REVIEW

Catalytic Decomposition of Diazo Compounds as a Method for Generating Carbonyl-Ylide Dipoles

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Dedicated to *Rolf Huisgen* on the occasion of his 85th birthday

The transition metal catalyzed reaction of α-diazo carbonyl compounds has found numerous applications in organic synthesis, and its use in either heterocyclic or carbocyclic ring formation is well-precedented. In contrast to other catalysts that are suitable for carbenoid reactions of diazo compounds, those constructed with the dirhodium(II) framework are most amenable to ligand modification that, in turn, can influence reaction selectivity. The reaction of rhodium carbenoids with carbonyl groups represents a very efficient method for generating carbonyl ylide dipoles. Rhodium-mediated carbenoid–carbonyl cyclization reactions have been extensively utilized as a powerful method for the construction of a variety of novel polycyclic ring systems. This article will emphasize some of the more recent synthetic applications of the tandem cyclization/cycloaddition cascade for natural product synthesis. Discussion centers on the chemical behavior of the rhodium metal–carbenoid complex that is often affected by the nature of the ligand groups attached to the metal center.

Introduction. – The stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans and tetrahydropyrans, has attracted considerable attention in recent years¹). These medium-size cyclic ethers are becoming increasingly recognized as common structural units in naturally occurring compounds such as the ionophores [2], the brevetoxins [3], and other marine natural products [4]. Due to the increasing interest in these bioactive molecules and the well-recognized problems in building medium-sized rings, the synthesis of such systems becomes a challenging objective. Although a variety of methods exist for dihydro- and tetrahydrofuran synthesis [1], few of these are based on an annulation strategy [5], and of those that are single-step procedures are uncommon²). Conceptually, the 1,3-dipolar cycloaddition of carbonyl ylides with π-bonds represents an attractive strategy for tetrahydrofuran formation [7]. Common methods for carbonyl-ylide generation involve the thermolysis or photolysis of epoxides possessing electron-withdrawing substituents [8–10], the thermal extrusion of N_2 from 1,3,4-oxadiazolines [11–13], and the loss of CO_2 from 1,3-dioxolan-4-ones [14]. One of the simplest routes for the generation of carbonyl ylides involves the addition of a carbene or carbenoid onto the O-atom of a carbonyl group [15].

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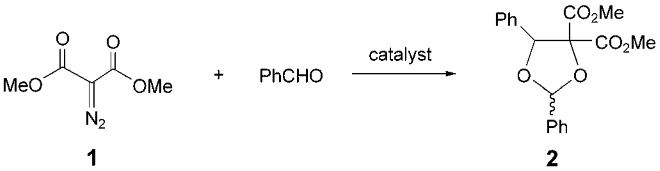
¹) For some examples of stereoselective tetrahydrofuran syntheses, see [1].
²) For some examples, see [6].

Carbonyl-Ylide Formation. – In recent years, a widespread upsurge of activity in the application of carbonyl ylides to new synthetic transformations has occurred [16]. This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for the generation of other types of ylides [17]. A diverse range of chemistry has already surfaced [15–18]. It is the intent of this commemorative article to *Rolf Huisgen* to broadly define the boundaries of our present knowledge in this field. Such an overview will put into perspective what has been accomplished, and will hopefully provide impetus for further investigation of this general approach for organic synthesis.

The Early *Huisgen* Observations. – Many studies support the intermediacy of carbonyl ylides in reactions involving the interaction of a carbene with a carbonyl O-atom [19–24]. Reactions of carboalkoxycarbenes with carbonyl compounds were described as early as 1885 [25], and the structures of the dioxolane products were proposed in 1910 [26]. The *Huisgen* group, however, was the first to examine the reaction in detail and to trap a carbonyl ylide with a number of reagents, including the carbonyl group itself to produce a dioxolane [27]. The early investigations by *Huisgen* and *de March* with dimethyl diazomalonate revealed that in reactions with benzaldehyde, a mixture of isomeric 1,3-dioxolanes was formed (*Scheme 1*) when $Rh_2(OAc)_4$, $Cu(acac)_2$, or CuOTF was used as the catalyst [28]. Since the initial *Huisgen* report, the catalytic generation of carbonyl ylides from diazo compounds has developed into a powerful reaction for organic synthesis [29].

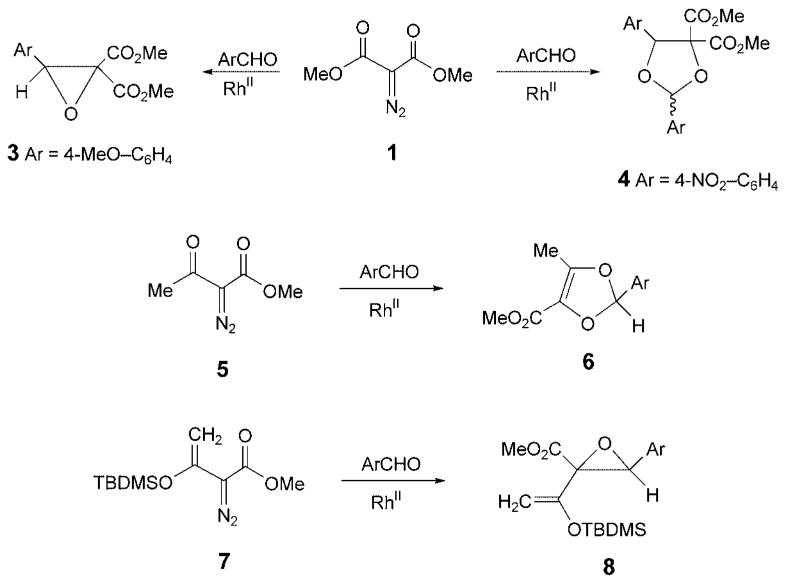
Scheme 1



In a more recent follow-up study to the earlier *Huisgen* publication, *Doyle* and coworkers showed that it was possible to direct the decomposition of diazomalonates to produce an epoxide or a dioxolane by influencing the stability of the intermediate carbonyl-ylide dipole [30]. With dimethyl diazomalonate, competition exists between dioxolane and epoxide formation. When *p*-anisaldehyde was used, only formation of epoxide **3** was observed, while with *p*-nitrobenzaldehyde, only 1,3-dioxolane products **4** were formed (*Scheme 2*). With methyl diazoacetoacetate (**5**), intramolecular trapping of the intermediate carbonyl ylide results in the sole production of 1,3-dioxole **6**. Vinyldiazoacetate **7**, on the other hand, retains the electrophilic control required for the collapse of the intermediate ylide dipole to form the corresponding epoxide **8**.

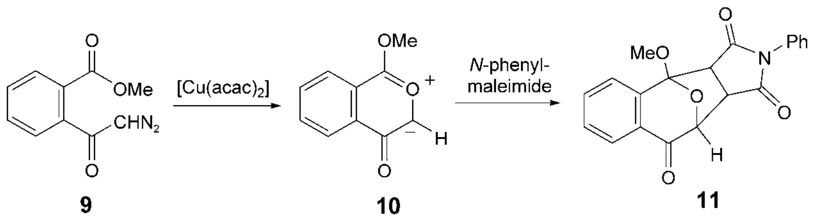
The intramolecular carbenoid–carbonyl cyclization sequence has now become the premier method for generating carbonyl ylides. *Ibata et al.* [31] were the first to demonstrate the utility of the method by studying the transition metal catalyzed decomposition of *o*-(alkoxycarbonyl)-α-diazo-acetophenone in the presence of various dipolarophiles. A typical example involves treating methyl 2-[(diazomethyl)carbo-

Scheme 2



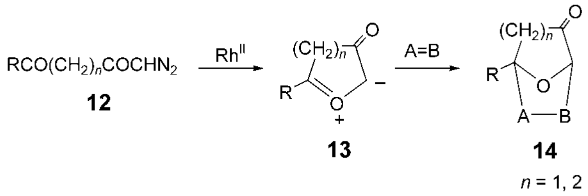
nyl]benzoate (**9**) with a catalytic amount of copper acetylacetonate ([Cu(acac)$_2$]; *Scheme 3*). Evolution of N_2, followed by carbonyl-ylide formation, generated a reactive dipole, which could be trapped by *N*-phenylmaleimide to give cycloadduct **11** in high yield. Cycloadditions using the benzopyrylium oxide **10** have been extensively studied by *Ibata et al.* [31].

Scheme 3



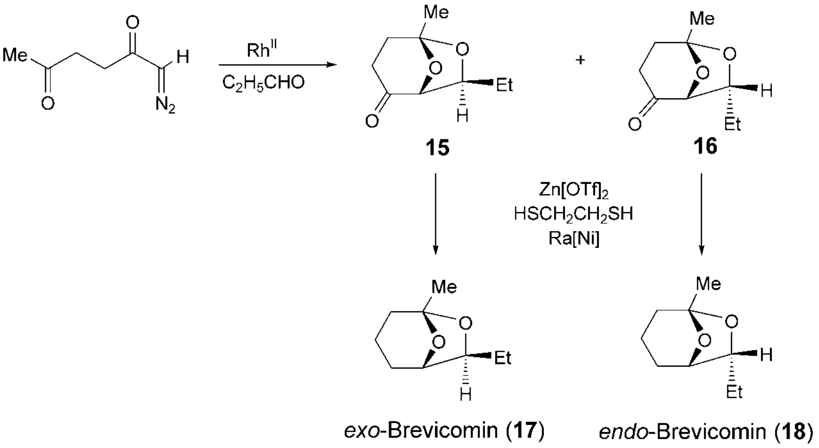
Carbonyl-Ylide Cycloadditions. – In 1986, our research group at the Emory University started a program to synthesize bridged hetero-substituted bicycloalkanes from the Rh^{II}-catalyzed cyclization cascade of 1-diazoalkanediones [32]. The domino reaction was shown to proceed by the formation of a Rh-carbenoid intermediate and subsequent transannular cyclization of the electrophilic C-atom onto the adjacent keto group to generate a cyclic carbonyl ylide, followed by 1,3-dipolar cycloaddition (*Scheme 4*) [33]. Most of our studies were carried out with five- and six-membered ring systems [34]. The resulting cyclic dipole (*i.e.*, **13**) always contained a C=O group within the ring. We [16] and others [17] have found that the intramolecular trapping of carbonyl-ylide dipoles with tethered alkenes represents an extremely effective method for the synthesis of a variety of natural products.

Scheme 4



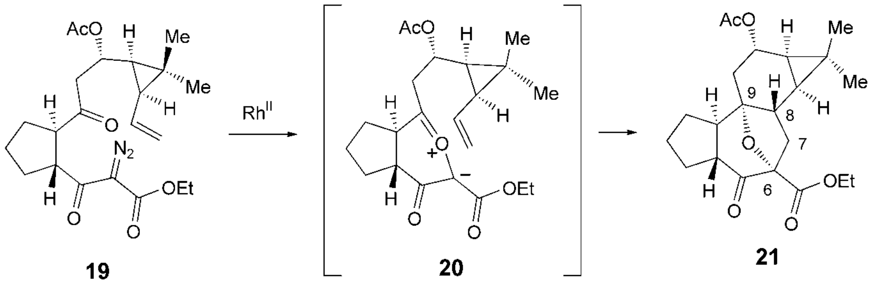
This methodology was initially applied to the synthesis of *exo*- and *endo*-brevicomin [35], **17** and **18**, respectively (*Scheme 5*). The *exo*- and *endo*-isomers of brevicomin are excluded by the female Western Pine Beetle and the *exo*-isomer **17** is known to be a key component of the aggregation pheromone of this destructive pest [36]. Cycloaddition of 1-diazohexane-2,5-dione with $Rh_2(OAc)_4$ in the presence of propanal afforded the 6,8-dioxabicyclo[3.2.1]octane ring system in 60% isolated yield as a 2 : 1 mixture of *exo*- and *endo*-isomers, **15** and **16**, respectively. The isomers were separated by silica-gel chromatography and were subsequently carried on to *exo*- and *endo*-brevicomin (**17** and **18**, resp.) in good yield.

Scheme 5



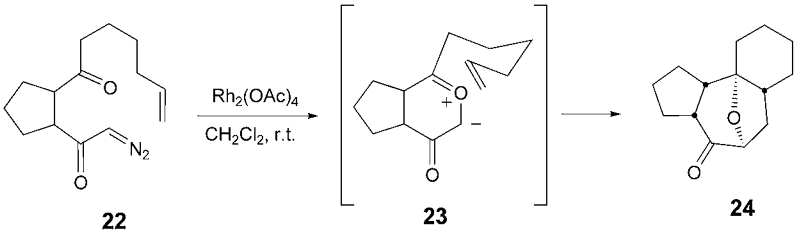
Application of the Method toward Complex Natural Products. – The intramolecular trapping of carbonyl-ylide dipoles with an alkene has evolved into an extremely effective cascade for the synthesis of a variety of novel oxypolycyclic ring systems since the original *Huisgen* report [27]. An interesting application of this method is found as the central step of *Dauben*'s synthesis of the tigliane ring system (*Scheme 6*) [37]. Carbonyl ylide **20**, generated from the diazocarbonyl **19** in the presence of a catalytic amount of rhodium(II) acetate, underwent an intramolecular addition with the olefin to form the C_6,C_9-oxido-bridged tigliane ring system **21**. The two new stereocenters at C(8) and C(9) were formed with the correct configurations relative to C(14) and C(15) presented by the natural tigliane compounds. The high stereospecificity in the ring-closure reaction could be related to steric interactions or the introduction of conformational strain in the tether which disfavors the transition state where the cyclopropane ring and the oxido bridge are on the same side of the molecule.

Scheme 6

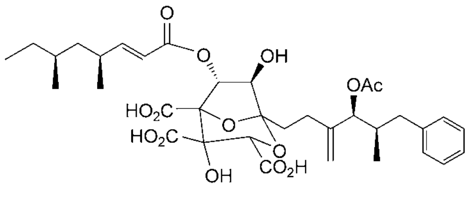


Another successful cyclization of this type was carried out by *McMills et al.* [38] to produce a simple phrobol analog devoid of most of the oxygenation (*Scheme 7*). Reaction of diazo ketone **22** with $Rh_2(OAc)_4$ produced the transient oxonium ylide **23**, which was trapped by the tethered olefin in a 1,3-dipolar cycloaddition reaction to form tetracyclic ether **24** as a single isomer in 55% yield. An X-ray crystal-structure analysis showed the H-atom at C(8) to be located in a *syn*-relationship with the H-atoms which are *cis* at the A–B ring fusion. The stereoselectivity of addition of the tethered olefin to the 1,3-dipole was attributed to nonbonded interactions in the transition state where the olefinic side chain adopts a chair-like conformation in the *endo*-mode. This tandem cyclization–cycloaddition strategy represents a particularly efficient approach for the construction of the basic phorbol skeleton [39].

Scheme 7

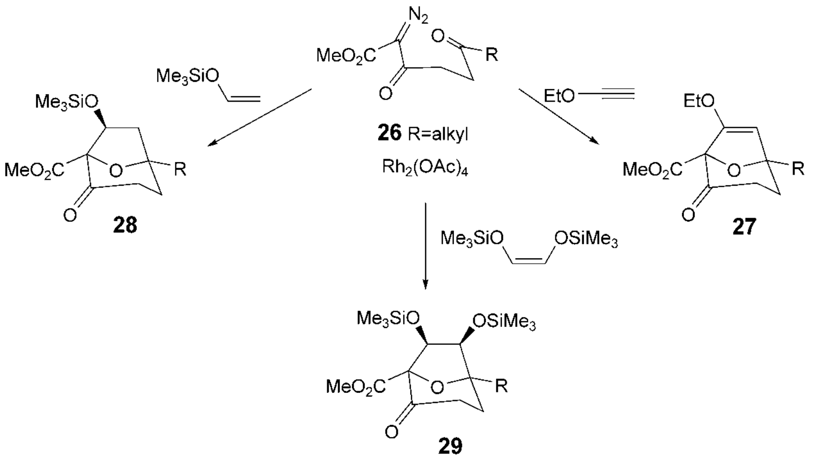


The Rh^{II}-induced tandem cyclization–cycloaddition process has also been applied with notable success to the core structure of zaragozic acid (**25**) by the *Merck* research group [40]. Compound **25** was discovered as a metabolite from an unidentified sterile fungus and was identified as a potent inhibitor of squalene synthase. This compound has been actively pursued as a synthetic target because of its potential as a cholestorol-lowering agent as well as its unique structure [41]. The Rh-carbenoid cycloaddition cascade allows for the rapid assemblage of the bicyclic core structure of **25** in a single step. The configuration of the resulting cycloadducts (*i.e.*, **27**–**29**) was confirmed by NOESY spectra as well as single-crystal X-ray analysis. The cycloadditions represent the first examples of using vinyloxytrialkyl silanes and an alkoxyacetylene as dipolarophiles in the cyclization–cycloaddition reaction. Interestingly, relatively electron-deficient dipolarophiles such as methyl acrylate or methyl propiolate failed to trap the 1,3-dipole, even though they added smoothly to simpler diazo ketones. Thus, the order of dipolarophile reactivity switches depending on the presence or absence of an extra carboxy group on the dipole and can be well accounted for by FMO theory (*Scheme 8*).



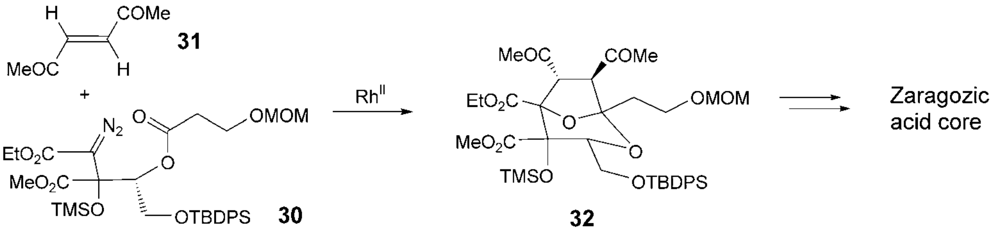
Zaragozic acid A (**25**)

Scheme 8



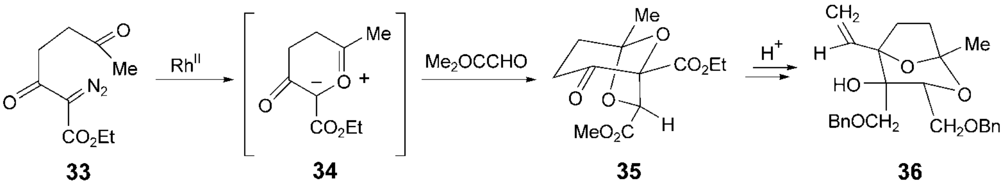
A highly efficient construction of the 2,8-dioxabicyclo[3.2.1]octane core structure of **25** was achieved by *Hashimoto* and co-workers by exploiting the sequence of Rh^{II}-mediated intramolecular carbonyl-ylide formation from α-diazo ester **30**, followed by a stereocontrolled 1,3-dipolar cycloaddition with (*E*)-hex-3-ene-2,5-dione (**31**; *Scheme 9*) [42]. The cascade sequence proceeded in 47% yield and afforded a single diastereoisomer **32**, whose structure was established by ^{1}H-NOE experiments. Addition of the dipolarophile is presumed to proceed exclusively from the β-face of the carbonyl-ylide intermediate so as to avoid non-bonding interaction with the pseudoaxial trimethylsilyloxy (TMSO) group at C(4) in the transition state. The activating groups in the dipolarophile are better accommodated in a less-crowded space. A remaining task for the *Hashimoto* group is to convert cycloadduct **32** to various members of the zaragozic acid family.

Scheme 9



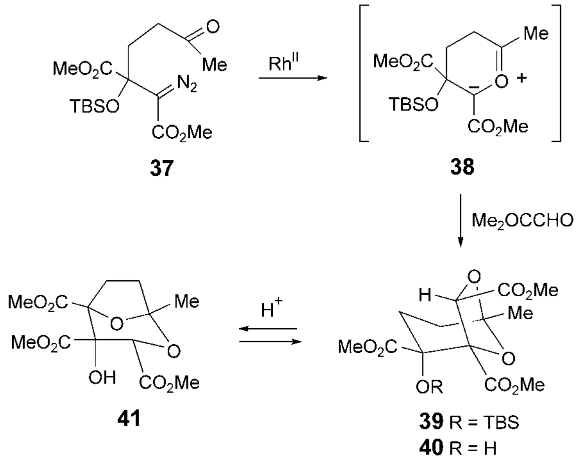
A related dipolar-cycloaddition approach toward zaragozic acid (**25**) was reported by *Hodgson et al.* who investigated the $[3+2]$ cycloaddition of carbonyl ylide **34** derived from α-diazo-β,ε-diketo ester **33** and methyl glyoxylate (*Scheme 10*) [43]. The resulting cycloadduct **35** was converted to a substrate which underwent an acid-catalyzed rearrangement to the 2,8-dioxabicyclo[3.2.1]octane **36**. However, the incorrect relative configuration of zaragozic acid (**25**) was obtained, and this originates from a favored *endo*-cycloaddition. The preference for *endo*-attack was suggested to be due to a preferred secondary orbital overlap between the ester C=O group of the glyoxylate (in the s-*trans*-conformation) and the C=O group of the carbonyl-ylide intermediate **34**.

Scheme 10



In a follow-up report, *Hodgson* and *Villalonga-Barber* found that the Rh^{II}-catalyzed cycloaddition of diazo-keto diester **37** with methyl glyoxylate furnished cycloadduct **39** ($R = (t\text{-Bu})Me_2Si$ (TBS)) whose configuration now corresponds to that required for a zaragozic acid synthesis (*Scheme 11*) [44]. Replacement of the β-keto group found in α-diazo-β,ε-diketo ester **33** with the bulky α-silyloxy ester functionality in diazo-keto diester **37** resulted in the formation of ylide **38** where cycloaddition preferentially occurred on the less-hindered face opposite to the silyloxy group. With this system, methyl glyoxylate prefers to orient itself in such a manner as to avoid steric interactions between its ester group, and the ester group of the α-silyloxy ester functionality thereby accounting for the cross-over in configuration. Deprotection of cycloadduct **39** gave alcohol **40**, which, when subjected to trifluoroacetic acid (TFA), resulted in an acid-catalyzed rearrangement to produce the 2,8-dioxabicyclo[3.2.1]octane skeleton of the zaragozic acids. That a true acid-induced equilibrium had been reached was established by subjecting core **41** to the TFA conditions, which resulted in the same ratio (*i.e.*, 1:2)

Scheme 11

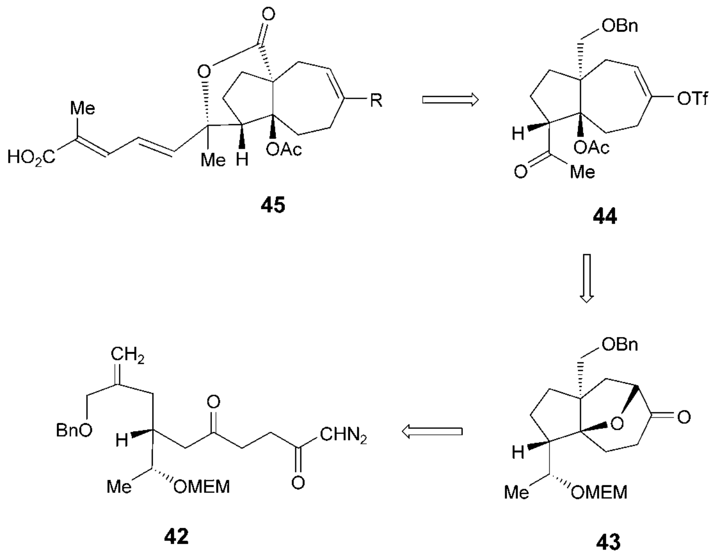


of alcohols **40**/**41**. Further studies by the *Hodgson* group are still in progress with the fully oxygenated 6,7-dioxy core of zaragozic acid (**25**).

Another application of the tandem carbenoid cyclization–intramolecular cycloaddition reaction for the synthesis of a complex natural product is found in some work of *Chiu et al.* who used this methodology to prepare advanced intermediates directed toward the synthesis of pseudolaric acids [45]. Pseudolaric acids are a family of diterpenes isolated from the root bark of a tree native to the Zhejiang province in China [46]. These novel compounds show both antimicrobial activity and cyctotoxicity against several cancer cell lines. *Chiu*'s retrosynthetic analysis is outlined in *Scheme 12* and is related to that previously used by *Dauben et al.* [37] and *McMills et al.* [38]. Oxatricyclic ketone **43** was envisioned as the key intermediate that could be constructed by a reaction cascade initiated by the decomposition of an appropriately functionalized acyclic diazo ketone **42**. The metal carbenoid was expected to undergo cyclization intramolecularly with the C=O group to form a cyclic carbonyl ylide, and this would be followed by intramolecular [3+2] cycloaddition with the 2,2-disubstituted olefin to give the oxatricyclic intermediate. Enol trifluoromethanesulfonate (triflate) **44** was envisaged as being formed by reductive elimination from the oxatricyclic ketone **43**, in which the tertiary acetate has been masked as an O-bridge. *Chiu et al.* found that substrate-controlled diastereoselectivity of the tandem sequence was preferential for the undesired diastereoisomer [45], but reagent control through the use of a chiral Rh^{II} catalyst (*vide infra*) [17] reversed the selectivity in favor of cycloadduct **43**. Ring opening of the oxabicyclic nucleus to give a hydroxycycloheptene was demonstrated in a model study. Elaboration of **43** toward the completion of the total synthesis of the pseudolaric acids and their analogues is currently being pursued by the *Chiu* group.

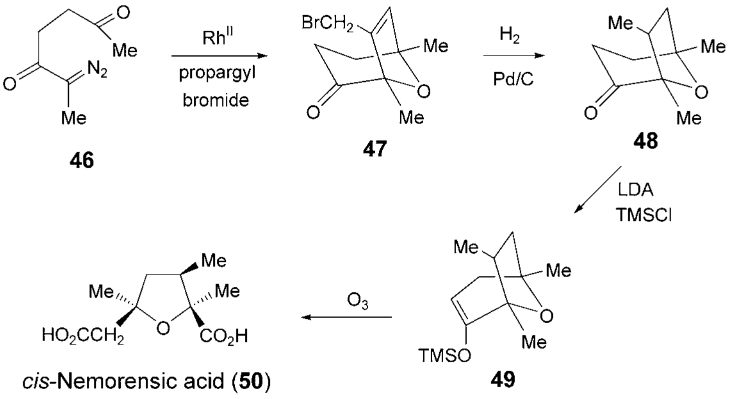
A further example that highlights the versatility of the tandem cascade sequence for the synthesis of structurally complex tetrahydrofurans was recently reported by *Hodgson et al.* [47]. 1,3-Dipolar cycloaddition of propargyl bromide with the carbonyl

Scheme 12



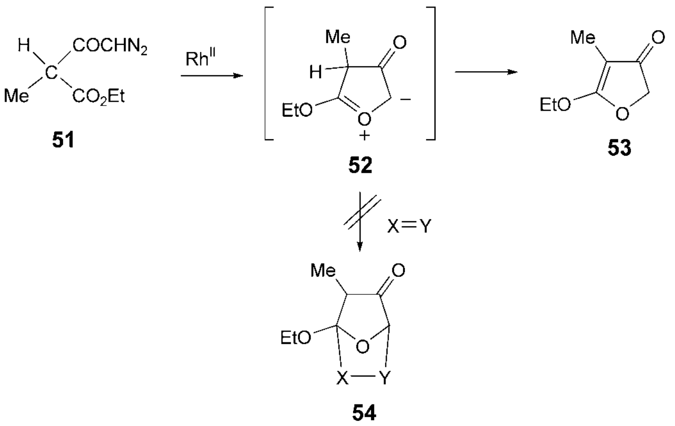
ylide derived from 6-diazoheptane-2,5-dione represents the key step in a concise synthesis of *cis*-nemorensic acid (**50**) [48]. Thus, diazo dione **46** underwent $Rh_2(OAc)_4$-catalyzed tandem carbonyl-ylide formation–cycloaddition with propargyl bromide to give cycloadduct **47** in good yield (*Scheme 13*) [47]. Reaction of cycloadduct **47** with H_2-Pd/C in MeOH led to both hydrogenolysis of the C–Br bond and *exo*-selective alkene hydrogenation to furnish a single saturated ketone **48** with the correct relative configuration at all three stereocenters for *cis*-nemorensic acid synthesis. Formation of the silyl enol ether **49** under standard conditions was followed by oxidative cleavage to give *cis*-nemorensic acid (**50**).

Scheme 13



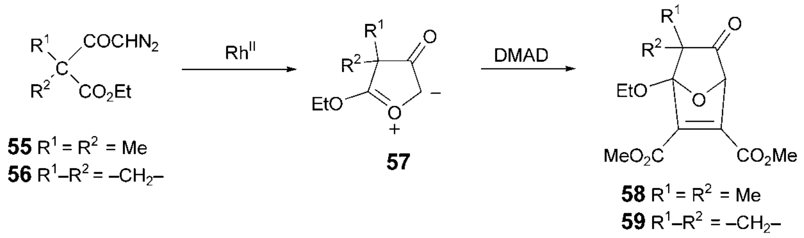
Five-Membered-Ring Dipole Formation. – The primary spatial requirement for carbonyl-ylide formation is that the distance between the two reacting centers should be sufficiently close so that effective overlap of the lone pair of electrons on the C=O group with the metallocarbenoid center can occur. The effect that variation in the spatial proximity between the C=O group and the diazo ketone would have on the course of the reaction was studied by varying the length of the CH_2 tether separating the two functionalities [34]. The majority of systems examined in the literature involved the formation of a six-membered ring carbonyl-ylide intermediate. The ease of ring closure as a function of ring size generally increases on going from three- to five-membered rings and then decreases rapidly [49]. This observation is perfectly compatible with the fact that five-membered-ring carbonyl-ylide formation occurs smoothly upon treatment of 1-diazobutanediones with Rh^{II} carboxylates [34]. For example, the reaction of ethyl 4-diazo-2-methyl-3-oxobutyrate (**51**) with the Rh^{II} catalyst afforded 2,3-dihydro-5-ethoxy-4-methylfuran-3-one (**53**) in 90% isolated yield (*Scheme 14*). The mechanism by which **51** is converted to **53** involves rapid cyclization of the Rh-carbenoid onto the neighboring C=O group to give the five-membered-ring carbonyl ylide **52**, which undergoes a subsequent proton transfer [50]. All attempts to trap the suspected 1,3-dipole **52** with a variety of dipolarophiles failed to produce a dipolar cycloadduct. Apparently, the highly stabilized dipole **52** transfers a proton at a faster rate than bimolecular cycloaddition. The formation of furanone **53** comes as no real surprise, since one of the characteristic reactions of carbonyl ylides derived from the reaction of α-diazoalkanes with ketones consists of an intramolecular proton transfer [50].

Scheme 14



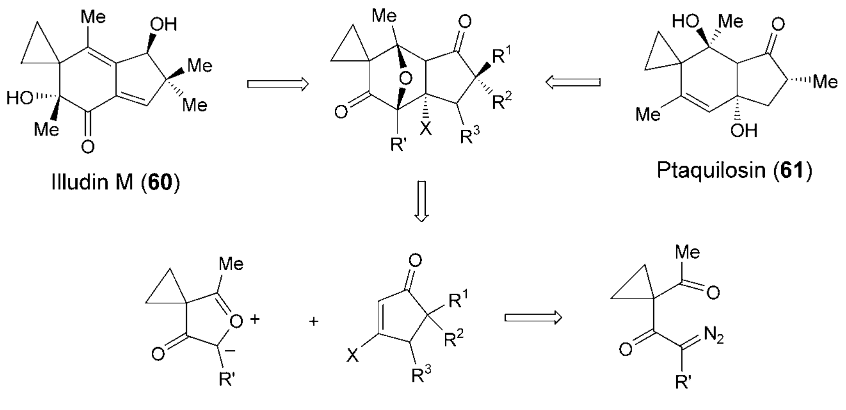
When the α-position of the 1-diazobutanedione skeleton was blocked with two substituent groups (*i.e.*, **55** or **56**), the Rh^{II}-catalyzed cycloaddition with dimethyl acetylenedicarboxylate (DMAD) led to the carbonyl-ylide cycloadducts **58** (85%) or **59** (55%), respectively (*Scheme 15*) [34].

Scheme 15



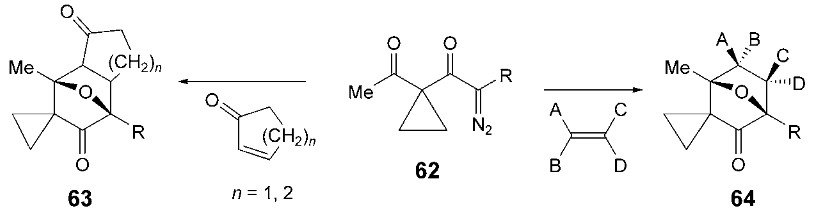
Products of five-membered-ring carbonyl-ylide cycloaddition derived from α-diazo ketone **62** can undergo cleavage of the oxabicyclic ring system to produce the core structure of the illudin M (**60**) and ptaquiloxin (**61**) family of sesquiterpenes [51]. This strategy provides a rapid assembly of the basic core unit of the target molecules having most of the functionality in place (*Scheme 16*). Thus, the Rh^{II}-catalyzed cycloaddition reaction of cyclopropyl-substituted α-diazo ketones of type **62** with a variety of acyclic and cyclic alkenes gave 7-oxabicyclo[2.2.1]octanes **63** and **64**. These could be readily cleaved with base or samarium iodide to produce the desired skeleton (*Scheme 17*).

Scheme 16

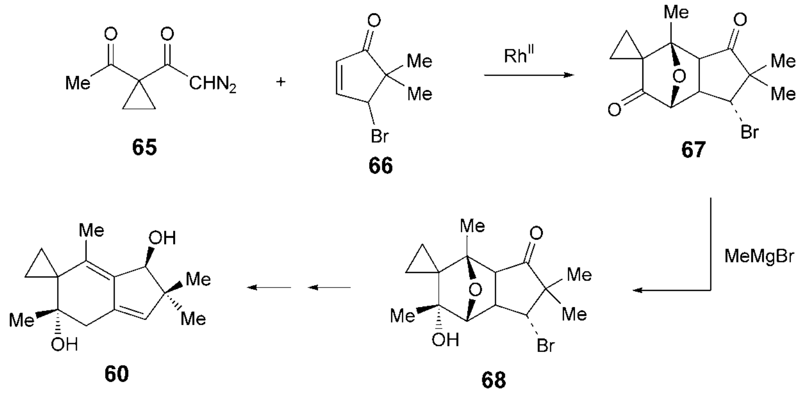


(±)-Illudin M (**60**), a toxic sesquiterpene isolated from the jack-o'-lantern mushroom, has been synthesized *via* the same tandem cyclization–cycloaddition strategy involving diazo ketone **65**. The first and key step of the synthesis consisted of a carbonyl-ylide 1,3-dipolar cycloaddition reaction with cyclopentenone **66** to form cycloadduct **67** with high diastereoselectivity. Several functional group manipulations were carried out to eventually give illudin M (**60**) in modest yields (*Scheme 18*) [52].

Scheme 17



Scheme 18

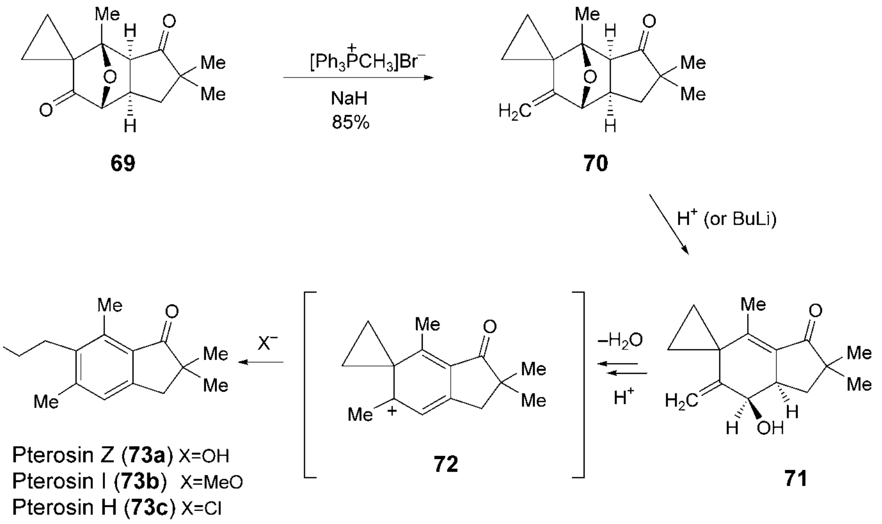


Several members of the pterosin family of sesquiterpenes were also synthesized by a related tandem-cyclization approach [52]. A major obstacle to the synthesis of the pterosins is the problem of regioselective construction of the penta-substituted aromatic ring. The earlier approaches have relied heavily on classical electrophilic substitution reactions with their inherent problems of regiocontrol [53]. The facile preparation of pterosins H, I, and Z was reported by the author's group [54] and relies on a dipolar cycloaddition of a cyclic carbonyl-ylide dipole as the key step of the synthesis. The synthesis involved treating cycloadduct **69** with $[Ph_3PMe]^+Br^-$ in the presence of NaH and isolating the expected *Wittig* product **70**. By using the appropriate acid–solvent combination, it was possible to obtain each of the pterosins **73a**–**73c** in one step from the key reactive intermediate **72** (*Scheme 19*).

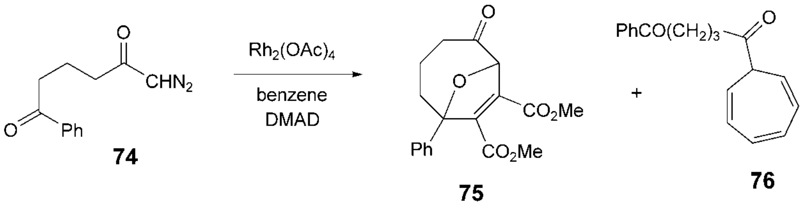
Separating the C=O group from the carbenoid center with three CH_2 units resulted in the formation of a seven-membered-ring carbonyl-ylide intermediate [34]. Thus, the Rh^{II}-catalyzed reaction of 1-diazo-6-phenylhexane-2,6-dione (**74**) in benzene with DMAD afforded a 2:1 mixture of cycloadduct **75** (45%) as well as cycloheptatriene **76** (22%; *Scheme 20*). It would appear that, by extending the tether to three CH_2 groups, the rate of intramolecular cyclization is sufficiently retarded to allow the bimolecular reaction with benzene to occur.

Varying the length of the tether that separates the olefin from the carbonyl-ylide dipole also allows for the synthesis of a variety of interesting oxopolycyclic ring systems. Diazo ketones tethered to the C=O group by three CH_2 units were shown to cyclize

Scheme 19



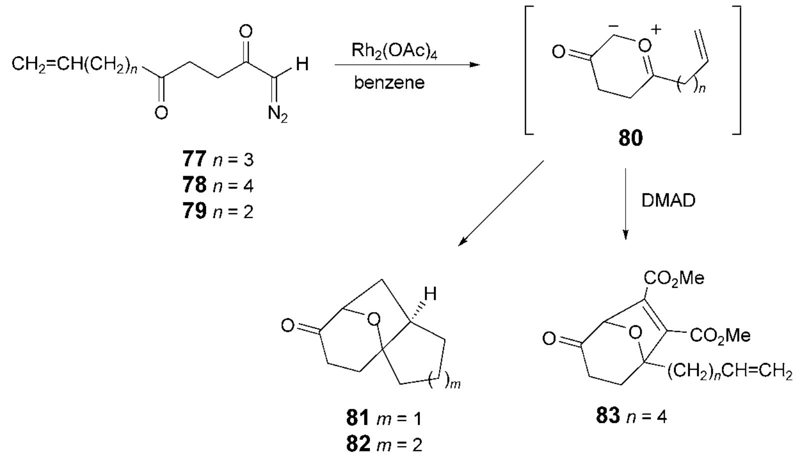
Scheme 20



most efficiently. For example, treatment of diazo ketone **77** with $Rh_2(OAc)_4$ in the presence of DMAD gave cycloadduct **81** in high yield [34]. In this case, the intramolecular trapping reaction occurs at such a fast rate that the bimolecular cycloaddition reaction cannot compete with it. The homologous diazo ketone **78** was also treated with catalytic $Rh_2(OAc)_4$ in benzene at 25° producing cycloadduct **82** in 50% yield. With this system, the carbonyl ylide was readily trapped with the added dipolarophile affording the bimolecular cycloadduct **83** as the exclusive cycloadduct (*Scheme 21*). Increasing the length of the tether to five CH_2 units gave no internal cycloadduct. Apparently, the π-bond is not in close enough proximity to the dipole centers to allow the cycloaddition to occur. Diazo ketone **79**, which contains only two CH_2 units in the tether, produced none of the internal cycloadduct. Clearly the intramolecular trapping of carbonyl ylides by tethered olefins occurs best when the tether contains three or four CH_2 units.

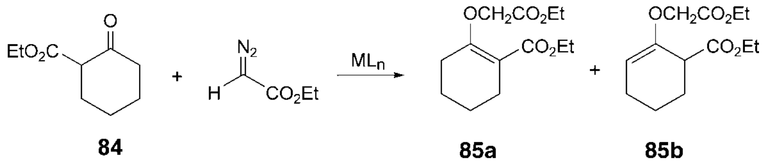
Metal-Complexed Carbonyl Ylides. – One of the first suggestions that carbonyl ylides derived from metal-catalyzed diazo decomposition could proceed *via* a metal-complexed dipole was made by *Landgrebe* and co-workers in 1989 [55]. The Rh^{II}-

Scheme 21



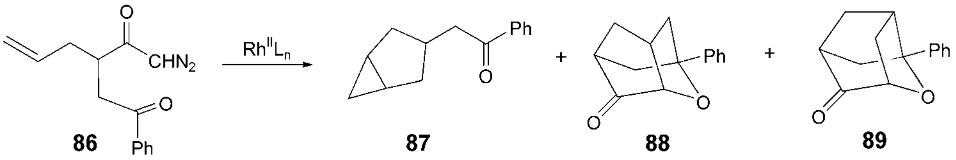
catalyzed reaction of ethyl diazoacetate with *β*-keto ester **84** afforded a mixture of enol ethers **85a** and **85b**, which are derived from an intermediate carbonyl-ylide intermediate (*Scheme 22*). Most interestingly, the ratio of regioisomeric enol ethers was found to be catalyst-dependent, which led *Landgrebe* and co-workers to conclude that the catalyst is present during the 1,4-sigmatropic shift of H [55].

Scheme 22



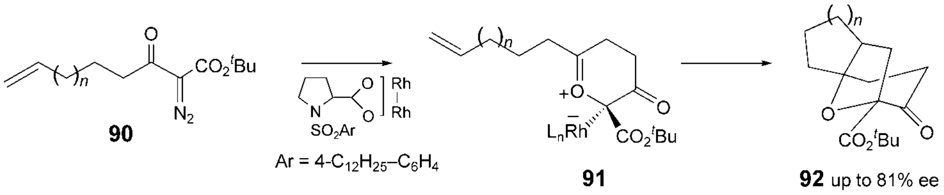
Another study originated from the author's laboratory provides even more definitive support for the involvement of a metal-associated dipole in a diazo-catalyzed cycloaddition reaction [56]. A series of competition experiments were carried out using diazo ketone **86** (*Scheme 23*). Although the chemoselectivity profile was found to be insensitive to the catalyst used, a regiochemical crossover in the carbonyl-ylide cycloaddition *vs.* cyclopropanation was observed on changing the catalyst. The major regioisomer formed used $Rh_2(OAc)_4$ or $Rh_2(cap)_4$ (cap = caprolactamate) was found to be **88**. However, cycloadduct **89** was the predominant product formed under $Rh_2(tfa)_4$ (tfa = trifluoroacetate) catalysis. Intramolecular cyclopropanation (*i.e.*, **87**) occurs to a considerable extent with all of the Rh^{II} catalysts and is significantly enhanced using $[Cu(acac)_2]$ or $[PdCl_2(PhCN)_2]$. These results strongly suggest that the catalyst is coordinated with the dipole, and this metal-complexed species is involved in the cycloaddition.

Scheme 23



Once the metal-complexed carbonyl ylide is formed from the diazo-catalyzed decomposition, there are two possibilities for the subsequent cycloaddition. If the catalyst remains associated with the carbonyl ylide during the [3 + 2] reaction, then asymmetric induction may be observed. Alternatively, the catalyst could dissociate and, therefore, not be involved in the subsequent carbonyl-ylide reaction. Recent developments over the past several years have shown that catalytic asymmetric synthesis in a number of carbonyl-ylide transformations is possible [17]. *Hodgson et al.* reported the first examples of enantioselective carbonyl-ylide cycloaddition (up to 81% ee) using unsaturated α-diazo-β-keto esters (*Scheme 24*) [57]. Because the catalyst-free carbonyl ylide would be achiral, the observation of enantioselectivity provides unambiguous evidence for an enantioselective ylide transformation taking place *via* a catalyst-complexed intermediate (*i.e.*, **91**).

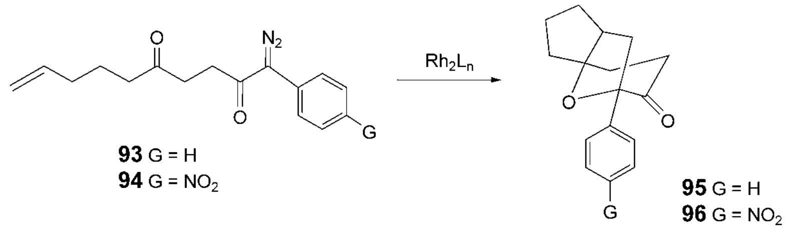
Scheme 24



In a later report by the same group, the scope and generality of the catalytic enantioselective tandem carbonyl-ylide cycloaddition was further evaluated using a series of related unsaturated 2-diazo-3,6-diketo esters [58]. The cycloadditions were found to proceed in moderate-to-good yields, with a difference in ee exhibited by the electronically different diazo keto esters used. Values for ee up to 90% for alkene dipolarophiles and up to 86% for alkyne dipolarophiles were obtained.

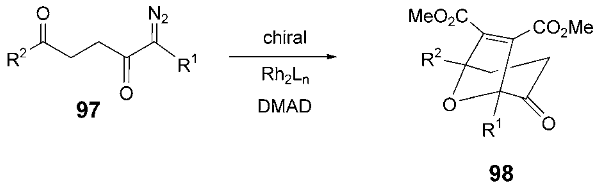
An evaluation of α-aryl-α-diazo diones in tandem carbonyl-ylide formation–enantioselective [3 + 2] cycloaddition was also carried out by *Hodgson et al.* [59]. The substrates were designed to allow investigation of the electronic characteristics of the dipole upon asymmetric induction. Once again, electronic factors were found to play a key role in determining the outcome of the cycloaddition reactions with enantioselectivities of up to 76% ee (*Scheme 25*) [60].

Scheme 25



Enantioselective tandem carbonyl-ylide formation–intermolecular cycloadditions have also been reported by *Doyle* and *Forbes* [61], *Ibata* and co-workers [62], and *Hashimoto* and co-workers [63]. The asymmetric induction in these cycloadditions was generally low (< 30% ee), aside from the work of *Hashimoto* and co-workers using α-diazo ketones with DMAD as the dipolarophile, where ee values up to 92% were reported (*Scheme 26*) [63]. Only a small range of dipolarophiles have been examined in asymmetric intermolecular cycloadditions of carbonyl ylides, and, of these, only DMAD, used by *Hashimoto* and co-workers has met with any real success [63]. More recent studies by *Hodgson et al.* with α-aryl-α-diazo diones suggest that a complex blend of electronic effects from the dipole and dipolarophile, together with the nature of the catalyst, contribute to the origin of asymmetric induction [60].

Scheme 26



Conclusions. – Tandem carbonyl-ylide generation from the reaction of metallocarbenoids with carbonyl compounds originates from the early studies of *Rolf Huisgen* and co-workers and continues to be of great interest both mechanistically and synthetically. Effective carbonyl-ylide formation in transition metal catalyzed reactions of diazo compounds depends on the catalyst, the diazo species, the nature of the interacting C=O group, and competition with other processes. The many structurally diverse and highly successful examples of tetrahydrofuran formation cited in this mini-review clearly indicate that the tandem cyclization–cycloaddition cascade of metallocarbenoids has evolved as an important strategy in carbocyclic synthesis. As is the case in all new areas of research using catalysts, future investigations of the chemistry of these transition-metal-catalyzed diazo decompositions will be dominated by the search for asymmetric synthesis. From the results already in hand, it seems that efficient catalyst control over enantioselectivity can eventually be developed. Future developments will also depend on gaining a greater understanding of the mechanistic details of these fascinating and synthetically important processes.

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REFERENCES

[1] J. Hartung, *Eur. J. Org. Chem.* **2001**, 619; P. A. Bartlett, J. Myerson, *J. Am. Chem. Soc.* **1978**, *100*, 3950; W. Friedrichson, in 'Comprehensive Heterocyclic Chemistry II', Ed. C. W. Bird, Pergamon Press, Oxford, 1996, Vol. 2, 351; M. C. Elliott, E. Williams, *J. Chem. Soc., Perkin Trans. 1* **2001**, 2303.

[2] J. W. Westley, 'Polyether Antibiotics: Naturally Occurring Acid Ionophores', Marcel Dekker, Vol. I and II, New York, 1982; Y. Kishi, G. Schmid, T. Fukuyama, K. Akasaka, *J. Am. Chem. Soc.* **1979**, *101*, 259.

[3] Y. Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James, K. Nakanishi, *J. Am. Chem. Soc.* **1981**, *103*, 6773; Y. Shimizu, H. N. Chou, H. Bando, G. Van Duyne, J. C. Clardy, *J. Am. Chem. Soc.* **1986**, *108*, 514.

[4] R. E. Moore, in 'Marine Natural Products: Chemical and Biological Perspectives', Ed. P. J. Scheuer, Academic Press, New York, 1978, Vol. 1.

[5] E. Piers, V. Karunaratne, *J. Org. Chem.* **1983**, *48*, 1774; P. Magnus, D. Gange, L. Bass, E. V. Arnold, J. Clardy, *J. Am. Chem. Soc.* **1980**, *102*, 2134; D. Gange, P. Magnus, *J. Am. Chem. Soc.* **1978**, *100*, 7746; C. Brückner, H. U. Reissig, *J. Org. Chem.* **1988**, *53*, 2440.

[6] K. Fugami, K. Oshima, K. Utimoto, *Tetrahedron Lett.* **1987**, *28*, 809; W. Eberbach, B. Burchardt, *Chem. Ber.* **1978**, *111*, 3665; T. Kauffmann, *Angew. Chem., Int. Ed.* **1974**, *13*, 627; H. Ochiai, T. Nishihara, Y. Tamaru, Z. Yoshida, *J. Org. Chem.* **1988**, *53*, 1343; S. E. Drewes, R. F. A. Hoole, *Synth. Commun.* **1985**, *15*, 1067; B. M. Trost, S. A. King, T. Schmidt, *J. Am. Chem. Soc.* **1989**, *111*, 5902.

[7] '1,3-Dipolar Cycloaddition Chemistry', Ed. A. Padwa, Wiley-Interscience, New York, 1984; A. Padwa, W. H. Pearson, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products', John Wiley & Sons, Inc., 2003.

[8] R. Huisgen, *Angew. Chem., Int. Ed.* **1977**, *16*, 572.

[9] G. W. Griffin, A. Padwa, in 'Photochemistry of Heterocyclic Compounds', Ed. O. Buchart, Wiley, New York, 1976, Chapt. 2.

[10] P. K. Das, G. W. Griffin, *J. Photochem.* **1984**, *27*, 317.

[11] M. Békhazi, P. J. Smith, J. Warkentin, *Can. J. Chem.* **1984**, *62*, 1646.

[12] N. Shimizu, P. D. Bartlett, *J. Am. Chem. Soc.* **1978**, *100*, 4260.

[13] R. W. Hoffmann, H. Luthardt, *J. Chem. Ber.* **1968**, *101*, 3861.

[14] D. Keus, M. Kaminski, J. Warkentin, *J. Org. Chem.* **1984**, *49*, 343; M. Bèkhazi, J. Warkentin, *J. Am. Chem. Soc.* **1983**, *105*, 1289; M. Bèkhazi, J. Warkentin, *Can. J. Chem.* **1983**, *61*, 619.

[15] M. P. Doyle, M. A. McKervey, T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds', John Wiley & Sons, New York, 1998.

[16] A. Padwa, S. F. Hornbuckle, *Chem. Rev.* **1991**, *91*, 263; A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223; A. Padwa, *Top. Curr. Chem.* **1997**, *189*, 121.

[17] D. M. Hodgson, F. Y. T. M. Pierard, P. A. Stupple, *Chem. Soc. Rev.* **2001**, *30*, 50; M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919; G. Mehta, S. Muthusamy, *Tetrahedron* **2002**, *58*, 9477.

[18] G. Maas, *Top. Curr. Chem.* **1987**, *137*, 75.

[19] H. Tomioka, T. Miwa, S. Suzuki, Y. Izawa, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 753.

[20] G. K. S. Prakash, R. W. Ellis, J. D. Felberg, G. A. Olah, *J. Am. Chem. Soc.* **1986**, *108*, 1341.

[21] P. C. Wong, D. Griller, J. C. Scaiano, *J. Am. Chem. Soc.* **1982**, *104*, 6631.

[22] J. C. Scaiano, W. G. McGimpsey, H. L. Casal, *J. Am. Chem. Soc.* **1985**, *107*, 7204.

[23] E. P. Janulis Jr., A. J. Arduengo III, *J. Am. Chem. Soc.* **1983**, *105*, 5929.

[24] R. S. Becker, R. O. Bost, J. Kolc, N. R. Bertoniere, R. L. Smith, G. W. Griffin, *J. Am. Chem. Soc.* **1970**, *92*, 1302.

[25] E. Buchner, T. Curtius, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2371.

[26] W. Dieckmann, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1024.

[27] P. de March, R. Huisgen, *J. Am. Chem. Soc.* **1982**, *104*, 4952.

[28] R. Huisgen, P. de March, *J. Am. Chem. Soc.* **1982**, *104*, 4953.

[29] M. Alt, G. Maas, *Tetrahedron* **1994**, *50*, 7435; M. P. Doyle, D. C. Forbes, M. N. Protopopova, S. A. Stanley, M. M. Vasbinder, K. R. Xavier, *J. Org. Chem.* **1997**, *62*, 7210; B. Jiang, X. Zhang, Z. Luo, *Org. Lett.* **2002**, *4*,

2453; C.-D. Lu, Z.-Y. Chen, H. Liu, W.-H. Hu, A.-Q. Mi, *Org. Lett.* **2004**, *6*, 3071; H. M. L. Davies, J. DeMeese, *Tetrahedron Lett.* **2001**, *42*, 6803.

[30] A. E. Russell, J. Brekan, L. Gronenberg, M. P. Doyle, *J. Org. Chem.* **2004**, *69*, 5269; M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 933.

[31] T. Ibata, J. Toyoda, M. Sawada, T. Tanaka, *J. Chem. Soc., Chem. Commun.* **1986**, 1266; T. Ibata, J. Toyoda, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2489 and refs. cit. therein.

[32] A. Padwa, S. P. Carter, H. Nimmesgern, *J. Org. Chem.* **1986**, *51*, 1157; A. Padwa, S. P. Carter, H. Nimmesgern, P. D. Stull, *J. Am. Chem. Soc.* **1988**, *110*, 2894; A. Padwa, P. D. Stull, *Tetrahedron Lett.* **1987**, *28*, 5407.

[33] A. Padwa, G. E. Fryxell, L. Zhi, *J. Org. Chem.* **1988**, *53*, 2875; A. Padwa, G. E. Fryxell, L. Zhi, *J. Am. Chem. Soc.* **1990**, *112*, 3100.

[34] A. Padwa, R. L. Chinn, S. F. Hornbuckle, L. Zhi, *Tetrahedron Lett.* **1989**, *30*, 301; A. Padwa, R. L. Chinn, S. F. Hornbuckle, Z. J. Zhang, *J. Org. Chem.* **1991**, *56*, 3271.

[35] A. Padwa, R. L. Chinn, L. Zhi, *Tetrahedron Lett.* **1989**, *30*, 1491.

[36] R. M. Silverstein, R. G. Brownlee, T. E. Bellas, O. L. Wood, L. E. Browne, *Science* **1968**, *159*, 889.

[37] W. G. Dauben, J. Dinges, T. C. Smith, *J. Org. Chem.* **1993**, *58*, 7635.

[38] M. C. McMills, L. Zhuang, D. L. Wright, W. Watt, *Tetrahedron Lett.* **1994**, *35*, 8311.

[39] P. A. Wender, H. Kogen, H. Y. Lee, J. D. Munger Jr., R. S. Wilhelm, P. D. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8957.

[40] H. Koyama, R. G. Ball, G. D. Berger, *Tetrahedron Lett.* **1994**, *35*, 9185.

[41] A. Nadin, K. C. Nicolaou, *Angew. Chem., Int. Ed.* **1996**, *35*, 1622.

[42] O. Kataoka, S. Kitagaki, N. Watanabe, J. Kobayashi, S. Nakamura, M. Shiro, S. Hashimoto, *Tetrahedron Lett.* **1998**, *39*, 2371.

[43] D. M. Hodgson, J. M. Bailey, T. Harrison, *Tetrahedron Lett.* **1996**, *37*, 4623.

[44] D. M. Hodgson, C. Villalonga-Barber, *Tetrahedron Lett.* **2000**, *41*, 5597.

[45] P. Chiu, B. Chen, K. F. Cheng, *Org. Lett.* **2001**, *3*, 1721.

[46] B. N. Zhou, B. P. Ying, G. Q. Song, Z. H. Chen, J. Han, Y. F. Yan, *Planta Med.* **1983**, *47*, 35.

[47] D. M. Hodgson, T. D. Avery, A. C. Donohue, *Org. Lett.* **2002**, *4*, 1809.

[48] B. Liu, K. D. Moeller, *Tetrahedron Lett.* **2001**, *42*, 7163; F. López, L. Castedo, J. L. Mascareñas, *Chem.–Eur. J.* **2002**, *8*, 884.

[49] J. F. Liebman, A. Greenberg, *Chem. Rev.* **1976**, *76*, 311.

[50] M. S. Kharasch, T. Rudy, W. Nudenberg, G. Büchi, *J. Org. Chem.* **1953**, *18*, 1030.

[51] A. Padwa, V. P. Sandanayaka, E. A. Curtis, *J. Am. Chem. Soc.* **1994**, *116*, 2667.

[52] F. R. Kinder Jr., K. W. Bair, *J. Org. Chem.* **1994**, *59*, 6965; E. A. Curtis, V. P. Sandanayaka, A. Padwa, *Tetrahedron Lett.* **1995**, *36*, 1989.

[53] S. J. Neeson, P. J. Stevenson, *Tetrahedron* **1989**, *45*, 6239.

[54] A. Padwa, E. A. Curtis, V. P. Sandanayaka, *J. Org. Chem.* **1996**, *61*, 73.

[55] A. C. Lottes, J. A. Landgrebe, K. Larsen, *Tetrahedron Lett.* **1989**, *30*, 4089; A. C. Lottes, J. A. Landgrebe, K. Larsen, *Tetrahedron Lett.* **1989**, *30*, 4093.

[56] A. Padwa, D. J. Austin, S. F. Hornbuckle, *J. Org. Chem.* **1996**, *61*, 63.

[57] D. M. Hodgson, P. A. Stupple, C. Johnstone, *Tetrahedron Lett.* **1997**, *38*, 6471.

[58] D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard, M. A. E. Castro, *J. Org. Chem.* **2003**, *68*, 6153.

[59] D. M. Hodgson, R. Glen, A. J. Redgrave, *Tetrahedron Lett.* **2002**, *43*, 3927.

[60] D. M. Hodgson, R. Glen, G. H. Grant, A. J. Redgrave, *J. Org. Chem.* **2003**, *68*, 581.

[61] M. P. Doyle, D. C. Forbes, *Chem. Rev.* **1998**, *98*, 911.

[62] H. Suga, H. Ishida, T. Ibata, *Tetrahedron Lett.* **1998**, *39*, 3165.

[63] S. Kitagaki, M. Anada, O. Kataoka, K. Matsuno, C. Umeda, N. Watanabe, S. Hashimoto, *J. Am. Chem. Soc.* **1999**, *121*, 1417; S. Kitagaki, M. Yasugahira, M. Anada, M. Nakajima, S. Hashimoto, *Tetrahedron Lett.* **2000**, *41*, 5931.

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