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Bond formations by intermolecular and intramolecular trappings of acylketenes and their applications in natural product synthesis†

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Abstract

The reactive intermediates known as acylketenes exhibit a rich chemistry and have been extensively utilized for many types of inter- and intramolecular bond-forming reactions within the field of organic synthesis. Characteristic reactions of acylketenes include cycloadditions, carbon–carbon bond-forming reactions, and nucleophilic capture with alcohols or amines to give β -keto acid derivatives. In particular, the intramolecular capture of acylketene intermediates with pendant nucleophiles represents a powerful method for forming both medium-sized rings and macrocycles, often in high yield. This *tutorial review* examines the history, generation, and reactivity of acylketenes with a special focus on their applications in the synthesis of natural products.

1. Introduction

Through research spanning a period of more than 180 years, chemists have made remarkable progress in the development of chemical reactions and strategies for transforming organic compounds in selective and efficient ways. These advances have been so profound that many of the most complex natural products are now within the reach of organic synthesis.¹ And yet it was not so long ago that the capabilities of this field were not well developed. In 1956, the structure of the natural product erythromycin A **1** induced R. B. Woodward to write: “Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers”, Fig. 1.²

Interestingly, even if one had an effective solution to the erythromycin stereochemical problem, a laboratory synthesis of this substance would not have been possible even as recently as 1970 owing to the total lack of viable methods for constructing large-ring systems. Rings of various sizes are everywhere in organic chemistry! They have fostered innovative methods for achieving their syntheses, and they constantly challenge the ingenuity of chemists engaged in syntheses of topologically complex molecules.

In 1974, Corey and Nicolaou described their general method for synthesizing large-ring lactones by electrostatically-driven cyclizations of hydroxy 2-pyridine thiol esters,³ the forerunner for a class of methods featuring the attack of a pendant hydroxyl group on an

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activated carboxylic acid.⁴ These powerful and reliable methods for forming macrocyclic lactones (also known as “macrolides”) have enabled many syntheses of complex natural products and have taken their place beside a large and diverse collection of ring-forming methods. Large ring-forming Wittig and Horner–Wadsworth–Emmons olefinations,⁵ pericyclic reactions,⁶ aldol additions,⁷ metal-catalyzed cross coupling reactions,⁸ free radical cyclizations,⁹ photochemical reactions,¹⁰ and olefin metathesis¹¹ are, like the macrolactonization methods alluded to above, often successful in a multitude of molecular settings; this circumstance has greatly benefited the general field of organic synthesis.

Another powerful method for building large-ring systems is founded on the intramolecular capture of a highly reactive, transient acylketene by an internal hydroxyl or amine nucleophile. This method, which gives direct access to β -keto lactones and β -keto lactams, respectively, has been effective in complex, target-directed synthesis and yet is relatively underutilized. Intermolecular or intramolecular trappings of reactive acylketenes by nucleophiles give rise to valuable structural types and enable the execution of challenging and delicate bond formations that might be difficult to achieve by alternative strategies for synthesis. The aim of this review article is to highlight the concept of bond and ring formations by the acylketene-trapping method with a particular emphasis on the use of acylketenes as reactive intermediates in complex natural product synthesis. The review is roughly chronological in its development.

2. Background

2.1 History

The first reference to an acylketene in the chemical literature appeared in 1908 when Wilshire and Chick described the preparation and chemical properties of a substance formed from the dimerization of ketene **2** (Scheme 1).¹² In particular, they noted that when this compound reacted with sodium ethoxide, the sodium salt of ethyl acetoacetate **3** was obtained in high yield; similarly, reaction with aniline gave acetoacetanilide **4**. Based on these observations and refractive index data, Wilshire and Chick proposed that this compound was “an internal anhydride of acetoacetic acid” and assigned its structure as acetylketene **5**. In actuality, they had isolated the isomeric substance diketene **6**, but this structural reassignment was not definitively made for another forty years.¹³

In 1953, Carroll and Bader examined the reaction of diketene with various ketones in the presence of an acid catalyst (Scheme 2).¹⁴ When a solution of **6** in acetone was heated with catalytic *p*-toluenesulfonic acid, a solid product **7** was formed in 91% yield. Analysis of the UV-visible and infrared spectra of this diketene–acetone adduct suggested that it had the structure of a 1,3-dioxinone.

This heterocycle was found to be less reactive towards nucleophiles than diketene but more reactive than acetoacetate esters. Dioxinone **7** was also found to be a convenient substitute for diketene in acetoacetylation reactions; for example, refluxing a solution of **7** and cholesterol **8** in toluene with trace *p*-toluenesulfonic acid gave cholesteryl acetoacetate **9** in high yield (Scheme 3).¹⁴

2.2 Mechanism

Although this acetoacetylation reaction had proven useful in a synthetic context, the mechanism had not yet been elucidated. In 1976, Jäger and Wenzelburger suggested that thermolysis of 1,3-dioxinones initiates a retro-hetero-Diels–Alder reaction, releasing acetone to form a transient acylketene (Scheme 4).¹⁵ They observed that this reactive intermediate could then participate in a hetero-Diels–Alder reaction with cyanates, isocyanates, or

cyanamides to give 1,3-oxazines. For example, dioxinone **7** reacts with phenyl isocyanate **10** under thermal conditions to give 1,3-oxazine-2,4-dione **11** in 68% yield.

Further evidence for the intermediacy of an acylketene was provided by Hyatt *et al.* in 1984.¹⁶ When **7** was heated in refluxing xylenes in the absence of a nucleophile, dehydroacetic acid **12** was isolated in 93% yield; presumably, this product arises from the Diels–Alder dimerization of two molecules of acylketene **5** (Scheme 5).

Furthermore, Hyatt and Clemens found that an acid or base catalyst was not necessary in the reaction of **7** with nucleophiles, and the corresponding β -keto acid derivatives could be obtained in high yield under thermal conditions alone.¹⁷ This observation can be rationalized by invoking the same acylketene intermediate, which is simply trapped by the ambient nucleophile to give the observed β -keto ester or amide.

The mechanism of nucleophilic addition of alcohols and amines to acylketenes has also been studied extensively through both competition experiments and computational methods.¹⁸ When the attacking nucleophile bears a proton, addition is believed to occur *via* a concerted, pseudopericyclic transition state, as shown in Scheme 6. This reaction requires that the acylketene adopt an *s-cis* conformation, and the initial product of the reaction is the *cis*-enol ether **13**, which can subsequently tautomerize to the β -keto acid derivative **14**.

In accordance with this proposed mechanism, steric effects that destabilize the *s-cis* conformation of the acylketene result in a slower reaction. Thus, the hydration of phenylbenzoyl-ketene **16** occurs over 200 times more slowly than the hydration of acetylketene **5** due to an unfavorable steric interaction between the two phenyl groups in the required *s-cis* conformation (Scheme 7).

The rate of reaction is also dependent on the steric bulk of the approaching nucleophile. Competition experiments show that primary alcohols react with acetylketene three times faster than secondary alcohols and eight times faster than tertiary alcohols.¹⁸ Presumably, unfavorable steric congestion destabilizes the planar, pseudopericyclic transition state, decreasing the rate of nucleophilic addition. Finally, higher reactivity in the addition reaction correlates with increased nucleophilicity of the attacking species. In competition experiments, butanol reacted with acetylketene six times faster than 2,2,2-trifluoro-ethanol due to the reduced nucleophilicity of the latter species. Similarly, alcohols were found to outcompete water, and amines will outcompete alcohols, providing an opportunity for chemoselectivity in the reaction of polyfunctional molecules with acylketenes.

It is also interesting to note that the reaction of nucleophiles with acylketenes is reversible at high temperatures; in fact, acylketenes are implicated as reactive intermediates in the thermal transesterification of β -keto esters.¹⁹ Therefore, β -keto esters can serve as convenient precursors to acylketenes *via* the thermal elimination of an alcohol.

2.3 Precursors

By far, the most commonly used method for generating acylketenes is *via* the thermolysis of functionalized 1,3-dioxinones. These heterocycles can be prepared in a variety of ways, including derivatization of commercially available trimethyl-dioxinone **7**.²⁰ However, numerous other acylketene precursors are known, as shown in Fig. 2.

These and various other methods for preparing acylketenes have been comprehensively reviewed and will not be discussed in detail.²¹ In general, acylketenes are highly reactive species, and only sterically hindered or inductively stabilized acylketenes are isolable. Therefore, acylketenes are almost always generated *in situ* and trapped with a species

already present in solution. The following sections will demonstrate how acylketenes have been used as reactive intermediates to enable the rapid formation of molecular complexity in the field of organic synthesis.

3. Cycloadditions

3.1 Diels–Alder reactions

Acylketenes are excellent 4π components for inverse electron demand hetero-Diels–Alder reactions. As alluded to previously, acylketenes will react with ketones or aldehydes to give 1,3-dioxinones. Even somewhat hindered ketones are able to react; for example, the steroid allobetulone **18** reacts with benzoylketene to give a mixture of regioisomeric 1,3-dioxinones **20** and **21** (Scheme 8).²² In this case, the acylketene is formed by thermal extrusion of carbon monoxide from 5-phenyl-2,3-dihydrofuran-2,3-dione **19**.

In 2006, Crimmins and Smith reported an improved synthesis of the AB spiroketal fragment **26** of spongistatin utilizing an acylketene Diels–Alder reaction (Scheme 9).²³ When dioxinone **22** was heated in the presence of the electron-rich diene *n*-butyl vinyl ether, cycloadduct **23** was obtained in high yield. Subsequent acid-catalyzed elimination of 1-butanol gave 4-pyrone **24** in 65% yield over the two steps. Removal of the PMB group with DDQ gave the free alcohol, which cyclized to spiroenone **25** in the presence of catalytic trifluoroacetic acid (TFA). Intermediate **25** could then be converted to the spongistatin AB spiroketal fragment **26** in three steps.

A similar inverse electron demand Diels–Alder reaction was used by Coleman and Fraser in a facile synthesis of 2,6-dideoxy pyranosides.²⁴ Cycloadduct **27**²⁵ proved to be a versatile intermediate that could be elaborated to form various *arabino*-, *ribo*-, *xylo*-, and *lyxo*-hexapyranosides, which are found in many natural products and antibiotics. The representative synthesis of *n*-butyl β -DL-olivose **29** is outlined in Scheme 10.

In the absence of nucleophiles or suitable dienophiles, acylketenes will dimerize, as shown in Scheme 5. Although this reaction has found little synthetic utility, the Diels–Alder reaction of an acylketene with a ketene can be used to form pyrone ring systems. This strategy was used by Upjohn Laboratories in the synthesis of the novel HIV protease inhibitor **31** as shown in Scheme 11.²⁶ In this case, the ketene component is formed *in situ* by base-induced elimination of HCl from acyl chloride **30**. When this reaction was carried out in refluxing toluene in the presence of dioxinone **29**, the desired [4+2] cycloaddition occurred, giving 2-pyrone **31** in 79% yield after treatment of the initial adduct with sodium hydroxide.

3.2 [2+2] Cycloadditions

Unlike ketenes, acylketenes infrequently participate in [2+2] cycloadditions. However, Almqvist *et al.* have reported several interesting examples of [2+2] reaction between acylketenes and thiazolines to form β -lactams, which are known to exhibit antimicrobial activity (Scheme 12).²⁷ In this reaction, the acylketene precursor is **32**, which is readily prepared *via* acylation of Meldrum's acid. Heating compound **32** under anhydrous acidic conditions initiated the formation of an acylketene with concomitant loss of acetone and carbon dioxide. The transient acylketene then underwent a [2+2] cycloaddition with thiazoline **33** to form β -lactam **34** in 81% yield.

4. Carbon nucleophiles

4.1 Enolate additions

Although less frequently observed than oxygen or nitrogen capture, acylketenes are subject to attack by carbon nucleophiles *via* a non-concerted addition mechanism. For example, enolates are known to add to acylketenes to give 1,3-diones. Trauner *et al.* utilized this strategy to enable a late-stage pyrone formation in an elegant synthesis of the ichthyotoxic natural product photodeoxytridachione **41** (Scheme 13).²⁸

Treating a mixture of **35** and malonyl chloride **36** with excess base simultaneously promoted enolate formation and acylketene formation through separate deprotonation events. Acylketene **38** was then captured by enolate **37** to give stabilized carbanion **39**; upon aqueous workup, β,δ -diketo ester **40** was isolated in 59% yield. Next, treating **40** with the amidine base DBU at high temperature effected a hetero-cyclization to form an intermediate 2-pyrone. Finally, selective methylation with methyl fluorosulfonate (“magic methyl”) gave the desired 4-pyrone, completing the synthesis of photo-deoxytridachione **41**.

4.2 Friedel–Crafts reactions

As strongly electrophilic species, acylketenes can also participate in Friedel–Crafts acylation reactions with electron-rich aromatic rings. An impressive example of a tandem double annulations making use of this reaction was reported by Fillion and Fishlock in the synthesis of the diterpenoid taiwaniaquinol B **45** (Scheme 14).²⁹ In the key Friedel–Crafts acylation–alkylation reaction, treatment of substituted Meldrum’s acid derivative **42** with trimethylsilyl triflate (TMSOTf) in refluxing nitromethane gave tricycle **43** in 73% yield. Next, selective demethylation of intermediate **43** with boron trichloride proceeded in 90% yield to give **44**. Oxidation with ceric ammonium nitrate (CAN) gave an intermediate *p*-quinone which was then hydrogenated to give the natural product **45** in 52% yield over the two steps.

The proposed mechanism for the key cyclization event is shown in Scheme 15. First, silylation of the 1,3-diketone gives dioxinone **46**, liberating one equivalent of trifluoromethane-sulfonic (triflic) acid. Extrusion of acetone *via* a retro-Diels–Alder reaction gives the reactive acylketene intermediate **47**, which is captured by the electron-rich aromatic ring in an intramolecular Friedel–Crafts reaction; aromaticity is then reestablished *via* proton transfer to give an enol. Next, protonation of the trisubstituted olefin with the triflic acid liberated in the first step gives tertiary carbocation **48**, which is intercepted intramolecularly by the enol in an α -*tert*-alkylation reaction to give intermediate **49**. Finally, decarboxylation of the β -keto acid under the thermal reaction conditions generates *cis*-fused tricycle **43** as a single diastereomer in 73% yield. In this efficient tandem sequence, the use of a reactive acylketene intermediate enables the formation of two carbon–carbon bonds to rapidly produce the carbon framework of taiwaniaquinol B.

5. Intermolecular capture to give β -keto amides and β -keto esters

By far, the most commonly used application of acylketenes in organic synthesis is in the preparation of β -keto esters and β -keto amides. The concerted, nucleophilic addition of alcohols or amines can occur either intermolecularly to couple fragments or intramolecularly to form lactones or lactams. One example of an intermolecular β -keto amide coupling of industrial significance occurs in Merck’s synthesis of the anti-diabetic drug Januvia® (Sitagliptin) **55** (Scheme 16).³⁰

The key acylketene intermediate is derived from compound **52**, which is formed *in situ* by acylating Meldrum’s acid **51** with the mixed pivalic anhydride of **50** in the presence of mild base. When **52** is heated to 55 °C in trifluoroacetic acid, acetone and carbon dioxide are lost

to form an acylketene, which is captured by amino triazole **53** to give β -keto amide **54**. Finally, enamine formation followed by an asymmetric hydrogenation completes this efficient synthesis of Januvia®, giving **55** in greater than 95% yield with an enantiomeric ratio of 39 : 1.

In 1990, Sakaki *et al.* reported a facile method for synthesizing substituted tetronic acids, a structural motif found in many bioactive natural products.³¹ An application of this methodology as applied to a short synthesis of the fungal metabolite (–)-carlosic acid **60** is shown in Scheme 17.

Heating a mixture of alcohol **56** and dioxinone **57** in refluxing toluene cleanly led to the formation of β -keto ester **58** via the intermediacy of an acylketene. Treatment of **58** with the mild base tetrabutylammonium fluoride (TBAF) induced a Dieckmann condensation to give tetronic acid **59**. Finally, acidic hydrolysis of the methyl ester gave the natural product **60** in 42% yield over the three steps.

One final example of an intermolecular acylketene-trapping reaction is found in Chênevert's expedient synthesis of the nonprotein plant elicitor (–)-syringolide **67**.³² This route demonstrates the utility of coupling two fragments via an intermediate acylketene to rapidly synthesize an advanced substrate. In a key bond-forming step, heating Meldrum's acid derivative **61** and α -hydroxyketone **62** in refluxing tetrahydrofuran gave β -keto ester **63**. When treated with silica gel, this intermediate underwent an intramolecular condensation reaction to give **65**; subsequent removal of the PMB protecting group with DDQ gave key substrate **66**. Treating this compound with *p*-toluenesulfonic acid (*p*-TsOH) in wet acetone initiated a tandem ketal deprotection–conjugate addition–hemiketal formation sequence, producing (–)-syringolide **67** in 55% yield (Scheme 18).

6. Intramolecular capture to give macrolactones and macrolactams

The intramolecular capture of acylketenes under dilute conditions is an excellent method for synthesizing macrocyclic rings. Boeckman and Pruitt were the first to use dioxinones as precursors to acylketenes in the synthesis of complex natural products featuring macrolactones and macrolactams. To demonstrate the efficiency of this methodology, Boeckman devised a synthesis of (+)-diplodialide A **69** (Scheme 19), a steroid hydroxylase inhibitor featuring a strained 10-membered ring.³³

The presence of a *trans* double bond in this medium-ring lactone had made this natural product difficult to synthesize using conventional lactonization procedures, which only proceeded in 15–20% yield. In contrast, when a 0.1 mM solution of dioxinone alcohol **68** in toluene was heated to reflux for four hours, **69** was obtained in 68% yield. Carrying out this reaction at higher concentrations led to the formation of polymeric byproducts derived from intermolecular capture of the acylketene intermediate.

In the same communication, Boeckman also reported the total synthesis of the more complex 16-membered macrolide (–)-kromycin **71** (Scheme 20).³³ To this end, heating a dilute solution of substrate **70** using the previously described reaction conditions directly gave the natural product in 70% yield with no observable byproducts.

A more recent application of this macrolactonization strategy appears in Blechert's synthesis of the 16-membered macrolide antibiotic (–)-A26771B **75**.³⁴ In order to synthesize key substrate **73**, vinyl dioxinone **72** was first dihydroxylated with AD-mix α . This diol was then protected as the corresponding acetonide to yield cyclization precursor **73**. Refluxing a dilute solution of **73** in *n*-heptane initiated the formation of an acylketene which was trapped by the pendant secondary alcohol to give macrolactone **74** (Scheme 21). This advanced

intermediate could then be elaborated into (–)-A26771B **75** over the course of six steps in high yield.

6.1 Ikarugamycin

Boeckman and co-workers also pioneered the use of acylketene intermediates in the total synthesis of complex macrolactams such as the antiprotozoal, antibiotic natural product (+)-ikarugamycin **79** (Scheme 22).³⁵ The key transformation involved the thermal decomposition of dioxinone **76** to generate the acylketene, which was then trapped intramolecularly by the secondary amine to generate 16-membered lactam **77** in 77% yield.

The authors were able to achieve intramolecular ring closure in preference to competing intermolecular processes with substrate concentrations as high as 10 mM. β -keto amide **77** was then treated with potassium *tert*-butoxide to form tetramic acid **78** via a transannular Lacey–Dieckmann condensation; removal of the 2,4-dimethoxybenzyl (DMB) protecting group under acidic conditions afforded the natural product **79** in 41% yield over the two steps.

The same strategy was utilized by Paquette *et al.* in their synthesis of (+)-ikarugamycin (Scheme 23),³⁶ which was disclosed in a back-to-back publication following the Boeckman total synthesis described above. Despite slight differences in the macrocyclization precursor **80**, the desired transformation occurred when a dilute solution of this substrate was heated to reflux in toluene, giving macrolactam **81** in 94% yield. This advanced intermediate was then converted to the natural product over the course of five steps.

6.2 Cylindramide

Like ikarugamycin, the cytotoxic natural product cylindramide A **85** features a tetramic acid moiety within a macro-lactam ring.³⁷ Indeed, Laschat *et al.* envisioned a similar acylketene-trapping strategy in their synthesis of this natural product (Scheme 24).³⁸ In order to access the cyclization precursor, the authors first performed a Staudinger reduction of azide **82** to generate amino dioxinone **83**. Heating a dilute solution of this free amine in refluxing toluene produced the 21-membered ring lactam **84** in an impressive yield of 82% over the two steps. This intermediate could then be advanced to the natural product **85** in three additional steps.

A total synthesis of cylindramide A was also accomplished by Hart and Phillips utilizing a similar macrocyclization event (Scheme 25).³⁹ In this case, the trapping nucleophile was a secondary amine featuring a 2,4-dimethoxybenzyl (DMB) protecting group. Upon heating dioxinone **86** to reflux in toluene at a substrate concentration of 10 mM, the authors obtained a 65% yield of macrolactam **87**, which was elaborated to the natural product in two steps.

6.3 Callipeltoside

The antitumor agent callipeltoside A **91** has been a popular target for total synthesis due to its complex architecture and promising bioactivity.⁴⁰ In particular, this natural product features a 14-membered macrolactone, a transannular hemiketal, and an unusual chlorocyclopropane-containing side chain. In 2002, Trost and co-workers reported the total synthesis of callipeltoside A using an acylketene macrolactonization event as a key step (Scheme 26).⁴¹ In this reaction, heating dioxinone **88** in refluxing toluene at a substrate concentration of 0.5 mM afforded the macrolactone **89** in 82% yield. Removal of the silyl protecting groups with HF·pyridine followed by treatment of the diol with pyridinium *p*-toluenesulfonate (PPTS) in wet acetonitrile afforded the desired transannular hemiketal **90**. This structure was advanced to callipeltoside A aglycone in just three steps (59% overall yield), and, after glycosylation to give **91**, the authors were able to assign the absolute and relative configuration of the natural product.

A similar strategy targeting the central macrolide was reported by Marshall and Eidam in their formal synthesis of callipeltoside A (Scheme 27).⁴² However, they employed a simple β -keto ester as the acylketene precursor instead of the dioxinone utilized by Trost. Thus, heating a dilute solution of **92** in refluxing toluene induced the loss of ethanol to form the acylketene; trapping with the pendant secondary alcohol proceeded in 73% yield to give macrolactone **93**. Next, oxidative removal of the PMB protecting group with DDQ gave the free secondary alcohol which spontaneously formed the transannular hemiketal **94**. Cleavage of the TIPS protecting group with tetrabutylammonium fluoride and Lindlar hydrogenation of the resulting alkyne gave **90**, intercepting an intermediate in Trost's route to complete a formal total synthesis of callipeltoside A.

In studies towards the total synthesis of callipeltoside A, Hoyer and co-workers demonstrate the high degree of regioselectivity that can be achieved through an acylketene macrolactonization.⁴³ The acylketene precursor **95** contains four unprotected hydroxyl groups and yet only a single constitutional isomer **98** is observed upon heating this substrate in refluxing benzene at a substrate concentration of 0.1 mM (53% yield, NMR-based). The remarkable fact that they achieved complete selectivity for the desired secondary alcohol over the vicinal primary alcohol implicates a favorable conformational bias in their complex substrate. Furthermore, this impressive reaction sequence allows Hoyer and co-workers to accomplish both the macrolactonization and the transannular hemiketal formation in the same pot without the need for protecting groups (Scheme 28).

7. Tandem intermolecular acylketene-trapping–IMDA reactions

One of the most powerful strategies for the rapid generation of molecular complexity is the development of tandem (or cascade) reaction sequences in which a single reactive intermediate enables the sequential formation of multiple bonds. These tandem reactions offer several advantages within a synthetic route including increased reaction efficiency and a reduction in the overall number of steps and/or purifications required to obtain the desired product.

In the early 1990's, Boeckman imagined using a vinyl dioxinone of type **99** as the precursor for a tandem nucleophilic acyl-ketene capture–Diels–Alder sequence (Scheme 29).⁴⁴ As before, heating **99** induces a retro-Diels–Alder reaction to form a reactive acylketene intermediate **100** that is trapped inter-molecularly with a nucleophile to give a β -keto acid derivative. However, this thermolysis also leaves in its wake an α,β -unsaturated ketone, which, in the presence of a pendant diene, could undergo an intramolecular Diels–Alder reaction (IMDA) to give **101**. Such a strategy offers the potential for forming two rings, three bonds, and up to four contiguous stereocenters in a single step.

7.1 Tetronolide

In order to test the feasibility of this acylketene-trapping–Diels–Alder sequence, Boeckman investigated the synthesis of the antitumor agent (+)-tetronolide **107**.⁴⁵ This complex, spiro-tetronic acid-containing natural product is the aglycone of tetrocarcins A–H, which also exhibit a wide range of bioactivity. As a model system, Boeckman first explored the solvolytic capture of the acylketene intermediate derived from dioxinone substrate **102**.⁴³ When this compound was heated in toluene to 110 °C in the presence of methanol, bicyclic β -keto ester **103** was isolated in 54% yield (Scheme 30). The intra-molecular Diels–Alder reaction proceeds *via* the more stable *endo* transition state, which imparts greater than 10 : 1 diastereoselectivity in the formation of bicycle **103**.

Encouraged by this promising tandem reaction sequence, Boeckman and co-workers sought to achieve the total synthesis of tetronolide by capturing the acylketene intermediate with the

required (and more sterically demanding) tertiary alcohol **104** (Scheme 31).⁴⁴ When a mixture of alcohol **104** and polyene **105** was heated to 140 °C in xylenes, the desired bicyclic β -keto ester product **106** was obtained as a single diastereomer in 69% yield (97% based on recovered starting material). This efficient tandem reaction allowed for the direct coupling of two complex fragments under purely thermal conditions, producing an advanced intermediate that was further elaborated to complete the total synthesis of (+)-tetronolide **107**.

7.2 Studies towards kijanolide

A similar acylketene-trapping–Diels–Alder sequence was proposed by Roush and Brown in studies towards the synthesis of the related natural product kijanolide.⁴⁶ In a solvolytic acylketene capture analogous to that reported by Boeckman, heating a solution of vinylidioxinone **108** in xylenes to 120 °C in the presence of methanol afforded the desired bicyclic β -keto ester **109** in 60% yield (Scheme 32).

Roush and Brown were also able to achieve the intermolecular trapping of an acylketene intermediate with complex tertiary alcohol **110** to give β -keto ester **112** in up to 88% yield (Scheme 33).

However, the success of this reaction required the use of 1.8 equivalents of **110** and careful control of the reaction conditions to minimize the formation of methyl ketone **113** as an undesired byproduct. Presumably, this compound results from capture of the transient acylketene with adventitious water followed by decarboxylation of the resulting β -keto acid **116** at high temperature (Scheme 34). Despite the use of scrupulously dry solvent and the addition of 4 Å molecular sieves, **113** was always observed upon prolonged heating or when the reaction was conducted above 120 °C.

As previously discussed, the nucleophilic capture of an acylketene with an alcohol is reversible at high temperatures, allowing β -keto esters to serve as precursors to acylketenes. In particular, β -keto esters derived from tertiary alcohols are especially prone to elimination for steric reasons.⁴⁷ Therefore, the desired product **112** could undergo reversible elimination of **110** to regenerate the acylketene whereas the β -keto acid arising from water capture undergoes *irreversible* decarboxylation, producing a significant amount of methyl ketone **113**. Unfortunately, the same problem was observed in their desired system when they attempted the tandem acylketene capture–intramolecular Diels–Alder reaction of **118**, giving methyl ketone **119** in 70% yield (Scheme 35). An alternative, stepwise route also proved unsuccessful, prompting Roush *et al.* to abandon this approach in favor of a different strategy towards the total synthesis of kijanolide.⁴⁸

8. Application of acylketenes towards the total synthesis of the hirsutellones

Inspired by the precedents of Boeckman and Roush, we were intrigued by the possibility of using a tandem *intramolecular* acylketene-trapping–Diels–Alder sequence to access much of the core framework of the antitubercular natural product hirsutellone B **122**.^{49,50} Tethering both the nucleophile and the diene to a vinylidioxinone presents an opportunity to form three bonds, three rings (including a 14-membered macro-lactam) and four stereocenters in a single step. In order to test the feasibility of a tandem acylketene-trapping–Diels–Alder reaction in our system, we initially attempted a solvolytic capture with methanol to form the tricyclic core of the hirsutellones (Scheme 36).⁵¹

When a solution of triene **120** in an 8 : 1 mixture of toluene–methanol was heated to 110 °C in a sealed tube, the desired tricycle **121** was obtained in 85% yield. The relative

stereochemistry of **121** was determined using NOE correlation data and was found to match that of the natural product, indicating that the intramolecular Diels–Alder reaction occurs through an *endo* transition state.

Encouraged by this result, we next synthesized substrate **123** in order to test the intramolecular acylketene-trapping reaction to form the macrolactam.⁵² However, when a dilute solution of **123** was heated to 110 °C in toluene, only a trace amount of the desired product was observed; instead, we could only isolate methyl ketone **124** (Scheme 37).

Presumably, this product is formed *via* capture of the intermediate acylketene with water followed by irreversible decarboxylation, as observed in Roush's system. In order to overcome this problem, we consulted the work of Danielson and Hoyer, who had extensively screened conditions to optimize the macrolactonization step in the synthesis of callipeltoside A (Scheme 28).⁵³ In particular, they had also observed methyl ketone formation when the acylketene capture was carried out at high temperatures in solvents such as toluene. However, methyl ketone formation could be virtually eliminated simply by azeotropically removing any water from the system with a Dean–Stark apparatus. Thus, when macrolactamization of substrate **123** was carried out under Hoyer's conditions (Scheme 38), we observed formation of the desired product **125** with only a trace amount of the methyl ketone byproduct.⁵⁰

Having tested both the intramolecular Diels–Alder reaction and the macrolactamization separately, we were now ready to attempt the tandem reaction sequence using fully elaborated substrate **126**. When a dilute solution of triene **126** was heated in refluxing toluene using a Dean–Stark apparatus, we were pleased to isolate the desired tandem product **127** as a single diastereomer in 50% yield.⁵⁰ Furthermore, NOE studies showed that the IMDA reaction occurs *via* an *endo* transition state to give the same stereochemistry about the tricyclic ring system that is observed in hirsutellone B (Scheme 39). Thus, we have demonstrated the feasibility of a tandem intramolecular ketene-trapping–IMDA reaction, and attempts to complete the total synthesis of this natural product are currently in progress.

9. Conclusion

The inherent reactivity and diverse applications of acylketenes make them valuable reactive intermediates within the field of organic synthesis. The nucleophilic capture of an acylketene is an excellent strategy for synthesizing β -keto acid derivatives under neutral conditions, and this method is applicable even in complex molecular settings. Intramolecular captures of acylketenes are especially useful in a synthetic context in that they allow for the formation of medium and large rings which are often difficult to synthesize using other methods. Finally, the bifunctional nature of α,β -unsaturated acylketenes allows for the rapid generation of molecular complexity through tandem ketene-trapping–Diels–Alder reaction sequences. It is our hope that organic chemists will continue to utilize acylketenes in their synthetic endeavors and make use of these reactive intermediates in the synthesis of even more complex natural product targets.

Biography

Keith P. Reber, Erik J. Sorensen and S. David Tilley

Keith Reber (center) received his Bachelor of Science degrees in Chemistry and Mathematics from the Pennsylvania State University where he was a Schreyer Honors Scholar. In 2007, he began graduate studies at Princeton University under the direction of Professor Erik Sorensen. He received his Master's degree in 2009 and is currently conducting research in the field of natural product synthesis. His interests within organic chemistry include the synthesis of natural and unnatural products, the chemistry of reactive intermediates, pericyclic reactions, and chemical education.

David Tilley (left) received his Bachelor of Science degree in Chemistry from the University of Georgia in 2002 where he engaged in research in the field of natural product synthesis with Professor George Majetich. He then pursued graduate studies in the field of chemical biology at the University of California, Berkeley under the direction of Professor Matthew B. Francis and received his Ph.D. in 2007. He then moved to Princeton University to perform postdoctoral studies with Professor Erik J. Sorensen, focusing on the synthesis of the natural product hirsutellone B.

Erik Sorensen (right) received his Bachelor of Arts degree in Chemistry from Syracuse University and began his graduate studies in chemical synthesis at The University of California, San Diego in 1989. Under the direction of Professor K. C. Nicolaou, he contributed to a laboratory synthesis of the cancer drug Taxols, co-authored Classics in Total Synthesis, and obtained his Ph.D. in 1995. After completing an NSF postdoctoral fellowship with Professor Samuel Danishefsky, he started his independent career at The Scripps Research Institute in 1997. In 2003, he moved his research group to Princeton University where he is the Arthur Allan Patchett Professor in Organic Chemistry.

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Fig. 1.
Structure of the natural product erythromycin A.

Fig. 2.
Common precursors for generating acylketene intermediates.

Scheme 1.

The discovery of a new compound (“acetylketene”) and its reactivity.

Scheme 2.

Acid-catalyzed formation of 1,3-dioxinones from diketene. $p\text{-TsOH}$ = p -toluenesulfonic acid.

Scheme 3.

Use of dioxinone **7** as an acetoacetylation reagent. *p*-TsOH = *p*-toluenesulfonic acid.

Scheme 4.

Generation and capture of an acylketene intermediate under thermal conditions.

Scheme 5.

Dimerization of acetylketene in the absence of reactive functional groups.

Scheme 6.
Concerted addition of nucleophiles to acylketenes. Nu = O, N, or S.

Scheme 7.

Relative rates of hydration for mono- and disubstituted acylketenes.

Scheme 8.
Derivatization of a sterically hindered ketone *via* a hetero-Diels–Alder reaction with benzoylketene.

Scheme 9.

Crimmins' synthesis of the AB spiroketal fragment of spongistatin. Bn=benzyl, PMB=4-methoxybenzyl, P=benzyloxymethyl (BOM), *p*-TsOH = *p*-toluenesulfonic acid, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Scheme 10.
A rapid synthesis of 2,6-dideoxypyranosides.

Scheme 11.
Synthesis of an HIV protease inhibitor *via* an acylketene–ketene Diels–Alder reaction.

Scheme 12.

A [2+2] cycloaddition reaction to access β -lactam derivatives.

Scheme 13.

Endgame of Trauner's synthesis of photodeoxytridachione. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Scheme 14.

A rapid synthesis of the carbon framework of taiwaniaquinol B. TMS = SiMe₃, CAN = ceric ammonium nitrate.

Scheme 15.
Proposed mechanism for the formation of tricycle **43**. TMS = SiMe₃.

Scheme 16.

Merck's synthesis of Januvia® utilizing a Meldrum's acid derivative as an acylketene precursor. DMAP = 4-(dimethylamino)-pyridine, DMA = *N,N*-dimethylacetamide, PivCl = trimethylacetyl chloride.

Scheme 17.

Synthesis of (–)-carlosic acid, a tetronic acid-containing natural product.

Scheme 18.

Total synthesis of (-)-syringolide. PMB = 4-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, *p*-TsOH = *p*-toluenesulfonic acid.

Scheme 19.
Boeckman's synthesis of (+)-diplodialide A.

Scheme 20. Final step in Boeckman's total synthesis of $(-)$ -kromycin.

Scheme 21.

A key acylketene lactonization enables the synthesis of a macrolide antibiotic. p -TsOH = p -toluenesulfonic acid.

Scheme 22.

Boeckman's total synthesis of (+)-ikarugamycin. DMB = 2,4-dimethoxybenzyl.

Scheme 23.

Key macrolactamization step in Paquette's total synthesis of (+)-ikarugamycin. DMB = 2,4-dimethoxybenzyl.

Scheme 24.

Key macrolactamization step in Laschat's synthesis of cylindramide A. TBS = *Si*-*t*-BuMe₂.

Scheme 25.

Key macrolactamization step in Hart and Phillips' synthesis of cylindramide A. DMB = 2,4-dimethoxybenzyl, TBS = *tert*-BuMe₂.

Scheme 26.

Macrolide formation in Trost's total synthesis of callipeltoside A. P = *Sit*-BuMe₂ (TBS), PPTS = pyridinium *p*-toluene-sulfonate.

Scheme 27.

Marshall's formal total synthesis of callipeltoside A. P = 4-methoxybenzyl (PMB), TBS = *Sit*-BuMe₂, TIPS = Si(*i*-Pr)₃, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Scheme 28.

Remarkable chemoselectivity in a tandem macro-lactonization–hemiketalization reaction.

Scheme 29.

A tandem acylketene capture–intramolecular Diels–Alder (IMDA) reaction. Nu = O, N, or S.

Scheme 30.

A tandem solvolytic acylketene capture-IMDA sequence. PMB = 4-methoxybenzyl, MOM = 2-methoxymethyl.

Scheme 31.

A key fragment coupling in Boeckman's total synthesis of (+)-tetronolide. TBDPS = *Si*-*t*-BuPh₂, PMB = 4-methoxybenzyl, MOM = 2-methoxymethyl, BHT = 2,6-di-*t*-butyl-4-methylphenol.

Scheme 32.

A solvolytic acylketene capture-IMDA sequence. BOM = benzyloxymethyl, P = *Si*-*t*-BuPh₂ (TBDPS).

Scheme 33.

Successful intermolecular acylketene capture with a tertiary alcohol. TBS = *Sit*-BuMe₂, TBDPS = *Sit*-BuPh₂.

Scheme 34.

Formation of a methyl ketone byproduct *via* water capture–decarboxylation. TBDPS = *tert*-BuPh₂.

Scheme 35.

Roush's attempted tandem acylketene capture–IMDA towards kijanolide. TES = SiEt₃, TBS = Si*t*-BuMe₂, TBDPS = Si*t*-BuPh₂.

Scheme 36.
Synthesis of the decahydrofluorene core of the hirsutellones.

Scheme 37.

Attempted macrolactamization leading exclusively to methyl ketone byproduct **124**. TBS = *Si**t*-BuMe₂, P = 2-bromobenzyl.

Scheme 38.

Successful macrolactamization using Hoye's conditions. TBS = *Si**t*-BuMe₂, P = 2-bromobenzyl.

Scheme 39.

Successful intramolecular acylketene capture-IMDA to give an advanced intermediate in a proposed synthesis of hirsutellone B. TBDPS = *Si**t*-BuPh₂, DMB = 2,4-dimethoxybenzyl.