (**52**).[29] The highly unusual trans intrabridgehead stereochemical relationship in **52** was confirmed by X-ray crystallographic analysis. At the time at which we did this work, this was the smallest bridged bicycloalkanone with "inside-outside" or trans intrabridgehead stereochemistry.[30]

Scheme 17

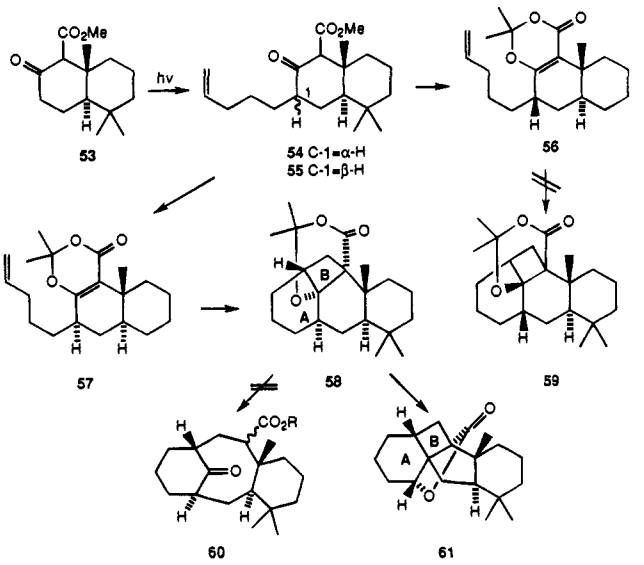


We proposed that the stereoselectivity could be a consequence of the chairlike folding of the nascent six-membered ring, shown in conformation **A**, which leads to photocycloaddition. While the trans-bridged bicyclo[5.3.1]undecan-11-on-3-carboxylic acid, **52**, is ca. 10 kcal/mol more strained than the corresponding cis-bridged isomer, no trans–cis isomerization was observed under either acidic or basic reaction conditions, a consequence of the rigidity of the trans-bridged bicyclic system and nearly parallel orientation of the bridgehead hydrogens (dihedral angles of 27° and 150°) with respect to the carbonyl group.

C. Tricyclic Taxane Model System

The extension of these results to the synthesis of the tricyclic ring system of the taxanes led to some unanticipated problems. First, the introduction of the 4-pentenyl substituent did not proceed with the establishment of the correct C-1/C-3 relative stereochemistry as anticipated, via axial alkylation of either the dioxinone or the corresponding dianion of β-keto ester **53**, but instead produced a 1:1 mixture of **54** and **55**, epimeric at C-1 (Scheme 18).[31] Irradiation of the separated epimeric dioxinones **56** and **57** gave very different results. The epimer **57** with the incorrect C-1/C-3 relative stereochemistry for taxol gave a single photoadduct **58** in excellent yield with the same trans A/B ring fusion that had been observed in the model study (Scheme 17). Unfortunately, the epimer **56** with the correct C-1/C-3 relative stereochemical relationship was destroyed under the reaction conditions.

Scheme 18



A final complication was observed on exposure of photoadduct **58** to the standard acidic conditions for dioxinone fragmentation. Instead of the desired taxane tricyclic compound **60**, the rearranged lactone **61** was obtained in high yield. Isomerization of the bicyclo[4.2.0]octyl moiety from a trans AB ring fusion in photoadduct **58** to a cis AB ring fusion in lactone **61** provides the driving force for this unusual rearrangement.

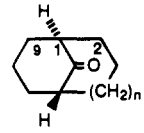
Intrigued by the highly stereoselective formation of trans photoadduct, **58** (Scheme 18) and the ensuing fragmentation reaction to give bicycloalkanones with trans intrabridgehead stereochemistry, we elected to explore the scope of this methodology for the synthesis of these highly unusual trans-bridged bicyclic ring systems and to study their structure and reactivity. For example, we sought to determine the [*n*.3.1] ring size for which trans–cis interconversion and ring flipping (which should make the bridgehead carbons equivalent and therefore be readily observed by NMR) could be detected.

III. Synthesis and Reactivity of Several [n.3.1] Bridged Bicyclic Compounds

As one might expect, the calculated strain energy of these trans-bridged ring systems increases signficantly on decreasing *n* in the [*n*.3.1] moiety. While molecular mechanics calculations reveal that **62** is ca. 10 kcal/mol more strained than the corresponding cis-bridged [5.3.1] ketone, the strain energy difference jumps to 20 kcal/mol in the case of the bicyclo[4.3.1]-

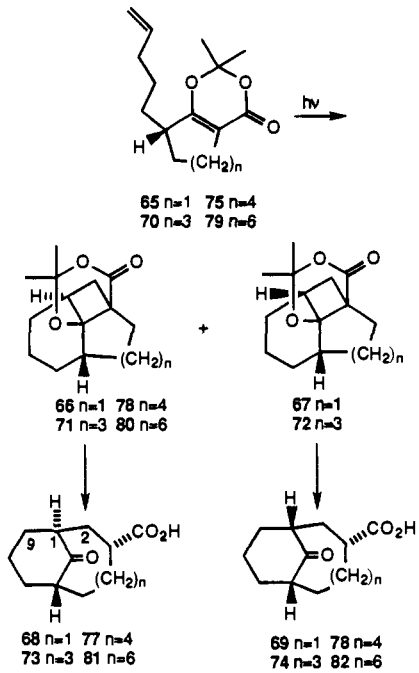
decan-10-one (**63**, Scheme 19) and 40 kcal/mol for the bicyclo[3.3.1]nonan-9-one (**64**).[29b] A series of five-, seven-, eight-, and 10-membered ring dioxinone photosubstrates, shown in Scheme 20, was prepared to determine what [*n*.3.1] ring size is required for trans−cis interconversion to occur.[29b] In the process of answering this question, we observed that these bridged bicyclic systems underwent other interesting chemistry as well.

Scheme 19



62 n=3
63 n=2
64 n=1

Scheme 20



A. Synthesis

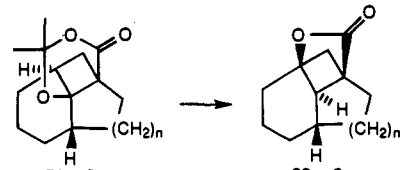
Irradiation of **65** resulted in a 1:5 mixture of trans/cis-bridged products, **66** and **67** respectively (Scheme 20). The selective formation of the less strained cis isomer **67** could be a reflection of a later transition state for this reaction, in which the final trans product, **68**, is ca. 20 kcal/mol more strained than the corresponding cis isomer **69**. The most prominent structural manifestation of the strain energy of the *trans*-bicyclo[4.3.1]decan-10-on-3-carboxylic acid (**68**) is the deformation of the C-9/C-1/C-2 bond angle to 130°, the most obtuse sp^3 C−C−C bond angle reported to date.[32]

Photocycloaddition of the seven-membered ring substrate **70** led to the formation of a 4.5:1 mixture of trans/cis-bridged products, **71** and **72**, respectively. Neither ring flipping nor isomerization of the trans to cis-bridged product was observed in the fragmented *trans*-bicyclo[6.3.1]dodecane keto acids **73** and **74**. However, trans → cis isomerization was observed with the *trans*-bicyclo[7.3.1]tridecanone (**77**) and *trans*-bicyclo[9.3.1]pentadecanone (**81**) ring systems derived from the eight- and 10-membered ring photosubstrates, **75** and **79**. Irradiation of **75** and **79** resulted in the stereoselective formation of unique trans-photoadducts, **76** and **80**, respectively, which on basic fragmentation led only to the cis-bridged keto acids, **78** and **82**.

The exclusive trans stereochemistry of the photoadducts, **76** and **80**, was verified by reductive (DIBAL-H) fragmentation of each photoadduct and oxidation to the corresponding keto acids, **77** and **81**. These trans-bridged keto acids, **77** and **81**, undergo isomerization to the cis-bridged keto acids, **78** and **82** respectively, under basic reaction conditions. These results establish that *trans*-bicyclo[7.3.1]tridecan-13-one (**77**) is the smallest [*n*.3.1] "inside−outside" bicyclic ring system in which trans → cis isomerization via bridgehead enolization is possible.

Attempted fragmentation under acidic conditions gave even more unusual results. Treatment of **71** with methanolic acid led to the expected keto ester, the methyl ester of **68**, as the major product, accompanied by the formation of the rearranged product **83**, as shown in Scheme 21. Exposure of either **76** or **80** to acidic methanol resulted in exclusive conversion to the tetracyclic γ-lactone products, **84** and **85**, respectively, the formation of which could be rationalized by a 1,2-hydride shift of the intermediate tertiary carbonium ion.

Scheme 21



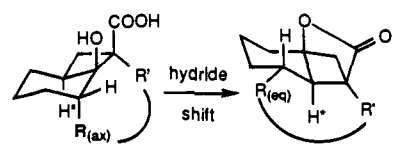
71 n=3
76 n=4
80 n=6

83 n=3
84 n=4
85 n=6

B. Fragmentation Pathways for Dioxinone Photoadducts

Three different fragmentation pathways have thus been observed with the dioxinone photoadducts: first, heterolysis to give keto ester products (Scheme 20); second, 1,2-alkyl shift that led to a ring contracted lactone in the taxane model system (Scheme 18); and third, hydride transfer leading to the formation of γ-lactone products (Scheme 21). The differences in product formation can be attributed to the inherent difference in the stabilities of **B**, which represents a hydrolyzed dioxinone photoadduct before C−C bond fragmentation, and its rearrangement product **C** (Scheme 22). These stabilities appear to be a function of the R−R′ tether length. As a consequence of the trans fusion of the bicyclo[4.2.0]octane moiety in **B**, substituent R is pseudoaxial. After the rear-

Scheme 22



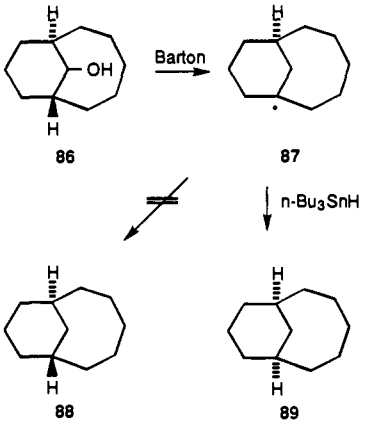
B C

rangement, R assumes the more favorable pseudoequatorial position in **C**. When the R–R′ tether is large enough, the hydride shift occurs to alleviate 1,3-diaxial interactions between H* and $R_{(ax)}$ in **B**. The rearrangement becomes a competing pathway, in the case of **71**, and the exclusive pathway in the case of **76** and **80**.

C. Transannular Radical Reactions

The observation of exceptionally facile transannular hydrogen atom abstraction reactions is a second chemical manifestation of the unique structure of the inside–outside compounds. For example, attempted formation of *trans*-bicyclo[5.3.1]undecane (**88**) by Barton deoxygenation[33] of the xanthate derived from alcohol **86** gave exclusive formation of the cis-bridged hydrocarbon product **89** via radical **87** (Scheme 23)![34] This result can be attributed to a series of transannular hydrogen atom abstractions that produce the tertiary bridgehead radical, which on reduction gives the more stable cis-bridged product, **89**.

Scheme 23

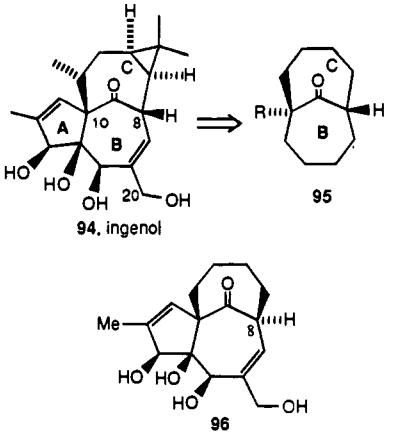


In addition, while the Barton decarboxylation of the trans-bridged [4.3.1] and [5.3.1] keto acids **52** ($n = 1$ and 2, respectively) proceeds via radical **90** (Scheme 24), to give trans-bridged ketone products **93**, the same reaction of the trans-bridged bicyclo[6.3.1], [7.3.1], and [9.3.1]alkanones ($n = 3$, 4, and 6, respectively), produced cis-bridged ketones **92**. The secondary radical **90** cannot abstract the "outside" hydrogen" (H_{out}) via a 1,4-hydrogen abstraction unless a ring flip occurs, which is only possible where $n > 2$ (i.e., from **D** to **E**). The ring flip converts H_{out} from an equatorial to an axial position, H_{in}', which is in close proximity to the secondary radical center. Transannular abstraction of the bridgehead hydrogen (H_{in}') is then possible and the resulting tertiary carbon radical, **91**, then leads to the more stable cis-bridged product.

IV. Synthesis of Ingenanes via the Intramolecular Dioxinone Photocycloaddition

This methodology was next applied to the first stereoselective construction of the ingenane diterpenes,[35,36] the only natural product class containing a trans intrabridgehead stereochemical relationship. Excision of the BC rings of ingenol, **94**, (Scheme 25) to give trans-bridged bicyclic undecanone **95** reveals the inside–outside nature of the BC ring system of ingenol, in which the R group represents the five-membered A ring. This stereochemical feature is critical to the potent biological activity of ingenol.[37] In fact, Paquette has reported the synthesis of a C-8-epimeric cis-bridged compound **96** which is entirely devoid of biological activity, emphasizing the importance of the inside–outside stereochemistry in the ingenanes.[38]

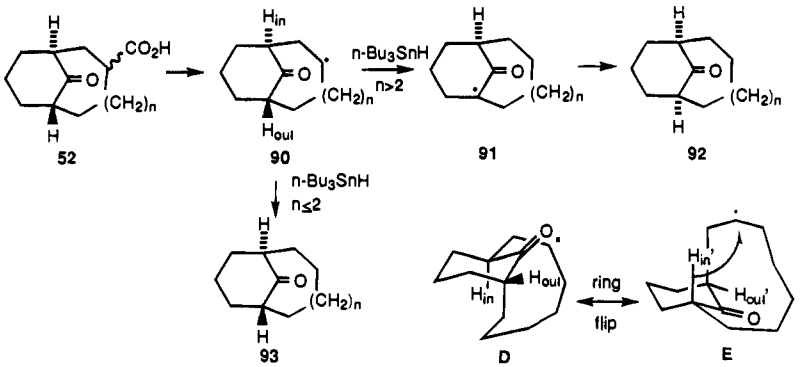
Scheme 25



A. Retrosynthetic Strategy

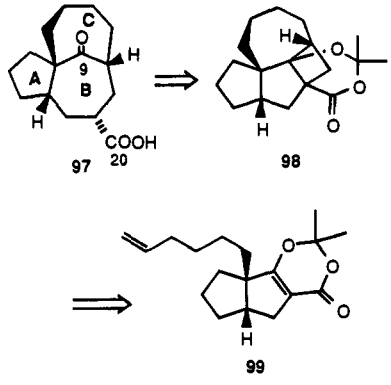
The retrosynthetic analysis for the preparation of the ingenane ring system using the intramolecular

Scheme 24



dioxinone photocycloaddition reaction is outlined in Scheme 26. The ingenane ring system in the form of keto acid **97**, containing both the C-9 carbonyl and the C-20 alcohol of ingenol (in the acid oxidation state) could be formed by photocycloaddition of dioxinone **99** and fragmentation of the resulting adduct **98**. This ingenane model system **97** could be formed by photocycloaddition of dioxinone **99** and fragmentation of the resulting adduct **98**.

Scheme 26

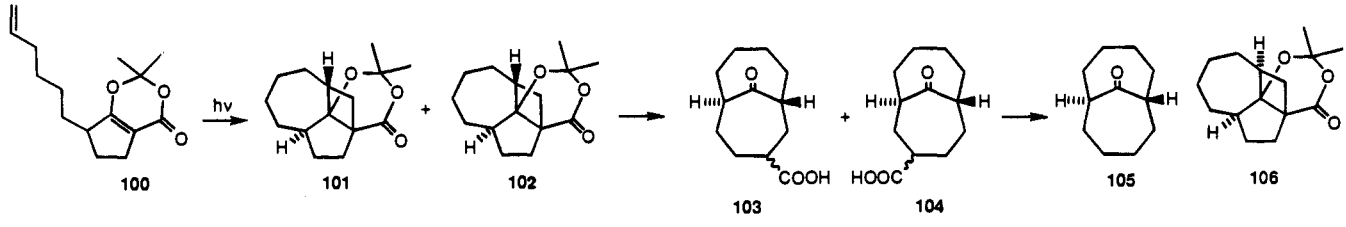


B. Bicyclic Ingenane Model System

The photocycloaddition of model system **100** (Scheme 27) was first examined in an effort to establish the feasibility of the dioxinone methodology for the synthesis of the *trans*-bicyclo[4.4.1]undecane moiety that constitutes the BC ring system of the ingenanes.[35a] Unfortunately, irradiation of **100** led to the formation of a <20% yield of photoadducts, which were isolated as a 1:1 mixture of diastereomers. Not only was the yield much lower than that which had previously been observed for the formation of cycloheptanone propionates via this methodology,[22] but the very high levels of stereoselectivity previously observed had completely vanished.

It was subsequently established that the photocycloaddition is in fact highly stereoselective. Fragmentation of the separated photoadducts **101** and **102** gave diastereomeric keto acid products, **103** and **104**, respectively. However, Barton decarboxylation of these keto acid products gave the same trans-bridged ketone **105**, indicating that none of the cis-bridged photoadduct, **106**, was formed in the irradiation of dioxinone **100**. These results can be explained by the formation of diastereomeric trans-bridged photoadducts **101** and **102** that arise from approach of the alkene of **100** to either face of the dioxinone heterocycle.

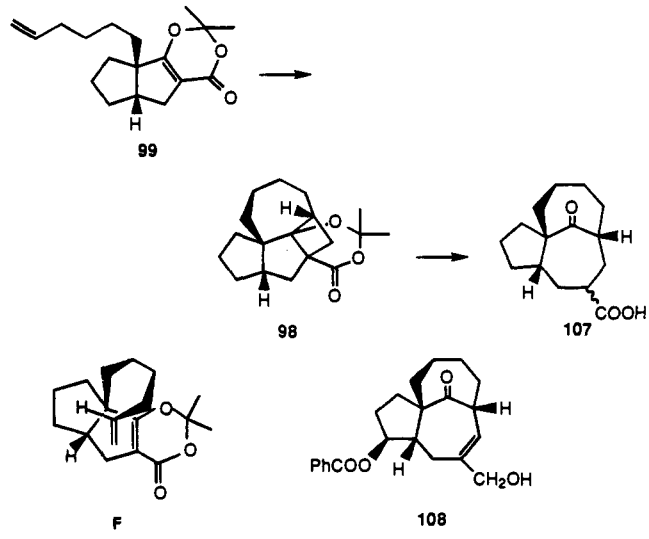
Scheme 27



C. Tricyclic Ingenane Model System

The successful extension of these preliminary results to the preparation of the trans-bridged ingenane tricyclic ring system is outlined in Scheme 28.[35a] Irradiation of the tricyclic dioxinone photosubstrate, **99**, afforded a single photoadduct, **98**, in excellent yield, which on fragmentation under basic reaction conditions gave the ingenane tricyclic ring system, **107** (Scheme 28). The stereoselectivity of the photocycloaddition can be rationalized by approach of the alkene to the dioxinone as shown in **F**, which would necessarily lead to the establishment of the inside–outside stereochemistry. This work has recently been extended to the preparation of ingenane **108**, the first analog of ingenol to have high-affinity for protein kinase C.[39]

Scheme 28

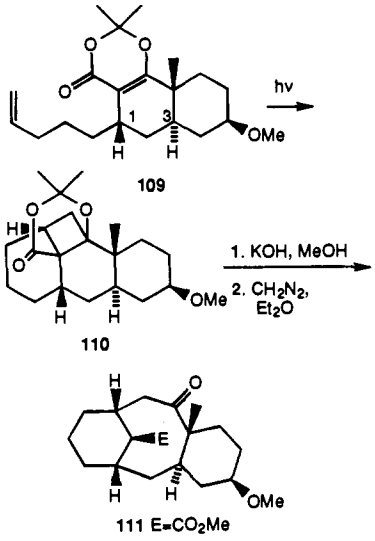


V. An Improved Approach to Taxane Synthesis

A. Transposition of the Dioxinone Chromophore

Returning to the application of the dioxinone photocycloaddition/fragmentation methodology to the synthesis of taxanes, we reasoned that transposition of the dioxinone chromophore should both facilitate the stereoselective introduction of the pentenyl side chain in photosubstrate **109** (Scheme 29), as well as permit the evaluation of the photochemical reactivity of the transposed chromophore.[40] This approach was outlined earlier as retrosynthesis **b** in Scheme 16 (see section II.A). In the event, photocycloaddition of dioxinone **109**, with the correct C-1/C-3 relative stereochemical relationship for taxane construction, led to the formation of a single diastereomer, **110**.

Scheme 29

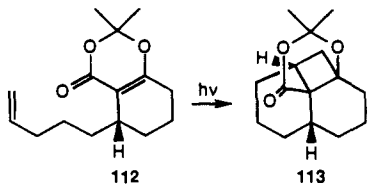


X-ray crystallographic analysis of photoadduct **110** revealed that it did not contain the trans intrabridgehead stereochemical relationship. Fragmentation under basic conditions gave the cis-bridged keto ester **111**.

This striking difference between the photoaddition stereoselectivity observed for **109** (Scheme 29) and that observed previously for **57** (Scheme 18) could be a consequence of two structural differences: (1) the orientation of the dioxinone chromophore, and/or (2) the C-1/C-3 relative stereochemistry. The C-1/C-3 relative stereochemistry in the trans-fused bicyclic system of photosubstrate **57** (Scheme 18) requires that the C-1 substituent be equatorial. In the case of **109**, however, the C-1 side chain is necessarily axial and the photocycloaddition produces only the cis-bridged photoadduct **110**.

In order to determine the factors governing the stereoselectivity of the photocycloaddition, irradiation of the bicyclic photosubstrate **112** (Scheme 30) was examined,[41] which resulted in the exclusive formation of cis-photoadduct **113**. As the stereochemical outcome of the photocycloaddition of **112** is consistent with **109** and not with **57**, it is the orientation of the dioxinone chromophore and not the stereochemistry of the pentenyl side chain on the tricyclic photosubstrates that determines the stereochemical outcome of the photocycloadditions.

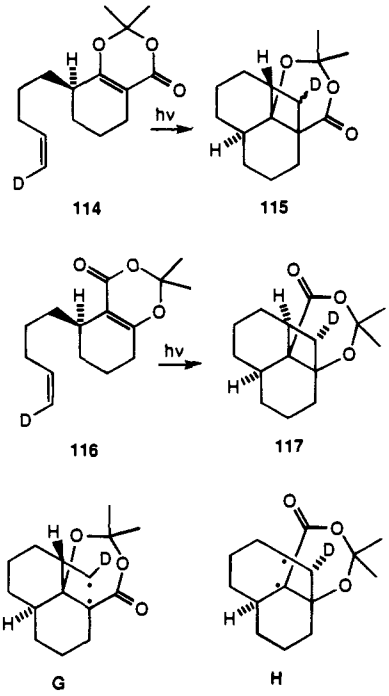
Scheme 30



B. Photocycloaddition of Isotopically Labeled Dioxinones

Deuterium labeling studies revealed that while irradiation of **114** led to the formation of trans-photoadduct **115** as a 1:1 mixture of epimers at the deuterium-bearing carbon, irradiation of the isomeric

Scheme 31

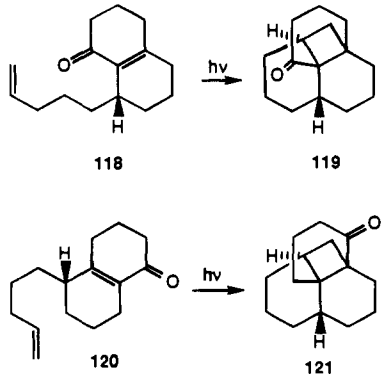


dioxinone **116** gave a single, deuterated cis-photoadduct, **117**[42] (Scheme 31). The observed stereoselectivity in the photocycloaddition of labeled dioxinone **114** is consistent with the initial formation of the six-membered diyl **G** which collapses to give the observed epimeric deuterated photoadducts, **115**. However, in the case of the isomeric dioxinone **116**, the cis stereoselectivity as well as the formation of a unique deuterated product, **117**, is consistent with initial eight-membered ring diyl formation as shown in **H**. Conformational relaxation of **H** prior to intersystem crossing of the triplet diradical then leads to the formation of the more stable cis-photoadduct **117** on cyclobutane formation.

C. Chromophore Transposition in Model Enones

To determine the role of the dioxinone chromophore on the complete reversal of stereoselectivity observed in the photocycloaddition of labeled dioxinones **114** and **116**, the photocycloaddition of the analogous enone photosubstrates **118** and **120** (Scheme 32), i.e., lacking the β-oxygen atom of the dioxinone chromophore, was examined.[42] In the event, irradiation

Scheme 32



of the enone photosubstrates provided exclusively the trans-fused photoadducts, **119** and **121**, respectively. This result indicates that the stereochemical outcome of the better-studied enone systems[43] is different from that of the dioxinone photocycloaddition.

The stereochemical outcome of the dioxinone photocycloaddition reactions is consistent only with initial bond formation from the β-carbon of the dioxinone to give a six-membered ring diyl intermediate in the case of **114** and an eight-membered ring diyl in the case of **116** (Scheme 31). These intermediates then result in the formation of trans- and cis-photoadducts, respectively. In contrast, the first bond in the enone photocycloadditions can be formed from either the α- or β-bond of the chromophore to give a six-membered ring triplet biradical which then collapses to trans-fused photoadducts, **119** and **121**, respectively (Scheme 32). The dioxinone photocycloaddition reaction can therefore be understood as a more highly regiospecific process than the reaction of the better-studied enone chromophores.

VI. Photocycloaddition/Fragmentation Reactions of Vinylogous Amides for the Synthesis of Natural Products

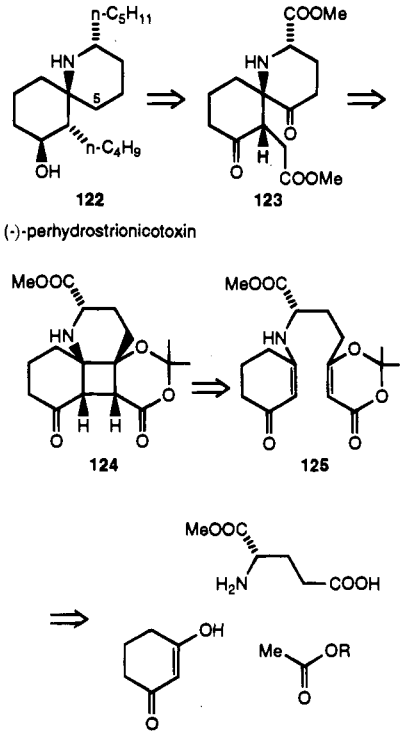
A. Synthesis of (−)-Perhydrohistrionicotoxin via the Photocycloaddition of a Vinylogous Amide with a Dioxinone

In an effort to extend the scope of this photoaddition/fragmentation strategy in synthesis, we chose to examine the application of this methodology to the construction of (−)-perhydrohistrionicotoxin (**122**).[44] While target **122** lacks the δ-keto ester retron that is produced in the dioxinone photoaddition/fragmentation reaction, it was reasoned that suitable functional group interconversion would readily permit the transformation of δ-keto ester **123** into **122**. The primary challenges were envisioned to be (1) the communication of stereochemical information from the piperidine ring through the spiro carbon to the stereogenic centers in the cyclohexane ring; and (2) the control of absolute stereochemistry in the construction of the histrionicotoxin alkaloids. Both of these issues have been successfully addressed in our synthesis of **122**, based on the retrosynthetic analysis shown in Scheme 33.[45]

Incorporation of the seemingly extraneous carbonyl group at C-5 as shown in **123** (histrionicotoxin numbering) permits the straightforward application of the dioxinone photochemical sequence using a photosubstrate, **125**, that contains a single stereogenic center derived from methyl L-glutamate.

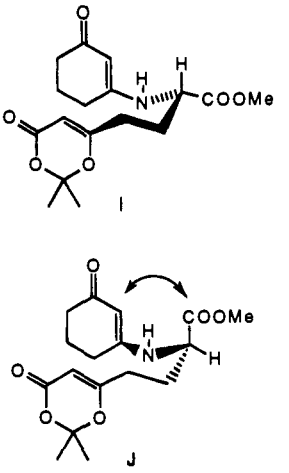
Irradiation of **125** leads to the quantitative formation of photoadduct **124** as a single stereoisomer, indicating that the amino acid stereocenter had effected complete stereochemical control in the establishment of each of the new stereocenters on the cyclobutane ring. While two of these centers of asymmetry are lost in the fragmentation of the photoadduct, the key relationship of the amino acid center to the spiro carbon is established in the photocycloaddition in an exceedingly efficient manner.

Scheme 33



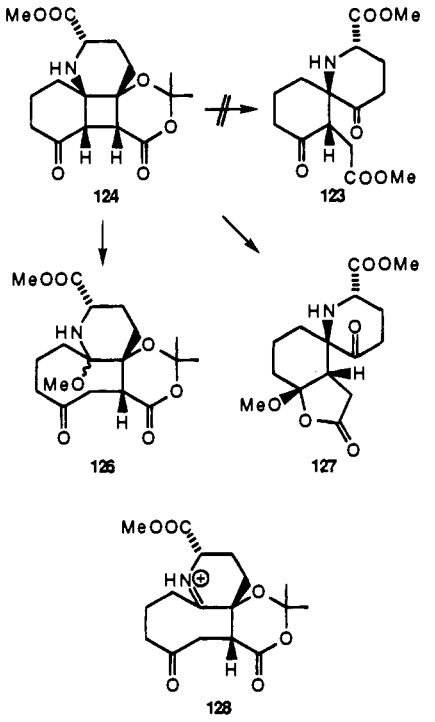
The asymmetric induction observed in the photocycloaddition can be attributed to the conformations shown in Scheme 34. Approach of the dioxinone from the β-face of the vinylogous amide results in a pseudoequatorial disposition of the carboxyl group on the nascent six-membered ring (**I**), while approach of the dioxinone from the α-face of the vinylogous amide forces the carboxyl group into a pseudoaxial orientation (**J**). Bond formation via **I** should therefore be favored and is consistent with the observed stereochemical outcome of the photocycloaddition.

Scheme 34



The efficiency of the photocycloaddition of **125** contrasts with the reluctance of the dioxanone photoadduct **124** to form **123** under the standard fragmentation reaction conditions (Scheme 35). Exposure of **124** to methanolic hydrochloric acid leads not to the expected spiroundecanone **123**, but instead predominantly to a diastereomeric mixture of aminals **126** along with a small amount of the internal ketal **127** of the desired azaspiroundecane product

Scheme 35



123. The presumed keto iminium intermediate, **128**, which leads to the formation of the aminal products, must result from retro-Mannich cleavage at the expense of dioxinone fragmentation. While this retro-Mannich fragmentation was successfully circumvented in our total synthesis of **122**, the formation and subsequent transformation of keto imines via photoaddition and retro-Mannich fragmentation of vinylogous amide chromophores has led to a powerful method for the synthesis of nitrogen-containing ring systems.

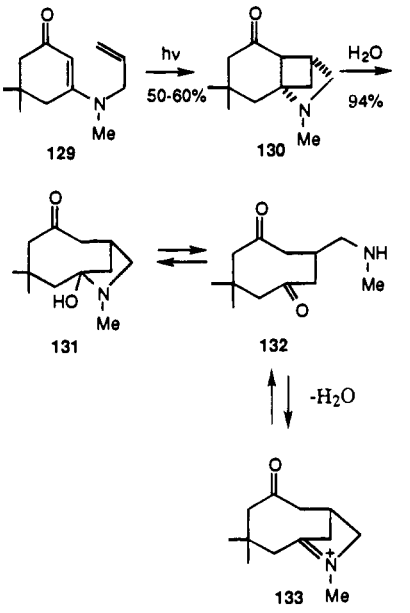
B. Initial Studies of the Photocycloaddition Reactions of Vinylogous Amides and Imides

The photocycloaddition/retro-Mannich fragmentation of a vinylogous amide was first observed by Tamura,[46] who reported that photolysis of **129** led to the exclusive formation of the crossed photoadduct **130** in 50 to 60% yield.[47] Retro-Mannich fragmentation of **130** occurred readily in refluxing water to give a 94% yield of an equilibrium mixture of tautomers keto aminal **131** and diketo amine **132**, as well as keto imminium **133** (Scheme 36).

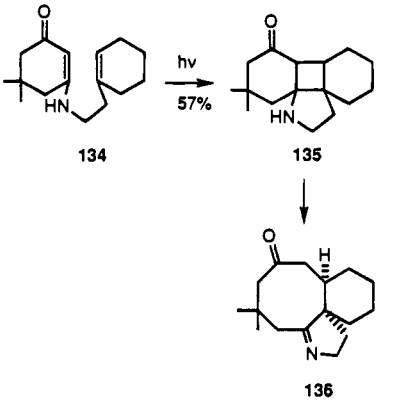
Similarly, Schell and Cook have investigated the cycloaddition/retro-Mannich fragmentation of secondary vinylogous amides.[48] Irradiation of **134** gave the retro-Mannich fragmentation product **136**, presumably through the intermediacy of cyclobutane **135** (Scheme 37).

An elegant example of the utility of the photocycloaddition of vinylogous imides in synthesis can be found in taxane synthetic studies by Swindell.[14] Irradiation of **137** produced **138**, which was converted to unsaturated keto imine **139** via Rubottom oxidation, ketone reduction, and Grob fragmentation as shown in Scheme 38. Hydrolysis of **139** gave the taxane BC system **140**.

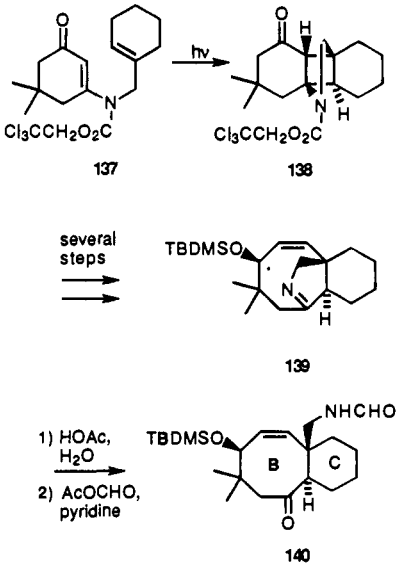
Scheme 36



Scheme 37

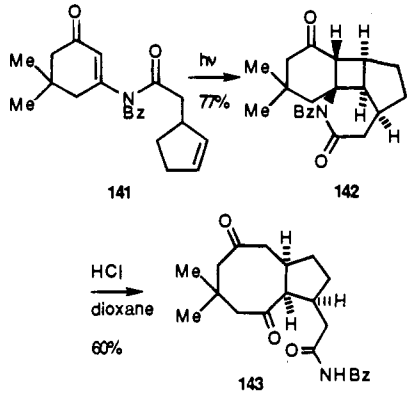


Scheme 38



A more recent example of the intramolecular photoaddition of vinylogous imides can be found in the work of Amougay and co-workers. The photocycloaddition/fragmentation of the highly substituted *N*-alkenoyl β-enaminone **141** afforded **142** as a single diastereomer (Scheme 39).[49] Fragmentation of pho-

Scheme 39

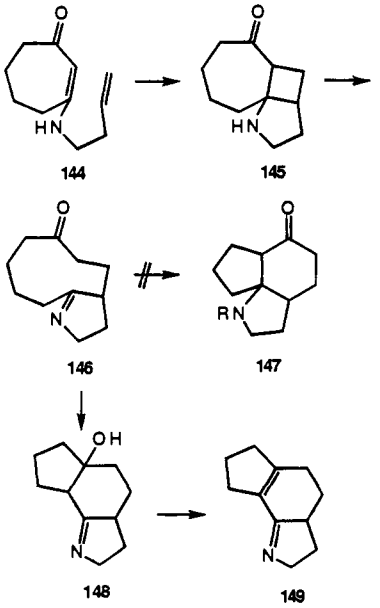


toadduct **142** occurs on reaction with hydrochloric acid in aqueous dioxane to give the fused bicyclic ring system **143**.

C. Photocycloaddition/Fragmentation Reactions of Secondary Vinylogous Amides: Syntheses of Mesembrine and Vindorosine

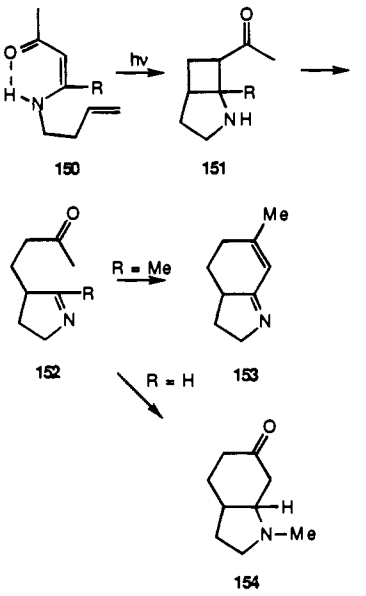
We envisioned that the coupling of the photocycloaddition and retro-Mannich fragmentation of vinylogous amides with a final Mannich ring closure could yield a general method for the synthesis of nitrogen-containing ring systems. Unlike keto iminium **128** (Scheme 35), which could undergo transannular Mannich closure only to generate a four-membered ring, keto imine **146** (Scheme 40), the product of the photoaddition/fragmentation of vinylogous amide **144**, could undergo transannular Mannich closure to generate a tricyclic ring system **147**, which contains a new five-membered ring. In the event, however, photocycloaddition of **144** produced not the expected cyclobutane **145**, nor the retro-Mannich fragmentation product keto imine **146**, nor the desired tricyclic keto amine **147**, but instead the unsaturated imine **149**. This product is formed via tautomerization of the intermediate keto imine to the enamine, followed by transannular closure to give **148**, which on dehydration gives **149**.[50]

Scheme 40



Reasoning that the formation of the unsaturated imine could be a consequence of the conformation of the nine-membered ring keto imine intermediate, **146**, the photocycloaddition of the acyclic vinylogous amide **150** (R = Me) was examined (Scheme 41). Irradiation of **150** (R = Me) resulted in the formation of the analogous unsaturated imine product **153** as the sole product of the reaction.[51]

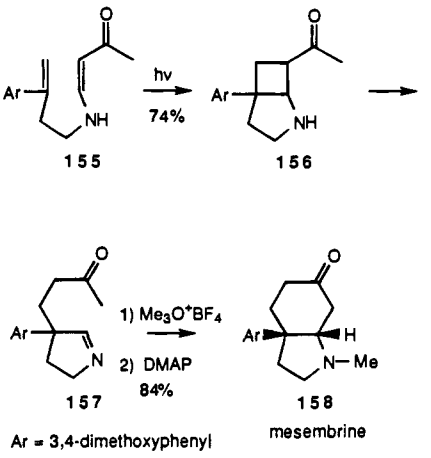
Scheme 41



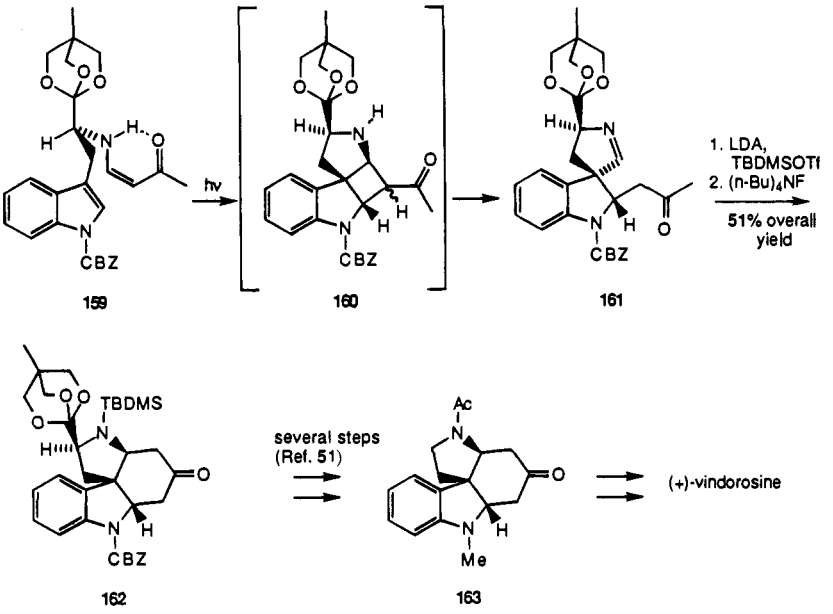
To preclude the generation of the enamine intermediate and thereby circumvent the formation of unsaturated imine products, the photocycloaddition of **150** (R = H), lacking the methyl group, was examined. Irradiation of the vinylogous amide, **150** (R = H), derived from formyl acetone, gave the keto imine intermediate, **152** (R = H). Activation of imine **152** (R = H) by alkylation with trimethyloxonium tetrafluoroborate gave the corresponding keto iminium, which, on treatment with (dimethylamino)-pyridine (DMAP), afforded the desired perhydroindole **154**.

This vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure sequence has been applied to the synthesis of mesembrine (**158**,[51] Scheme 42) and to a formal synthesis of the

Scheme 42



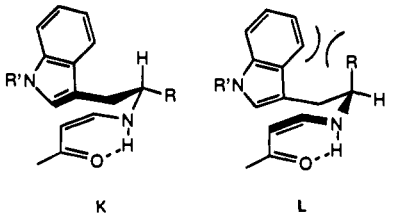
Scheme 43



aspidosperma alkaloid, (+)-vindorosine (**163**),[52] as outlined in Scheme 43.

The observed stereoselectivity in the photocycloaddition of **159** can be understood by examination of the conformations of vinylogous amide **159** shown in Scheme 44. While approach of the vinylogous amide from the β-face of the indole results in a pseudoaxial orientation of the R (orthoester) group, as indicated in **L**, approach of the vinylogous amide from the α-face of the indole leads to a pseudoequatorial orientation of the R group, as shown in **K**, and is consistent with the formation of the observed product **161**. Mannich closure, followed by hydrolysis of the orthoester and Barton decarboxylation, as outlined in Scheme 43, produces homochiral **163**, an intermediate in the Büchi synthesis of vindorosine.[53]

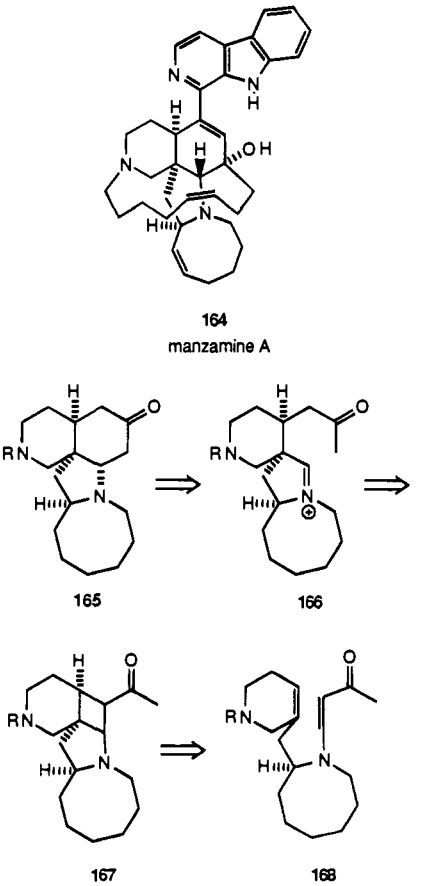
Scheme 44



D. Photocycloaddition/Fragmentation Reactions of Tertiary Vinylogous Amides: Synthetic Efforts toward Manzamine A and Other Nitrogen-Substituted Carbocycles

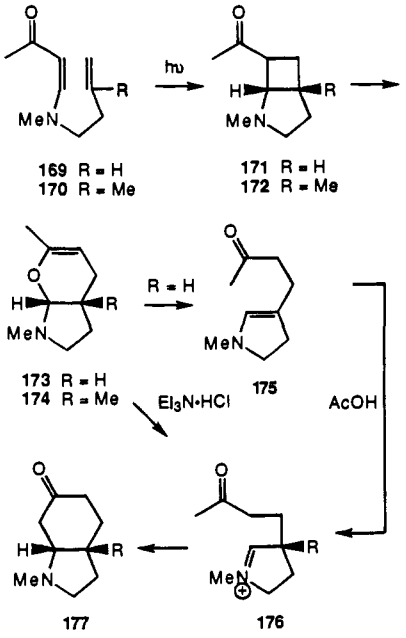
The most recent target of the vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure cascade is manzamine A (**164**).[54,55] As outlined in the retrosynthetic analysis in Scheme 45, β-amino ketone **165**, which forms the tetracyclic core of the manzamine alkaloids, could be derived from Mannich closure of keto iminium **166**. The keto iminium in turn could be derived from retro-Mannich fragmentation of photoadduct **167**, which would result from the photocycloaddition of **168**. As in the case of the synthesis of vindorosine (Scheme 43), this retrosynthetic analysis leads to a photosubstrate, **168**, containing a single stereogenic center. However, unlike the photosubstrates that lead to the formation of mesembrine and vindorosine, photosubstrate **168** is a tertiary vinylogous amide, i.e., no internal hydrogen bonding is possible to stabilize the excited state of the acyclic tertiary vinylogous amide chromophore.

Scheme 45



To determine whether the tertiary vinylogous amides would undergo the same photocycloaddition/retro-Mannich fragmentation process as that observed with the secondary vinylogous amides, i.e., **159** (Scheme 43) the reactivity of the model systems **169** and **170** was examined (Scheme 46).[56] Irradiation of **169** and **170** resulted in the formation of keto iminiums **176**, R = H and R = Me, respectively, albeit by somewhat different pathways. Irradiation of **169** gave a mixture of aminal **173** and keto enamine **175**. Exposure of the mixture to wet acetonitrile gave exclusively the keto enamine product **175**. Treatment of **175** with glacial acetic acid gave the keto iminium **176** (R = H).

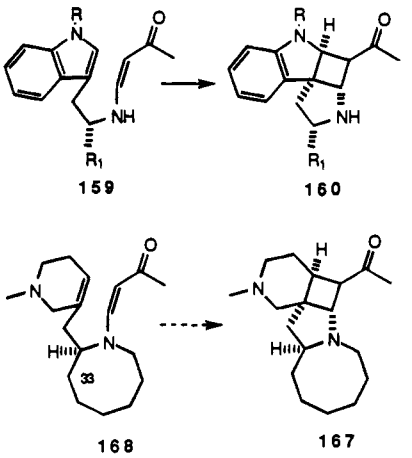
Scheme 46



The intermediacy of keto enamine **175** was precluded with photosubstrate **170**, which on irradiation gave aminal **174** in excellent yield. Treatment of **174** with triethylammonium hydrochloride in acetonitrile gave keto iminium **176** (R = Me) in 75% yield, which had previously been cyclized to give **177**.[51] Having demonstrated the viability of tertiary vinylogous amides in the photoaddition/retro-Mannich fragmentation sequence, we next examined the application of this methodology to the synthesis of the tetracyclic core of the manzamine alkaloids.

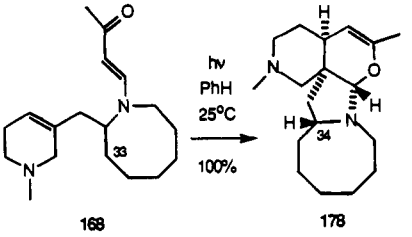
There is one other important difference between the proposed photocycloaddition of **168** and the results of our previous studies, i.e., **159** → **160** (Scheme 47). In the vindorosine series, irradiation of **159** led to the formation of photoadduct **160**, in which the R′ (orthoester) group is oriented on the concave face of the bicyclo[3.2.0]heptane moiety formed in the photocycloaddition. However, the sense of induction required for the stereoselective preparation of manzamine A from **168** requires that the methylene of the azocine ring (C-33, manzamine numbering) be oriented on the convex face of the analogous bicyclo[3.2.0]heptane moiety in **167** as shown in Scheme 47.

Scheme 47



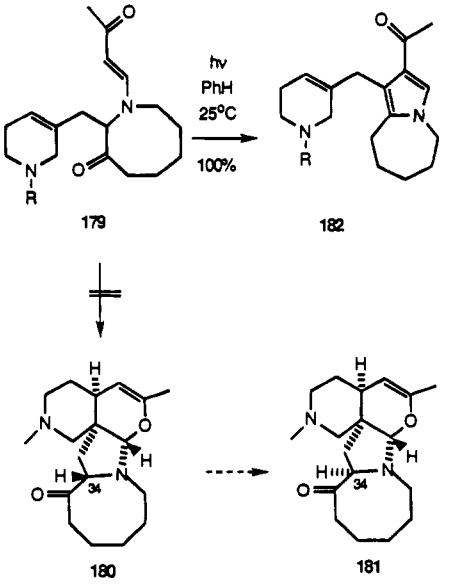
In the event, photocycloaddition of vinylogous amide **168**, as shown in Scheme 48, afforded **178** exclusively and in quantitative yield, a result that is consistent with the stereoselectivity observed in the photocycloaddition of **159**, but which gave the incorrect relative stereochemistry between the azocine and dihydropyran rings for the synthesis of manzamine.

Scheme 48



We next reasoned that incorporation of a carbonyl group at C-33 in photosubstrate **179** would lead to the formation of the analogous carbonyl-containing tetracyclic product **180** (Scheme 49). The ketone-containing tetracycle could then undergo epimerization at C-34 to give **181**, with the correct relative stereochemistry for the synthesis of manzamine, i.e., the eight-membered ring on the convex face of the

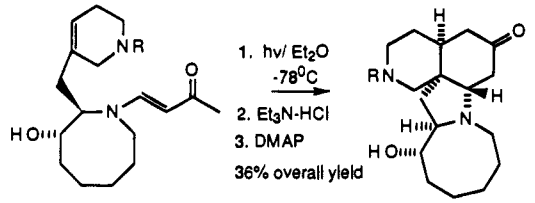
Scheme 49



tricyclic core. However, irradiation of **179** gave none of the desired photoadduct, but yielded instead only the rearranged pyrrole product, **182**.[57]

It was ultimately found that the photocycloaddition of the trans-alcohol **183** resulted in the formation of **184** with complete control of the requisite relative stereochemistry for the synthesis of the tetracyclic core of manzamine (Scheme 50).[58]

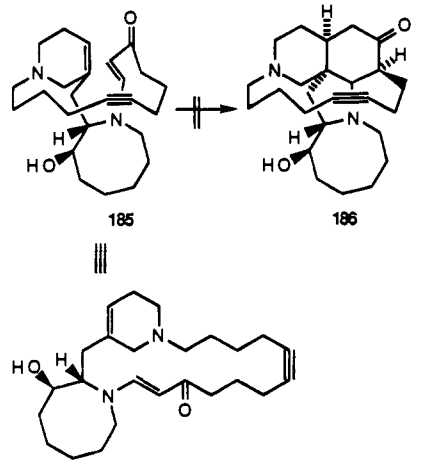
Scheme 50



183 184

The extension of these results to the synthesis of the pentacyclic manzamine ring system, i.e., **186** (Scheme 51) was next examined. It was reasoned

Scheme 51



185 186

that the most efficient way to introduce the 13-membered ring of the pentacyclic system of **186** would be to incorporate the requisite tether into the photosubstrate, i.e., **185**. The synthesis and photochemical reactivity of the macrocyclic vinylogous amide **185** was therefore examined. In the event, irradiation of **185** led to none of the desired photocycloaddition product, **186**, a consequence of the unfavorable orientation of the tetrahydropyridine ring relative to the vinylogous amide chromophore, as evidenced by the X-ray structure of photosubstrate **185**.

Since the direct incorporation of the fifth ring into photosubstrate **185** was not compatible with the desired cycloaddition, the alternative approach of macrocycle formation subsequent to the photochemical cascade was examined. We have recently completed the first synthesis of the manzamine pentacyclic ring system using this strategy. Photoaddition/retro-Mannich fragmentation/Mannich closure of **187**, which contains the carbons required for the formation of the macrocyclic ring, leads to the formation of **188**. Macrolactamization as outlined in Scheme 52 provides **190** in good overall yield, thereby completing the first stereoselective synthesis of the pentacyclic ring system of the manzamine alkaloids.[59]

VII. Conclusion

As outlined in this review, the [2 + 2] photocycloaddition/fragmentation of dioxinones and vinylogous amides leads to the highly efficient construction of diverse structural types. This methodology has been applied to a stereoselective construction of the tricyclic nucleus of the taxane diterpenes, as well as to unique approaches to the synthesis of bicycloalkanes with trans or "inside–outside" intrabridgehead stereochemistry. These efforts have culminated in the synthesis of biologically active analogs of the protein kinase C activating substance ingenol. In addition, the studies described herein have provided novel insights into the mechanistic pathways of these triplet photocycloaddition reactions.

The vinylogous amide photocycloaddition/retro-Mannich fragmentation/Mannich closure cascade has proven to be an equally powerful method for the stereoselective construction of complex ring systems, as evidenced by the efficient syntheses of mesembrine as well as the more structurally complex aspidosperma and manzamine alkaloids. As outlined in this review, the considerable structural variation in the targets that have been prepared using [2 + 2] photoaddition/fragmentation reactions underscores the utility of this methodology in organic synthesis.

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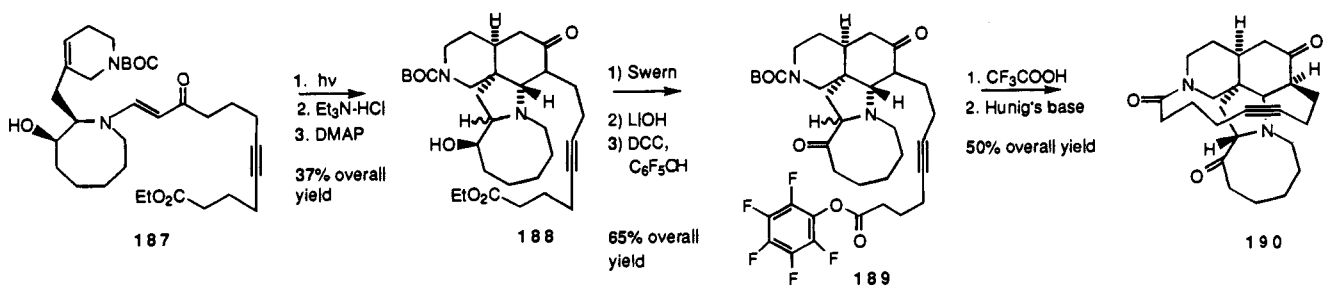
Scheme 52



187 188 189 190

gratitude collaborations with Dr. Peter Blumberg (National Institutes of Health), Professor Paul Williard (Brown University), Professor Stephen Darling (University of Akron) and Dr. James Springer (Merck & Co.) and the financial support of the National Institutes of Health (CA40250 and 45686) and American Cyanamid.

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