Natural Product Synthesis Using Multicomponent Reaction Strategies

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1. Introduction

The preparation of urea by Wöhler constituted a landmark achievement in organic chemistry, and it laid the ground for the early days of target-oriented organic synthesis.[1] Since then, significant progress has been achieved in this discipline; many powerful single bond forming reactions and asymmetric variants have been developed. These discoveries have paved the way for the stereoselective assembly of complex organic molecules, a task deemed inconceivable by early practitioners. A great many strategies were invented by chemists in order to facilitate the synthesis of complex natural products.[2] One avenue in emulating nature's efficiency would

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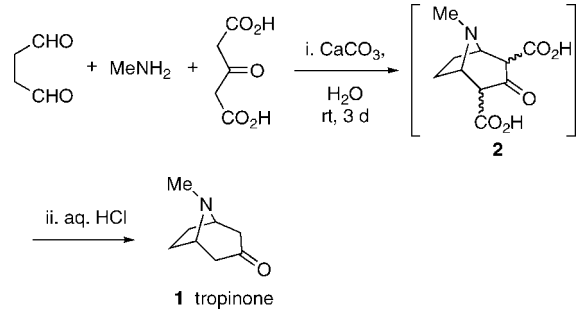
Barry Touré was born in Bamako (Mali). He obtained his undergraduate degree in Chemistry at the Université de Montréal in 1997. Then he moved to the Clinical Research Institute of Montreal (IRCM) to pursue his interest in enzymology and molecular and cellular biology, earning an M.Sc. degree in 1999 under the guidance of Dr. Nabil G. Seidah. He obtained his Ph.D. at the University of Alberta, in 2004, under the guidance of Professor Dennis Hall. He then spent a year and half as an NSERC Postdoctoral Fellow in the laboratory of Professor Dalibor Sames at Columbia University in New York. In 2006, he joined the Oncology Department of the Novartis Institutes for Biomedical Research Inc. in Cambridge, MA.

consist of merging compatible single bond forming processes so as to allow multiple bond forming events between several substrates, a concept generally termed multicomponent reactions (MCRs).

In the context of this review, MCRs are broadly defined, regardless of their mechanistic nature, as "one-pot" processes that combine three or more substrates either simultaneously (so-called "tandem", "domino",[3a,b] or "cascade"[3c] reactions) or through a sequential-addition procedure that does not involve any change of solvent. By minimizing the number of synthetic operations while maximizing the buildup of structural and functional complexity, these highly step-economical reactions are particularly appealing in the context of target-oriented synthesis. These advantages were demonstrated by Robinson as early as 1917, with the efficient one-pot synthesis of the bridged bicyclic alkaloid tropinone (**1**) using a double-Mannich reaction followed by decarboxylation of the MCR product **2** (Scheme 1).[4] Surprisingly, multicomponent reaction strategies remained underexploited for many decades. Their popularity, however, has literally exploded since the advent of combinatorial chemistry in the early 1990s, where MCRs were viewed as ideal reactions to assemble large compound libraries in medicinal chemistry efforts.[5] The current review surveys the applications of MCRs in the total synthesis of natural products reported since the late 1970s. An effort was made to cover the literature in a comprehensive fashion and to include all studies that featured an MCR as a key step in the completed synthesis of a natural product. In cases where no natural product was completed, only exceptionally new or efficient MCRs were included provided they led to a very advanced intermediate related to a specific class of natural products. The preparation of most natural biopolymers such as the synthesis of oligosaccharides by random glycosylation[6] were not described. A distinction was also made between "A + B + C" multicomponent reactions with three different components, and the "A + B + B" variants featuring two of the same or very similar components. Only examples of conceptually novel "A + B + B" MCRs were included. For example, in situ dialkylations of a ketone enolate were not included in this review. Likewise, three-component reactions where one of the components is carbon monoxide[7] (e.g., intermolecular Pauson−Khand reaction, or carbonylative cross-couplings) were not included in this review. The contents of this review cover the literature up until the early part of 2008 and were divided by general mechanistic classes of MCRs regardless of the particular natural product targeted.

Scheme 1. Synthesis of Tropinone Using a Double Mannich 3CR, by Robinson[4]



2. Tandem Conjugate Addition/Electrophilic Enolate Trapping on α,β-Unsaturated Carbonyl Compounds

2.1. Conjugate Addition/Enolate Alkylation

Prostanoids have long captivated scientists for their complex structure and their crucial roles as local hormones in several physiological processes in mammals and other animals.[8] These powerful signaling molecules have significant potential therapeutic value. Because they are produced in nature only in minute amounts, synthetic chemists have

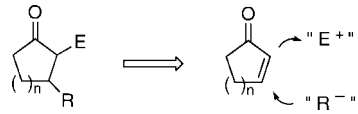
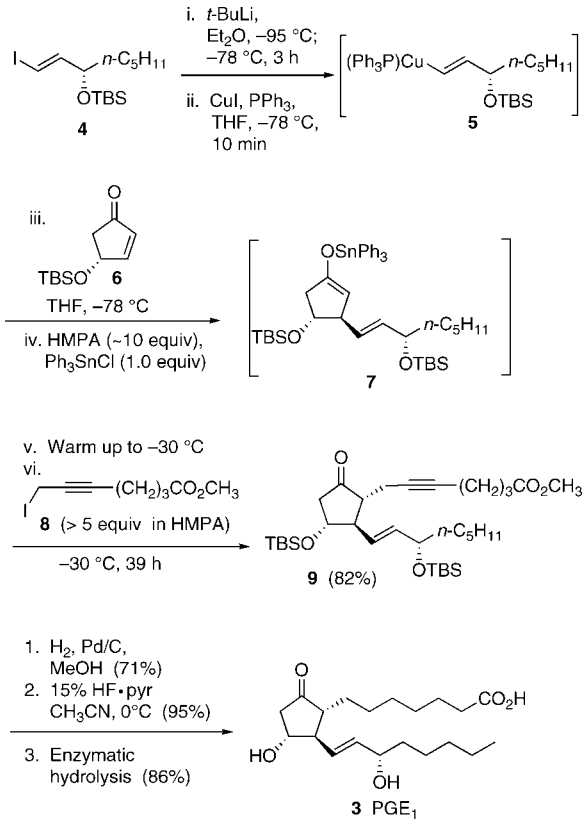


Figure 1. Tandem conjugate addition/electrophilic trapping for the three-component synthesis of 1,2-disubstituted cycloalkanones.

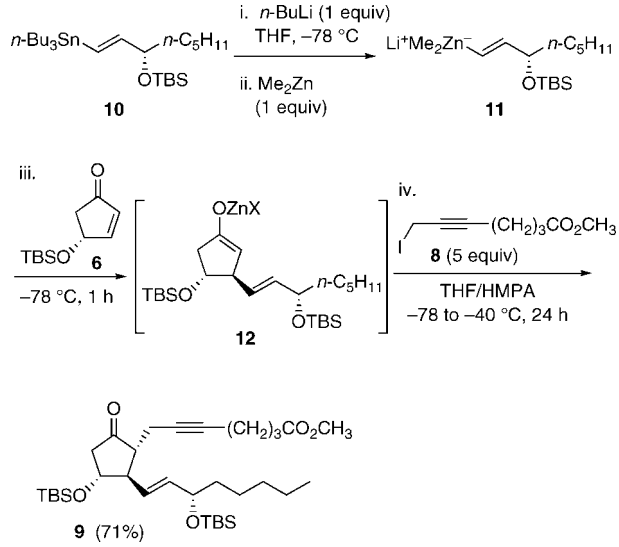
Scheme 2. Synthesis of Prostaglandin E1 Using a Tandem Three-Component Conjugate Addition/Enolate Alkylation on Cyclopentenones, by Noyori and coworkers[13]



devised several strategies with a view of providing practical, large-scale access to the prostaglandins and unnatural analogues thereof.[9] For more than two decades, the Noyori three-component reaction has been one of the most popular synthetic strategies to access *trans*-1,2-disubstituted cyclopentane systems related to prostaglandins and other cyclopentane-containing natural products. This direct and highly convergent three-component reaction strategy, shown in a conceptual way in Figure 1, is based upon the tandem conjugate addition on a cyclic enone followed by electrophilic trapping of the resulting enolate.[10]

Following a first demonstration of feasibility by Stork and Isobe,[11a] early efforts to turn this process into a practical and general procedure were moderately successful.[11] Although the conjugate addition of organocopper reagents was found to proceed efficiently with cyclopentenone derivatives, a one-pot sequential trapping of the transient lithium enolate proved low-yielding, probably due in large part to enolate equilibration.[12] A method was sought by Noyori and co-workers that would allow in situ transmetalation of the Li/Cu enolate into a new, highly nucleophilic metal enolate with a weaker basic character. In this perspective, the use of tin enolates proved highly successful.[13] Thus, as exemplified for the synthesis of prostaglandin E1 (PGE_1) (**3**) (Scheme 2), slow and constant addition of enone **6** into a solution containing the alkenylcopper(I)−triphenylphosphine complex **5** was followed by transmetalation with triphenyltin chloride to give tin enolate intermediate **7**. The reaction vessel was warmed up to −30 °C, and following the addition of propargyl iodide **8**, which was required in a large excess with added hexamethylphosphoramide (HMPA) as cosolvent, compound **9** was isolated in 82% yield. The efficiency of this MCR process was even proven on a multigram scale, and the synthesis of PGE_1 was pursued first through a careful hydrogenation of **9** to leave the C13−C14 double bond intact. Desilylation and enzymatic hydrolysis[14] afforded PGE_1 (**3**) in only four steps from **4**. Both partial hydrogenation of the alkyne and, alternatively, the use of the corresponding *Z*-alkenyl iodide in the trapping operation afforded PGE_2 in high yield (not shown).[13]

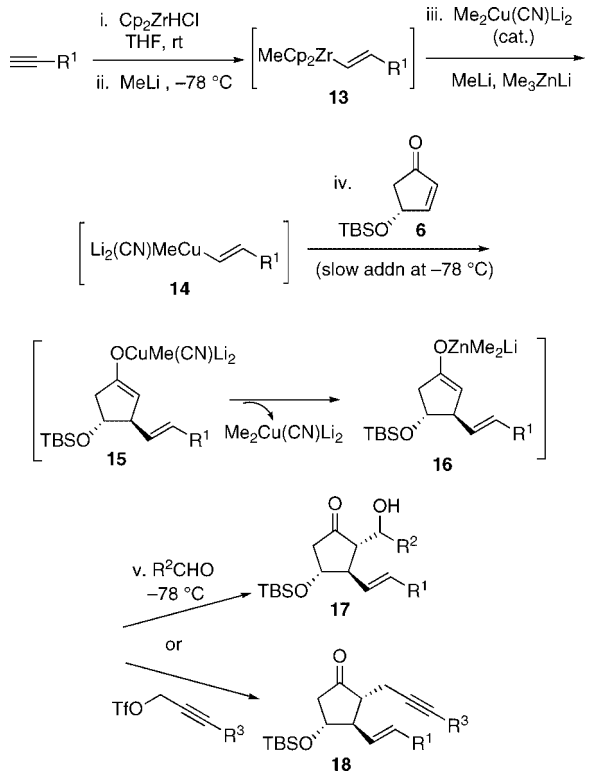
Scheme 3. Variant of the Tandem Three-Component Conjugate Addition/Enolate Alkylation Using Organozincates As Nucleophiles[15]



Furthermore, the synthesis of prostacyclin PGI_2, a potent inhibitor of blood platelet aggregation, further demonstrated that the use of propargylic halides as electrophiles provides optimal flexibility for a general access to naturally occurring prostaglandins.[13] A stereoselective reduction of the cyclopentanone also opened the doors to the synthesis of several other analogues of the D and F series.[13] Noyori and co-workers subsequently developed and optimized an environmentally friendlier (phosphine and tin-free) variant of the above MCR using in situ formed triorganozinc reagents (e.g., dimethylzincate **11**) that allows the process to occur through a more reactive zinc enolate intermediate **12** (Scheme 3).[15] This variant minimizes the undesirable exchange of α-hydrogens, which helps suppress further alkylation, and also leads to a more facile isolation of the final product. Yet, although these improvements expand the breadth of compatible components, in practice only highly reactive electrophiles can be employed (in a large excess) to assemble the α-side chain while minimizing undesirable enolate equilibration and competitive formation of side products. Although there was room left for further improvements, these early reports of one-pot three-component procedures to prostaglandin derivatives epitomized the enormous potential of multicomponent reactions as strategies in the total synthesis of natural products.

Concerned with the need for an exhaustive multistep preparation of the required alkenylcopper intermediate in Noyori's procedures, Lipshutz and Wood developed a highly

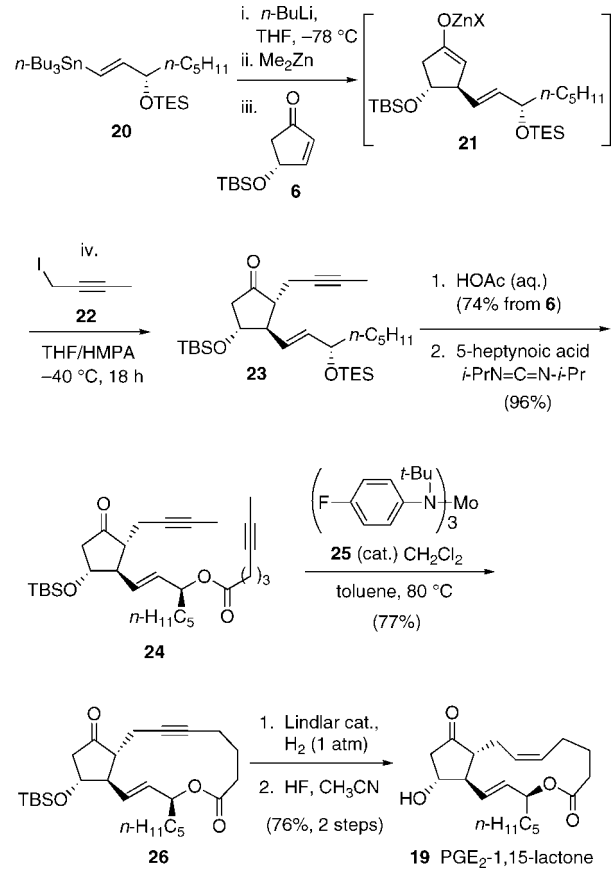
Scheme 4. Multiple Metal Variant of the Conjugate Addition/Enolate Trapping 3CR on Cyclopentenones, by Lipshutz and Wood[16]



practical "single-flask" variant that bypassed the need for the intermediacy of an alkenyllithium intermediate and rather allowed the use of simple alkynes as precursors.[16] Previous work from this group showed that alkyne hydrozirconation can be followed by in situ transmetalation with a higher-order cyanocuprate.[17] On the basis of this premise, Lipshutz and Wood rationalized that the entire process of sequential Zr-to-Cu transmetalation and the ensuing 1,4-addition into the enone could be made catalytic in copper by transmetalation of the resulting enolate with a suitable zincate reagent. In any event, the zincate reagent Me_3ZnLi was found to function extremely well in this multimetal transmetalation, because it does not compete for 1,4-addition with the higher-order alkenylcuprate and it provides a putative zinc enolate of high reactivity toward carbon based electrophiles. Thus, as shown in a general fashion in Scheme 4, room temperature hydrozirconation of an alkyne with Schwartz' reagent is followed by substitution of the Zr−Cl bond with methyllithium at −78 °C to give alkenylzirconocene **13**. Transmetalation of **13** to **14** with a catalytic amount of the higher-order cyanocuprate $Me_2Cu(CN)Li_2$, in the presence of Me_3ZnLi and with slow-addition of enone **6**, leads first to the initial conjugate addition product **15** and then to zinc enolate **16** after Cu-to-Zn transmetalation. The third component, the electrophile (either an aldehyde or a propargylic triflate), is then added at −78 °C to provide compounds **17** or **18**, respectively. Although no naturally occurring prostaglandins were formally synthesized using this impressive multimetal variant of the Noyori MCR, **17** and **18** are a proven class of useful intermediates toward prostanoids.

Fürstner and co-workers took advantage of their remarkable alkyne metathesis reaction[18] to synthesize cyclic lactone analogues of prostaglandins from precursors assembled using a traditional Noyori three-component reaction (Scheme 5). Prostaglandin lactones such as PGE_2-1,15-lactone (**19**) have

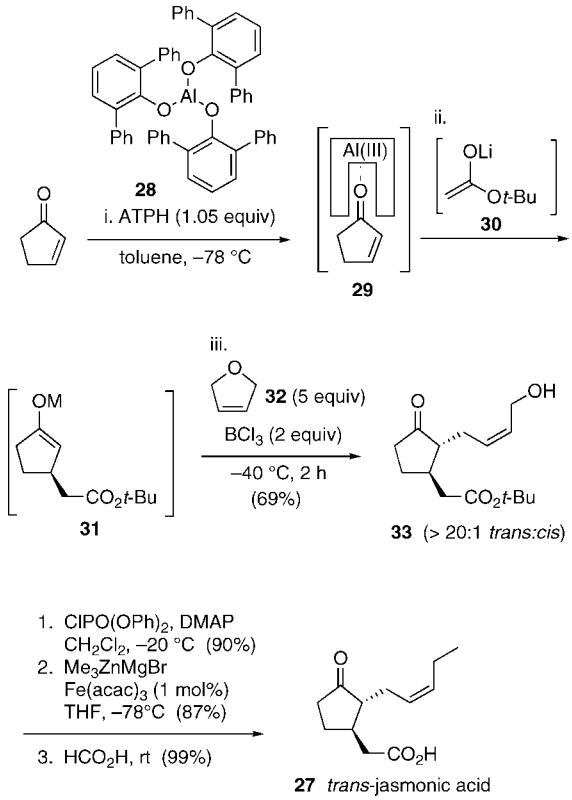
Scheme 5. Synthesis of PGE2-1,15-Lactone Using a Noyori-type 3CR, by Fürstner and Co-workers[21]



been isolated from the *T. fimbria* species of mollusks.[19] These ichtyotoxic compounds are secreted upon physical aggression as part of the animal's defense mechanism. On the standpoint of therapeutic applications in general, it has been proposed that prostaglandin lactones may possess unique properties for use as prodrugs with a localized, specific biological action.[20] The synthesis of **19** was achieved in optically pure form by Fürstner and co-workers[21] by using chiral alkenylstannane **20** (Scheme 5), which was accessed in two steps from a commercial, optically pure propargyl alcohol. Transmetalation of **20** with lithium and in situ formation of the dimethylzincate was followed by conjugate addition onto cyclopentenone **6**, and in situ trapping of the resulting zinc enolate **21** with 4-iodo-but-2-yne (**22**) provided the three-component reaction product, **23**. The latter, isolated in enantiomerically pure form (99% ee), was transformed into bis(methylalkyne) **24**, the required alkyne metathesis substrate. Treatment of the latter with molybdenum precatalyst **25**[22] and CH_2Cl_2 led to lactone **26** with a good yield. Semihydrogenation of the resulting alkyne and desilylation afforded **19** in 28% overall yield. By virtue of the well-precedented enzymatic hydrolysis of **19**, this route also provides a formal synthesis of PGE_2.

The jasmonates are a class of disubstituted cyclopentanoid natural products reminiscent of the prostaglandins. To assemble the jasmonate skeleton with high efficiency, Yamamoto and co-workers developed a clever three-component reaction methodology and demonstrated its usefulness in the total synthesis of both *trans*- and *cis*-methyl jasmonates (Scheme 6).[23] Highly reactive organolithium reagents, even lithium enolates, tend to have an intrinsic preference for 1,2-addition on cyclopentenone derivatives.

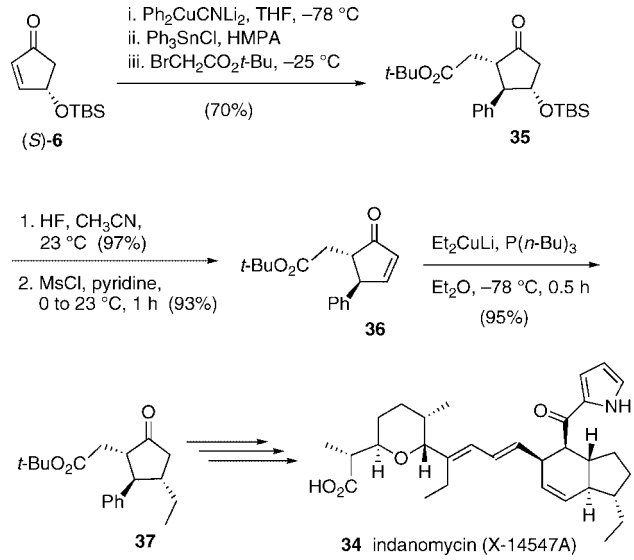
Scheme 6. Synthesis of *trans*-Jasmonic Acid Using a Noyori-type 3CR, by Yamamoto and Co-workers[23]



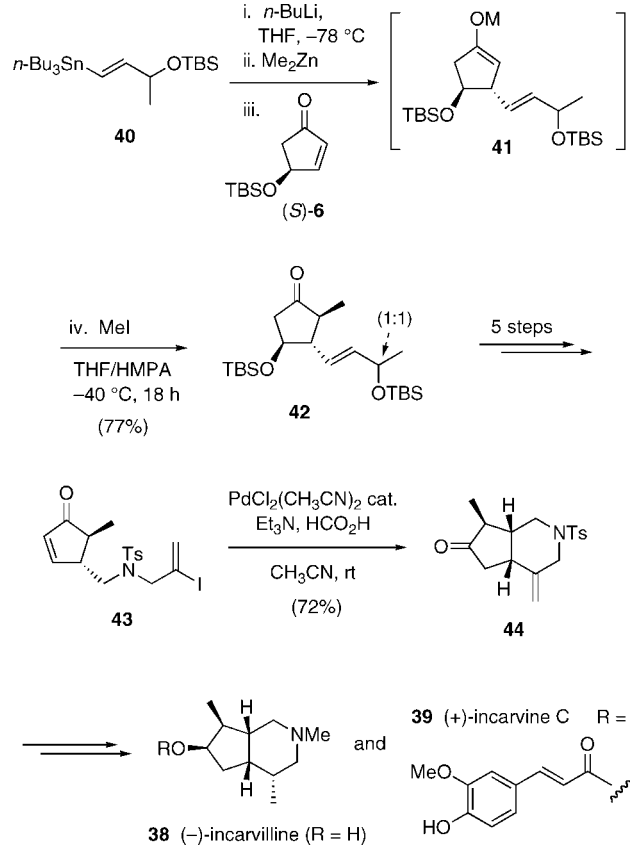
By using the very sterically hindering Lewis acid aluminum tris(2,6-diphenylphenoxide) (ATPH, **28**) to precomplex the carbonyl of enones,[24] however, Yamamoto and co-workers demonstrated that strong organolithium reagents can be forced to undergo conjugate addition. The resulting transient enolate can be trapped in situ with BCl_3-activated tetrahydrofuran or 3,4-dihydrofuran (DHF). Thus, precomplexation of cyclopentenone with a stoichiometric amount of **28** at −78 °C provides complex **29**. The lithium enolate of *t*-butyl acetate, **30**, was added, and after several hours DHF (**32**) and BCl_3 were added sequentially to the mixture containing enolate **31** at −40 °C. This three-component reaction provided the *trans*-disubstituted cyclopentanone product **33**, which was isolated in good yield and high selectivity. From **33**, the synthesis of methyl *trans*-jasmonic acid (**27**) was completed in just a few steps. Methyl *cis*-jasmonate was synthesized using the same methodology, however, starting with an alkynyl lithium reagent, which provided *cis*-selectivity in this particular tandem process.[23]

A Noyori three-component reaction was used by Burke and co-workers to access the highly decorated *anti,anti*-trisubstituted cyclopentanone **37**, a key intermediate in the total synthesis of the ionophore antibiotic X-14547A (indanomycin, **34**) (Scheme 7).[25] The homochiral (*S*)-4-siloxy cyclopentenone **6** was first submitted to conjugate addition with a higher-order cyanocuprate. Trapping of the resulting enolate with triphenyltin chloride at low temperature and in situ alkylation using *tert*-butyl bromoacetate in the presence of HMPA furnished the desired all-*trans* MCR adduct **35** in good yield. The latter compound was converted to enone **36** through a sequence of routine transformations. The efficient construction of the stereotriad was completed by a cuprate addition to enone **36**, which proceeded to give **37** with very high 1,2-asymmetric induction. Subsequent transformations

Scheme 7. Synthesis of Indanomycin Using a Noyori-type 3CR, by Burke and Co-workers[25]



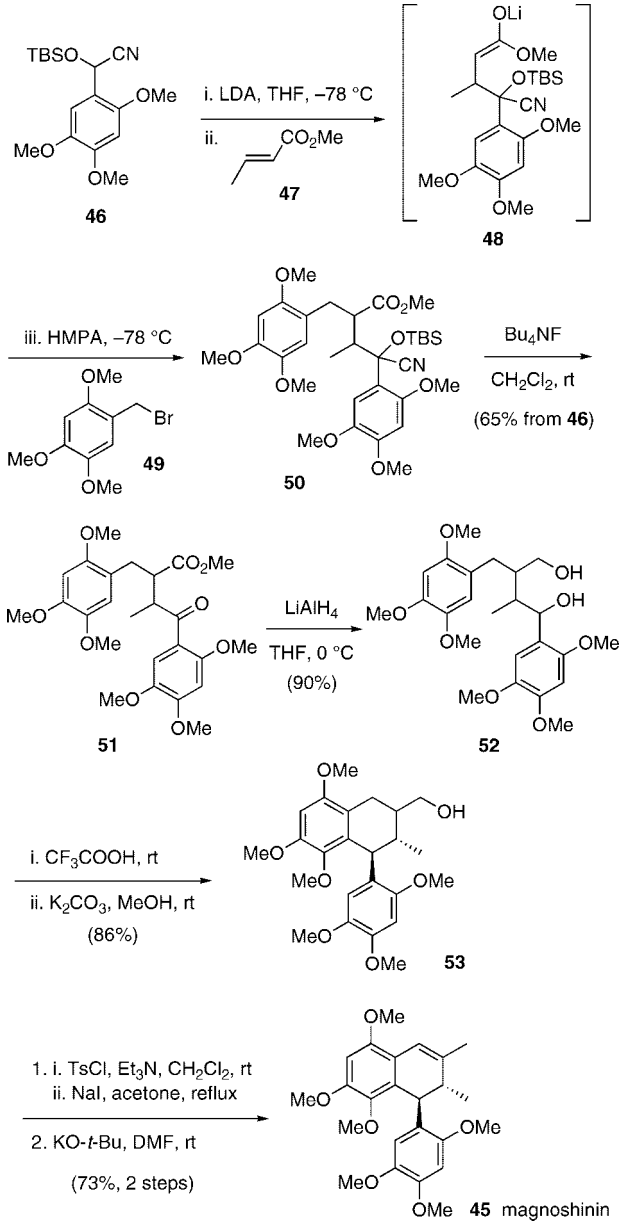
Scheme 8. Synthesis of Incarvilline and Incarvine Using a Noyori 3CR, by Kibayashi and Co-workers[26,28]



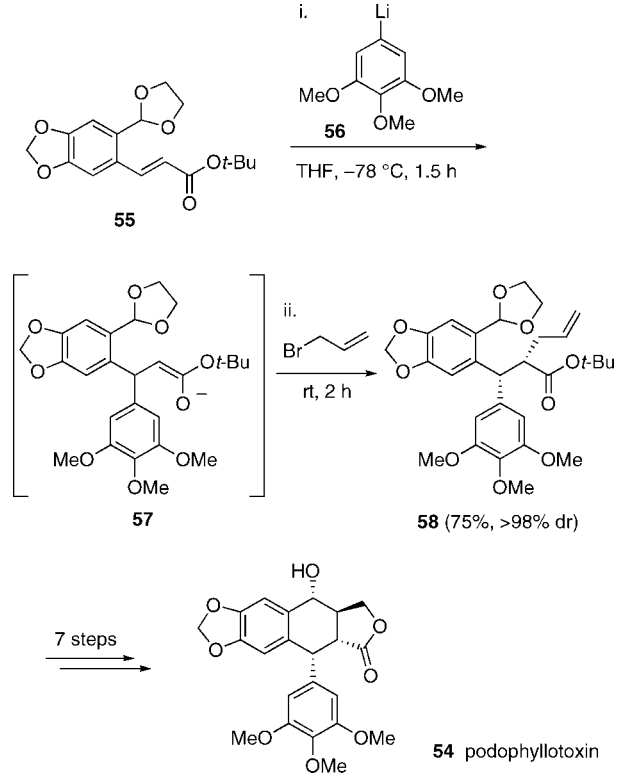
of this early precursor led to the author's completed total synthesis of **34**.

Kibayashi and co-workers utilized a similar protocol using an alkenyl zincate intermediate in their strategy to the syntheses of (−)-incarvilline (**38**), (+)-incarvine C (**39**), and (−)-incarvillateine (Scheme 8).[26] These alkaloids belong to a class of monoterpenes isolated from *Incarvillea sinensis* Lam.,[27] a wild plant distributed in Northern China and used for centuries in traditional medicine for treating rheumatism. To reach the desired bicyclic skeleton and control the stereochemistry around the cyclopentane unit, the authors

Scheme 9. Synthesis of Magnoshinin Using a Tandem Three-Component Conjugate Addition/Enolate Alkylation by Ohmizu, Iwasaki, and Co-workers[30]



Scheme 10. Synthesis of Podophyllotoxin Using a Tandem Three-Component Conjugate Addition/Enolate Alkylation by Wu et al.[33]

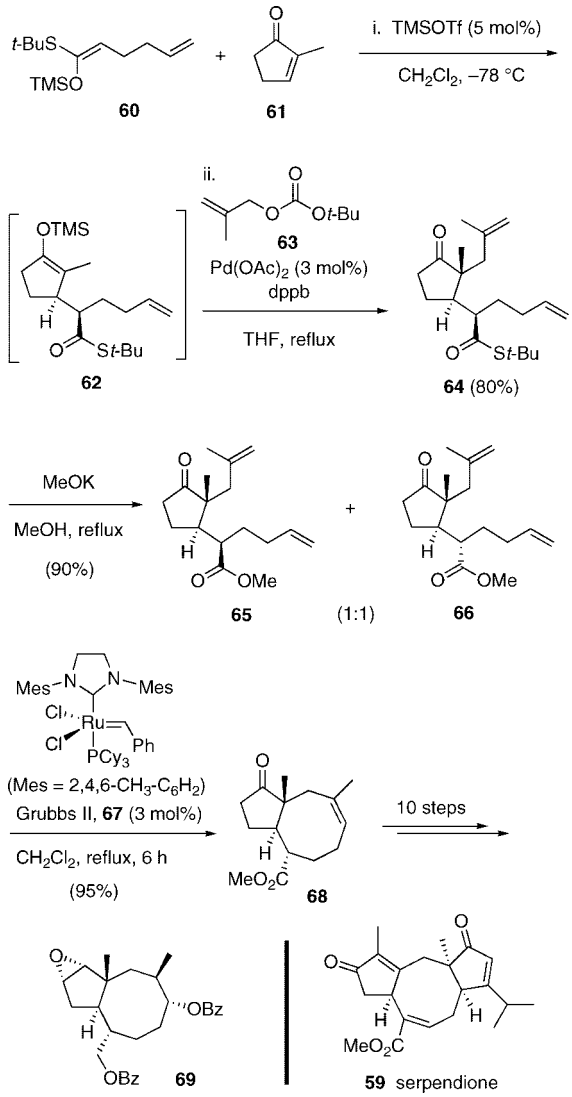


optimized the three-component coupling between alkenylstannane **40**, the (*S*)-enone **6**, and methyl iodide (Scheme 8). The resulting all-*trans* trisubstituted cyclopentanone product **42** was obtained in a very good yield and with very high diastereoselectivity. The siloxy group was formally eliminated and the pendent alkene chain was modified to provide intermediate **43**, which underwent a reductive Heck-type cyclization to afford the desired bicyclic building block **44**. A few more transformations led to (−)-incarvilline (**38**) and (+)-incarvine C (**39**). Incarvillateine, a photodimer of **39**, was also obtained using different routes. An improved synthesis of **38** using a similar 3CR but with a different end-game was subsequently reported.[28]

Examples of tandem conjugate addition/enolate alkylation reactions are less common with acyclic acceptors. The following synthesis of magnoshinin presents one such example. Magnoshinin (**45**, Scheme 9), which was isolated from the dry flower buds of *Magnolia ulicifolia*, has been shown to be the lignan responsible for the anti-inflammatory effect of the traditional Chinese herbal medicine Shin-i.[29] A synthesis of this compound was devised by Ohmizu, Iwasaki, and co-workers and featured a three-component tandem conjugate addition/enolate trapping as the key step (Scheme 9).[30] In this synthesis, an acyl anion equivalent, cyanohydrin **46**, was first treated with LDA and allowed to react with methyl crotonate (**47**). The resulting enolate **48** was trapped with 2,3,5-trimethoxybenzylbromide (**49**) to afford crude intermediate **50**, which was immediately deprotected in situ to afford ketone product **51**. Both the ester and the ketone functionalities were then reduced at low temperature to afford the corresponding diol **52**. Upon treatment with trifluoroacetic acid, the desired Friedel−Crafts cyclization product **53** was obtained. This tricyclic compound was then further elaborated to the final target **45** through a series of standard transformations.

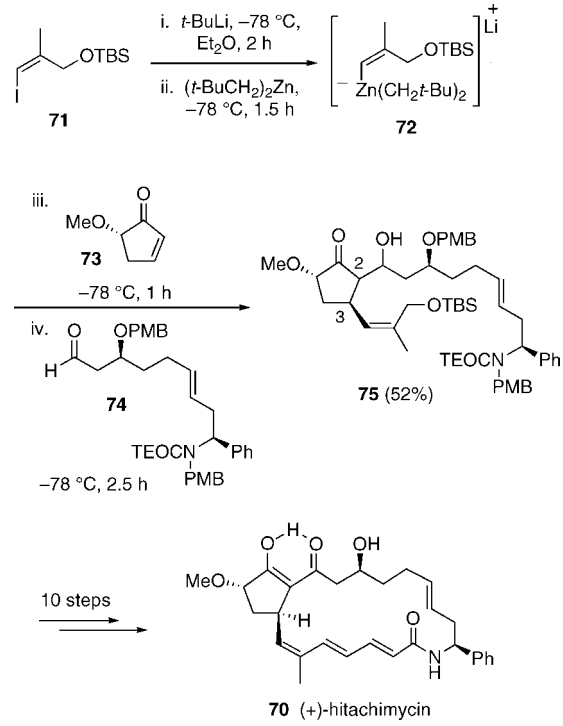
Podophyllotoxin (**54**, Scheme 10) is an important and structurally unusual natural product currently in use for the treatment of venereal warts, and it has served as a precursor to the clinical antitumor drugs etoposide and teniposide.[31] Biologically, it was characterized to be a potent inhibitor of microtubule assembly, and it was recently deemed a potential anti-HIV agent.[32] The importance of this substance has motivated the development of improved synthetic routes, and the use of MCR strategies is an obvious choice to fulfill this objective. Toward this end, Wu and co-workers have described a tandem conjugate addition/enolate alkylation on acyclic α,β-unsaturated ester **55** (Scheme 10).[33] Thus, conjugate addition of aryllithium reagent **56** gave transient enolate intermediate **57**, which was treated with added allylbromide to give diastereomerically pure three-component product **58**. The latter was obtained in good yield after separation of a minor double 1,2-addition product (not shown). A sequence of seven additional steps led to a synthesis of podophyllotoxin (**54**) and several analogues.

Scheme 11. Approach toward Serpendione Using a Tandem Conjugate Addition/Tsuji−Trost Alkylation by Wicha and Co-workers[34]



Wicha and co-workers designed a related three-component reaction initiated by a Mukaiyama−Michael addition and terminated by a Tsuji−Trost alkylation of the intermediate silyl enol ether.[34] Although no total synthesis was completed, this interesting variant using transition metal catalysis was employed to access an advanced intermediate toward the construction of complex sesqui- and sesterpenes of the ophiobolin and fusicoccin families. Members of these families possess a dicyclopenta[a,d]cyclooctane ring system and display interesting physiological properties, including antitumor activity. For instance, serpendione (**59**, Scheme 11) is a blood pressure lowering agent isolated in Madagascar from the herbaceous plant *Hypotheus serpens*.[35] In their approach to the preparation of advanced intermediates for the ophiobolin and fusicoccin families, the authors optimized a one-pot, three-component coupling involving, first, a Lewis acid-catalyzed Mukaiyama−Michael addition of ketene thioacetal **60** onto 2-methylcyclopent-2-en-1-one (**61**) (Scheme 11).[34] In the second stage, methallyl *tert*-butyl carbonate (**63**) was reacted with the silyl enol ether intermediate **62** under palladium-catalyzed conditions to provide the desired three-component product **64** in 80% yield.[36] A required S-to-O transesterification afforded two separable diastereomers **65** and **66**. The latter epimer was subjected to a high-yielding,

Scheme 12. Synthesis of (+)-Hitachimycin Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Smith and Co-workers[38]



ring-closing alkene metathesis with Ru alkylidene complex **67** to give the eight-membered carbocycle **68**. This [5.8]-bicyclic product was transformed after several functional group modifications into the key advanced intermediate **69**, which is expected to provide the target natural product **59** after elaboration of the third ring.

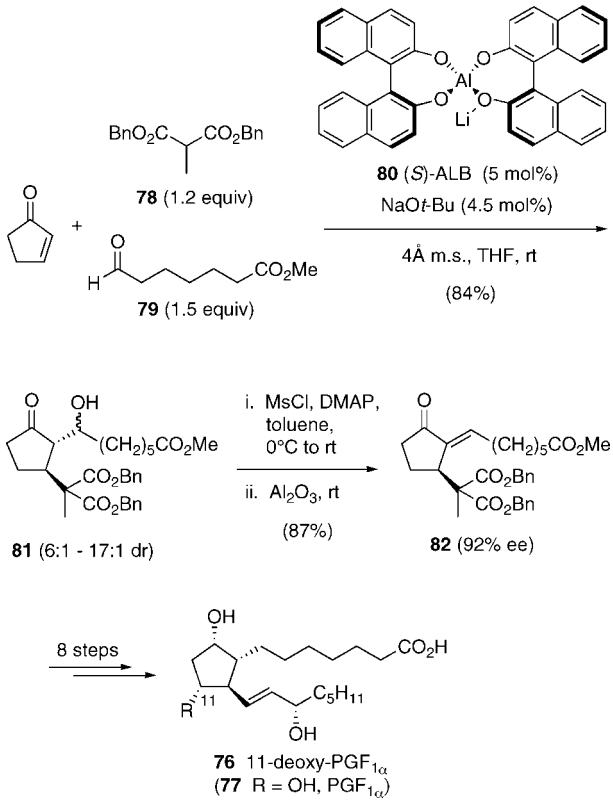
2.2. Conjugate Addition/Aldol Condensation

Aldehydes can also serve as effective electrophiles in the Noyori three-component reaction strategy. Their use, however, adds stereochemical complexity to the process with the potential generation of a third stereogenic center at the newly formed carbinol center. Oftentimes, this issue is inconsequential if the resulting alcohol is dehydrated or oxidized.

In this regard, Smith and co-workers reported the total synthesis of the antitumor antibiotic macrolactam (+)-hitachimycin (**70**)[37] using a Noyori three-component coupling with an aldehyde as electrophile to assemble the polysubstituted cyclopentanone unit (Scheme 12).[38] The required bis(neopentyl) alkenylzincate reagent **72**, derived from alkenyl iodide **71**, was added onto optically pure 5-methoxycyclopentenone **73**, followed by aldehyde **74** to provide the three-component coupling product **75** in a 52% yield. This key intermediate was formed with very high stereoselectivity at position-3 (i.e., the alkenyl side chain), which arose from a 1,4-addition opposite to the 5-methoxy substituent. The use of a bis(neopentyl) alkenylzincate was most desirable in order to optimize the selectivity of ligand transfer in the key tandem reaction. Other reagents such as the bis(methyl) zincate derivative gave significant amounts of product originating from methyl transfer. The synthesis of (+)-hitachimycin was completed in 10 more steps from key intermediate **75**.

Shibasaki and co-workers reported an elegant asymmetric total synthesis of 11-deoxy-PGF$_{1a}$ (**76**) using the Al−Li

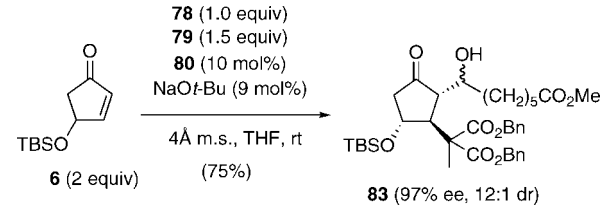
Scheme 13. Catalytic Asymmetric Synthesis of 11-Deoxy-PGF1a Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Shibasaki and Co-workers[39]



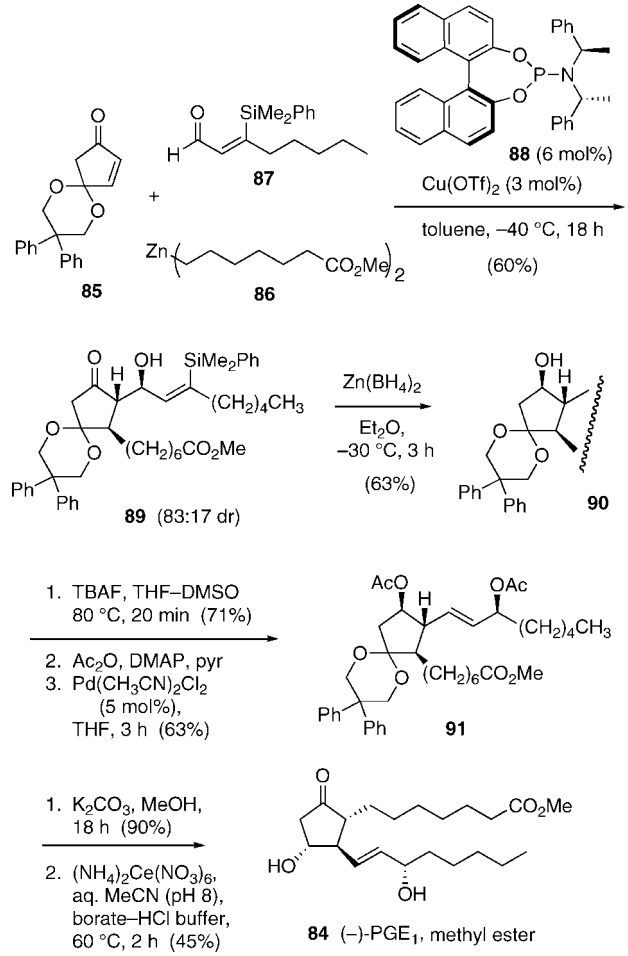
bis(binaphthoxide) complex (ALB) **80**,[39] a member of a novel class of heterobimetallic chiral catalysts showing dual behavior as both Brønsted base and Lewis acid (Scheme 13).[40] Thus, in a rare example of catalytic enantioselective multicomponent reaction, a mixture of cyclopentenone, dibenzylmethylmalonate (**78**), and aldehyde **79** were reacted in the presence of catalyst system (*S*)-ALB/NaO-*t*-Bu (Scheme 13).[41] The tandem Michael/aldol addition product **81** was obtained exclusively as the *trans*-disubstituted isomer, however, as a mixture of diastereomeric secondary alcohols in 84% yield.[39] Here, the presence of a mixture is inconsequent, as **81** was dehydrated to form alkene **82**. The enantioselectivity of the three-component reaction was assessed at this stage to be 92% ee. Following the enantioselective Michael addition step, this remarkable three-component reaction is thought to involve an aluminum enolate intermediate, which was found to be sufficiently reactive to trap the aldehyde prior to protonation by the malonate. From the key intermediate **82**, the synthesis of 11-deoxy-$PGF_{1\alpha}$ (**76**) was completed in eight steps.[39] The same catalyst system was employed to operate a kinetic resolution on racemic cyclopentenone **6**, providing compound **83** in 97% ee (Scheme 14). The latter could serve as a useful intermediate to reach a variety of prostaglandin analogues including $PGF_{1\alpha}$ (**77**).

Feringa and co-workers developed an efficient methodology for conjugate addition of dialkylzinc reagents to enones catalyzed by copper(II) and the remarkably versatile chiral monophosphoramidite ligand **88** (Scheme 15).[42] Of all the different cycloalkenone ring sizes, cyclopentenones tend to give lower yields of the desired 1,4-addition products in this system. When performed in the presence of an aldehyde to trap the zinc enolate and prevent side reactions, however, it

Scheme 14. Kinetic Resolution of 4-Siloxycyclopentenone Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Shibasaki and Co-workers[39]

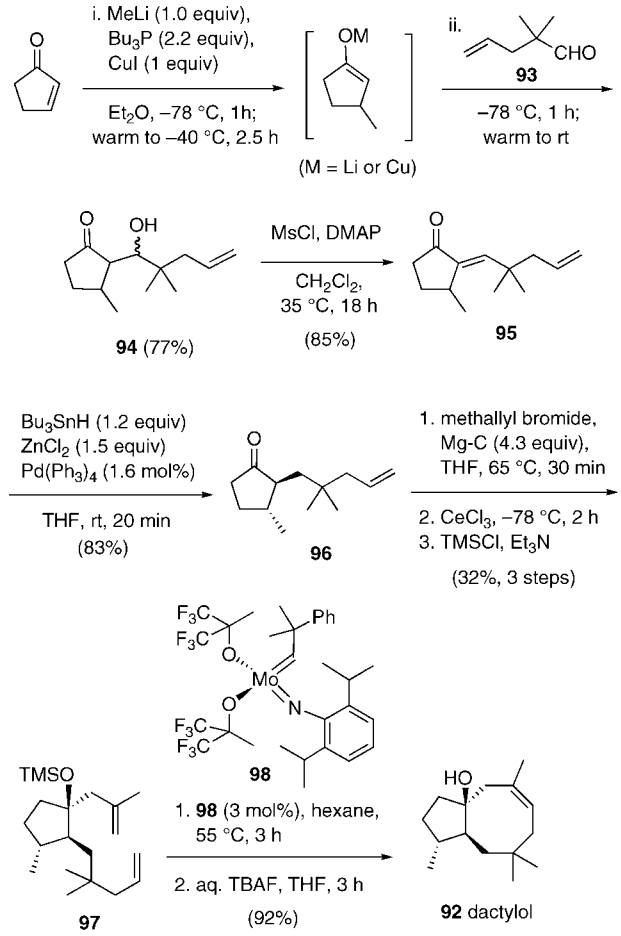


Scheme 15. Catalytic Asymmetric Synthesis of PGE1 Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Feringa and Co-workers[43]

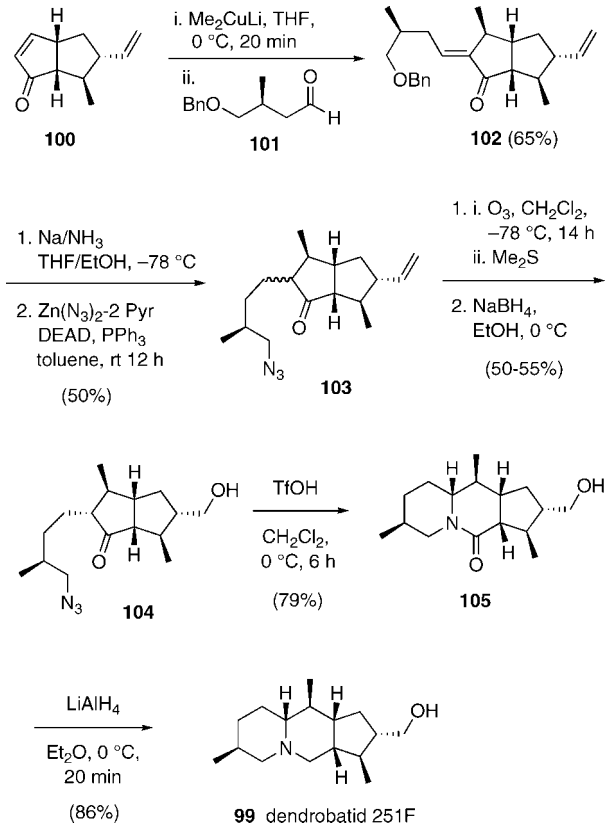


was found that the yields increase. Hence, this methodology was extended to a one-pot tandem conjugate addition/aldol reaction, and then successfully applied to a catalytic enantioselective total synthesis of PGE_1 methyl ester (**84**) using a Noyori-type three-component reaction strategy.[43] The use of dialkenylzinc reagents and aliphatic aldehydes failed under these reaction conditions; thus, the conceptually opposite stratagem was devised whereby the saturated side chain is introduced by conjugate addition, and an unsaturated aldehyde is employed to trap the transient enolate. To avoid competitive conjugate addition on the enal, a temporary silicon group was used to hinder the 3-position on the aldehyde. Thus, by reacting cyclopenten-3,5-dione monoacetal **85**[44] with reagent **86** and aldehyde **87** under 3 mol % of the chiral catalyst **88**·Cu(II), the three-component coupling product **89** was obtained in 60% yield (in a 83:17 diastereomeric mixture at the exocyclic secondary alcohol) (Scheme 15). Stereoselective reduction and chromatographic separa-

Scheme 16. Synthesis of Dactylol Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Fürstner and Langermann[45]



Scheme 17. Synthesis of Dendrobatid 251F Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Aubé and Co-workers[48]



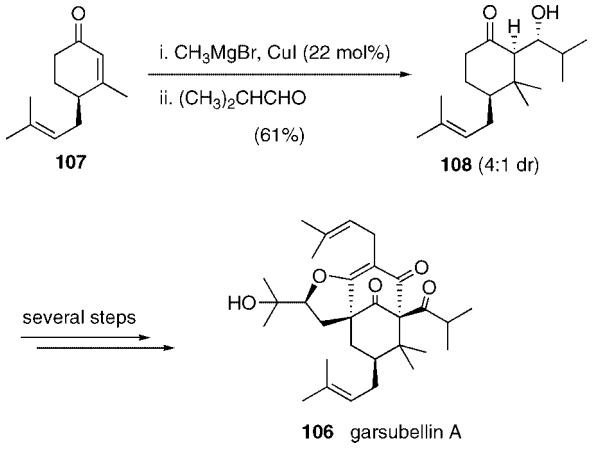
tion afforded diastereomerically pure derivative **90** in 94% ee. Removal of the silicon blocking group, followed by acetylation of the two secondary alcohols, set the stage for an elegant palladium-catalyzed allylic transposition that provided compound **91** with the required alkenyl side chain. A few more steps completed this new enantioselective route to PGE_1 methyl ester (**84**) in 7% overall yield and only seven steps from acetal **85**.

Cyclooctanoid terpenes represent a rapidly growing subfamily of natural products. A total synthesis of one member of this family, (±)-dactylol (**92**), first isolated from the carribean sea hare *Aplysia dactylomela*,[44] was disclosed by Fürstner and co-workers in 1996 (Scheme 16).[45] This synthesis featured a Noyori three-component reaction and employed the readily available cyclopentenone, methyl cuprate, and aldehyde **93**, which were rapidly converted to the highly functionalized β-hydroxyketone **94** through a tandem conjugate addition/aldol reaction. The molecule was first dehydrated, then selective hydrogenation of the enone **95** using tributyltin hydride in the presence of Pd(0) and zinc chloride furnished ketone **96**. A Grignard addition to the ketone followed by ring-closing metathesis (RCM) of intermediate **97**, catalyzed by Schrock's catalyst, **98**,[46] thus completed the total synthesis of dactylol (**92**).

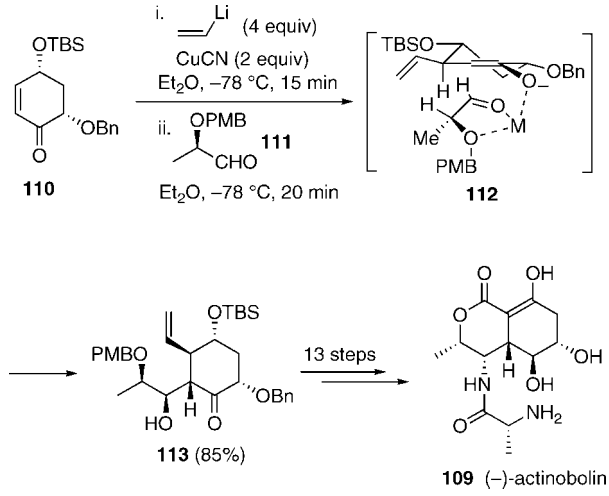
The dendrobatid alkaloid 251F (**99**, Scheme 17) was isolated from the skin exudates of a Columbian dendrobatid poison frog, *Minyobates bombetes*.[47] An asymmetric total synthesis of this molecule featuring an MCR was reported by Aubé and co-workers (Scheme 17).[48] The advanced enone intermediate **100**, which featured four of the six contiguous stereogenic centers present in the target, was obtained through an efficient tandem ROM/RCM reaction sequence (not shown). Bicyclic enone **100** was then engaged in a Noyori-type three-component reaction involving a methyl cuprate and aldehyde **101**. Cuprate addition to enone **100** occurred on the exposed *exo* face of this bowl-shaped molecule, and the resulting enolate underwent an aldol condensation to furnish a transient α-hydroxyketone, which suffered the loss of the β-hydroxy functionality in situ to afford enone product **102** as a single geometrical isomer. The concurrent chemoselective reduction of the enone and removal of the benzyl protecting group using dissolving metal conditions prepared the stage for the introduction of the key azide functionality. This transformation was accomplished under Mitsunobu reaction conditions, and the product **103** was isolated as a mixture of epimers in moderate yield. Ozonolysis of the olefin moiety followed by reduction of the aldehyde furnished the Schmidt rearrangement precursor **104**. Treatment of the latter with triflic acid provided the tricyclic intermediate **105**, and reduction of the lactam moiety of **105** furnished the target alkaloid **99**.

Although six-membered cycloalkenones are less prevalent as substrates in Noyori-type three-component reactions, their successful use has been documented. For example, Shibasaki and co-workers used a chiral cyclohexenone, **107**, as an early intermediate toward the total synthesis of the neurotrophic natural product garsubellin A[49] (**106**, Scheme 18).[50] A conjugate methylation of **107** followed by trapping of the transient magnesium enolate with isopropanaldehyde afforded three-component product **108** in good diastereoselectivity. The total synthesis of garsubellin A, a very

Scheme 18. Synthesis of Garsubellin A Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Shibasaki and Co-workers[50]



Scheme 19. Synthesis of Actinobolin Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Chida and Co-workers.[52]

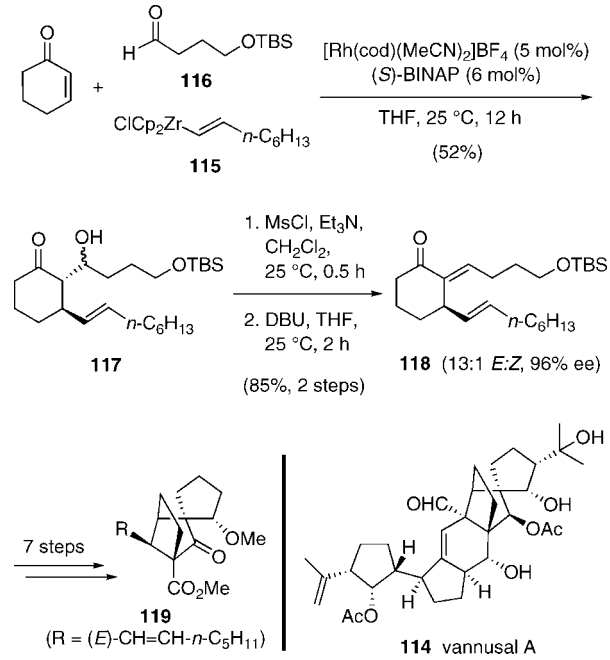


challenging synthetic target, was accomplished in just over 20 steps from the key tetrasubstituted cyclohexanone **108**.

The antibacterial and antitumor agent (+)-actinobolin (**109**, Scheme 19) was isolated from the culture broths of *Streptomyces*.[51] A formal total synthesis of this molecule as well as a total synthesis of its antipode were accomplished by Chida and co-workers using a Noyori-type three-component reaction as key step.[52] D-Glucose was first transformed into enone **110** in seven steps using a sequence of standard synthetic transformations (not shown). The key precursor **110** was then engaged in the crucial three-component reaction. Conjugate addition using a higher-order vinylcuprate proceeded *anti* to the bulky siloxy group, and the ensuing enolate was trapped with the chiral aldehyde **111** to afford the tandem conjugate addition/aldol adduct **113** in 85% yield. The aldol step occurred in a highly stereoselective manner via the proposed transition structure **112** (Scheme 19). From key intermediate **113**, the synthesis of the antipode of the natural product, (−)-actinobolin (**109**), was then completed in 13 steps. The synthesis of the natural enantiomer was completed using a similar strategy.

An impressive example of Noyori-type 3CR involving cyclohexenone was reported by Nicolaou and co-workers. Toward this end, they put to use an efficient enantioselective rhodium-catalyzed variant of the Noyori 3CR, employing

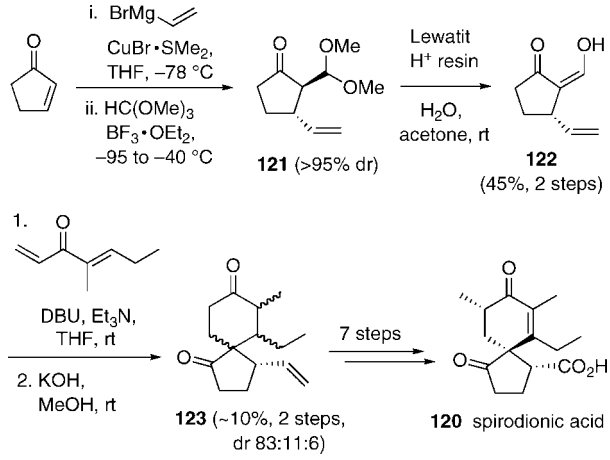
Scheme 20. Approach toward Vannusal A Using a Tandem Three-Component Conjugate Addition/Aldol Condensation, by Nicolaou and Co-workers[53]



alkenyl zirconium intermediates made very conveniently by hydrozirconation of terminal alkynes.[53] Thus, based on a report by Inoue and co-workers describing a mild rhodium-catalyzed conjugate addition of alkenyl zirconium species to enones under nonaqueous conditions,[54] Nicolaou and co-workers realized that the transient rhodium enolate could react with electrophiles to provide an attractive three-component reaction.[55] By using binap as ligand, the tandem conjugate addition/aldol reaction was shown to occur with up to 98% ee and good diastereoselectivity for a wide range of cyclic enones including cyclohexenone and cyclopentenone.[53] A mechanistic cycle initiated by transmetalation of the in situ formed alkenyl zirconium intermediate with rhodium was proposed. This three-component procedure was applied to the preparation of a tricyclic building block for a planned total synthesis of the highly complex polycyclic natural product vannusal A[53] (**114**, Scheme 20), a secondary metabolite isolated from marine ciliates.[56] To this end, the tandem conjugate addition/aldol reaction between cyclohexenone, in situ formed alkenyl zirconium reagent **115**, and aldehyde **116** provided the three-component product **117** as a 1.4:1 mixture of diastereomers. This low selectivity in the aldol step was inconsequential because an elimination was subsequently performed to give enone **118**. The optical purity of this intermediate ascertained the excellent enantioselectivity of the key three-component reaction. From **118**, seven steps were required to reach the spirocyclic intermediate **119**,[53] which is a key building block in a planned total synthesis of the very complex triterpene **114**.

ortho-Esters can also be employed as electrophiles in the three-component conjugate addition/enolate trapping reaction. This variant was employed in the total synthesis of spirodionic acid (**120**, Scheme 21), a novel metabolite from *Streptomyces sp*.[57] The strategy of von Zezschwitz and co-workers centered on a 2-fold Michael addition to elaborate the spirocyclic core of **120**.[58] The key intermediate **123** originated from the three-component product **121**, which was made by conjugate vinylation of cyclopentenone followed by *ortho*-ester trapping of the transient enolate (Scheme 21).

Scheme 21. Synthesis of Spirodionic Acid Using a Tandem Three-Component Conjugate Addition/Orthoester Condensation, by von Zezschwitz and Co-workers[58]



The use of an *ortho*-ester effectively provided a masked aldehyde in this strategy. Acid-catalyzed elimination of **121** afforded intermediate **122**, which was transformed in low yield into **123** via the planned double-Michael reaction.

3. Multicomponent Reactions Initiated by a Nucleophilic Addition to Carbonyl Compounds

3.1. Acylsilane Addition/Brook Rearrangement/ Carbanion Alkylation

Myriad natural products are constituted of multiple unsaturated C−C bonds. Although many approaches to the stereocontrolled synthesis of polyenes exist, their expedient assembly remains a synthetic challenge. An efficient route to unconjugated polyenes was devised by Corey and co-workers based on a three-component carbonyl addition/alkylation reaction sequence.[59] Crucial to this chemistry is the Brook rearrangement,[60] a process involving the migration of a silane group from carbon to oxygen, giving a carbanion. As depicted in Figure 2, the addition of alkenyllithium intermediates to acylsilanes triggers a tandem Brook rearrangement/double-bond isomerization to afford a putative, five-membered chelated silyl enol ether, which sets the *E*/*Z* geometry in the eventual olefin product. The desired tri- or tetrasubstituted olefin can then be isolated following the introduction of an alkyl halide in the reaction mixture.

This multicomponent coupling was key to the racemic total synthesis of the naturally occurring polyene *δ*-araneosene (**124**) by Hu and Corey (Scheme 22).[61] This efficient synthesis was initiated by the treatment of methyl *tert*-butyldimethylsilyl ketone (**125**) with 2-propenyllithium in

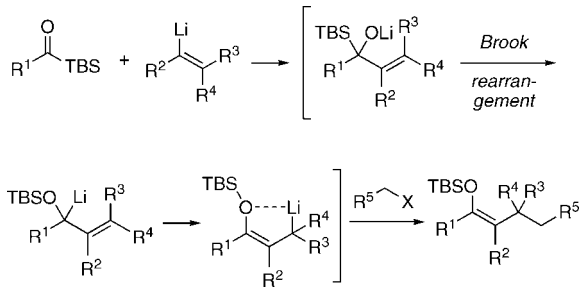
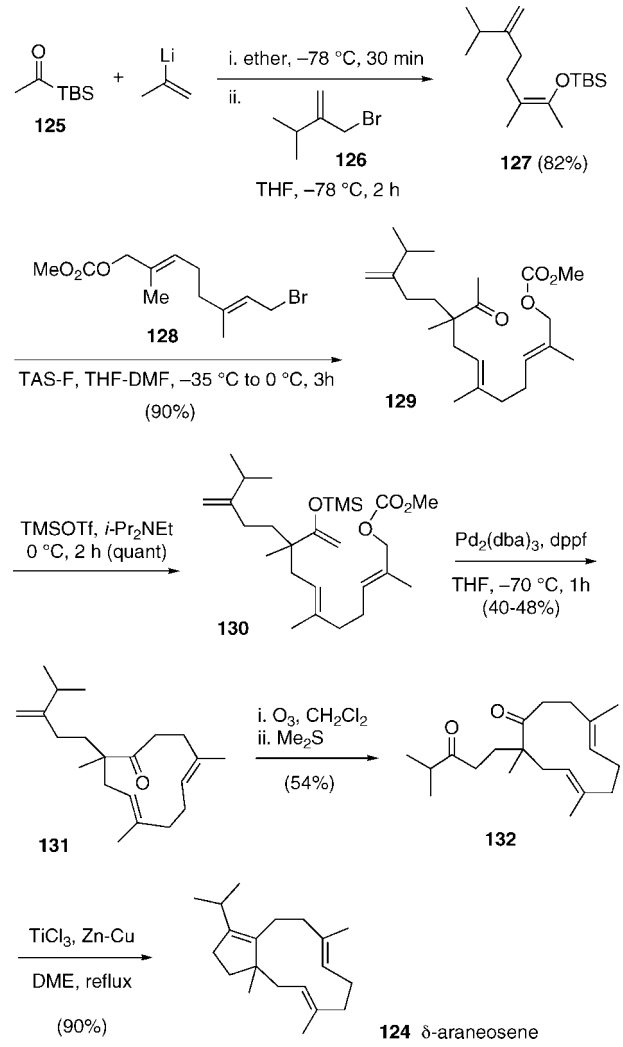


Figure 2. Mechanistic sequence for the tandem three-component nucleophilic addition on acylsilane/Brook rearrangement/carbanion alkylation.

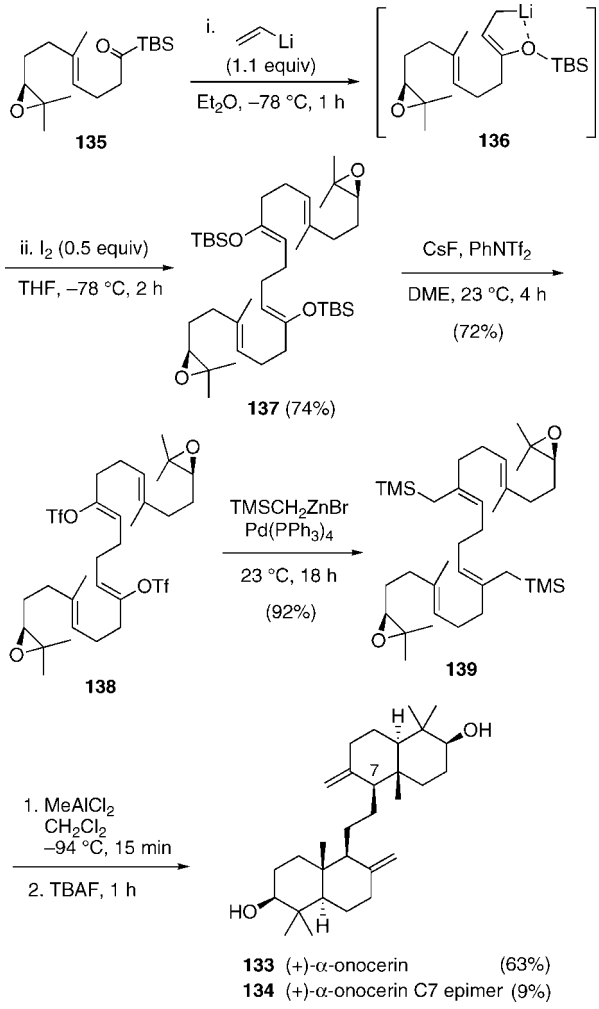
Scheme 22. Synthesis of Delta-Araneosene Using a Three-Component Nucleophilic Addition on Acylsilane/ Brook Rearrangement/Carbanion Alkylation, by Hu and Corey[61]



ether, followed by the introduction of a tetrahydrofuran solution of 2-propylallylbromide (**126**), affording *Z*-silyl enol ether **127** as a three-component product in 82% yield. The silyl enol ether functionality of **127** was first activated with fluoride, then the molecule was alkylated with allylic bromide **128** to afford methyl ketone **129**. The latter functional group was converted to its TMS−enol−ether equivalent **130**, followed by a palladium-catalyzed intramolecular allylic alkylation to form large-ring intermediate **131**. Selective ozonolysis of the exocyclic alkene of **131** and McMurry cyclization of the resulting diketone **132** completed this short synthetic sequence to afford target **124**. A similar synthetic strategy was also used for the synthesis of dammarenediol II (not shown).[62]

Using a similar process, (+)-α-onocerin (**133**, Scheme 23), a known acetylcholinesterase inhibitor,[63] was assembled by Corey and co-workers in only four steps starting from advanced acyclic intermediate **135**.[64] This synthesis featured an impressive four-component coupling involving an oxidative dimerization process. Treatment of the homochiral acyl silane **135** with vinyl lithium at low temperature led to allylic lithium intermediate **136**. This was followed by the addition of 1/2 equiv of iodine to the reaction mixture, furnishing the tetraene **137** in high yield and with a very high level of stereoselectivity (Scheme 23). The TBS ether was then

Scheme 23. Synthesis of α-Onocerin Using a Three-Component Nucleophilic Addition on Acylsilane/Brook Rearrangement/Carbanion Alkylation, by Corey and Co-workers[64]

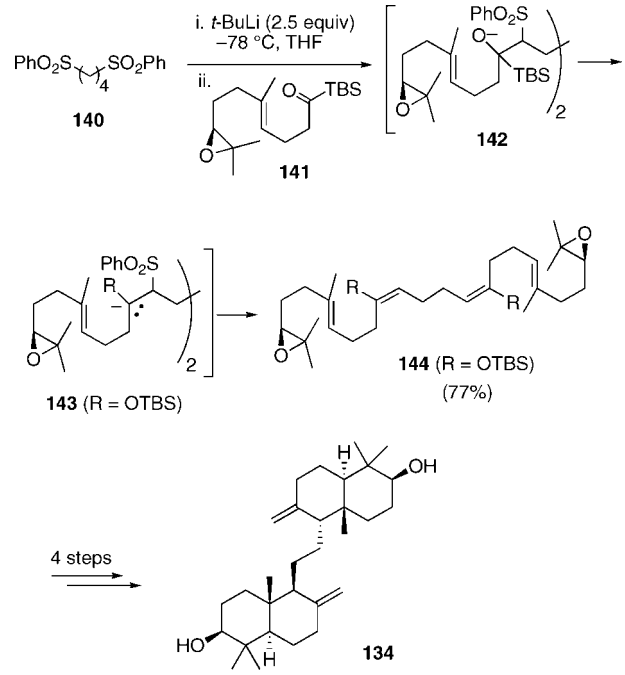


converted to its corresponding triflate **138** in a stereospecific manner, thereby setting the stage for a one-carbon homologation using a Negishi-type coupling that provided the key precursor **139** containing all carbon atoms of the natural product skeleton. The Lewis acid catalyzed cationic π-tetracyclization of **139** and treatment with TBAF delivered the desired target (**133**) in 31% overall yield accompanied by a small amount of its epimeric analogue **134**. The latter compound can also be efficiently assembled using a three-component reaction as outlined in Scheme 24.[64] Thus, the dilithio derivative of 1,4-bisphenylsufonylbutane (**140**) was formed prior to the introduction of the homochiral acylsilane **141** into the reaction mixture. The nucleophilic carbonyl addition/Brook rearrangement/elimination sequence delivered the bis *E*-vinyl silyl ether **144** in high yield and with very high selectivity through the intermediacy of anions **142** and **143**. This short and effective synthesis of **134**, this time made as the major isomer, was completed as described above for **133**.

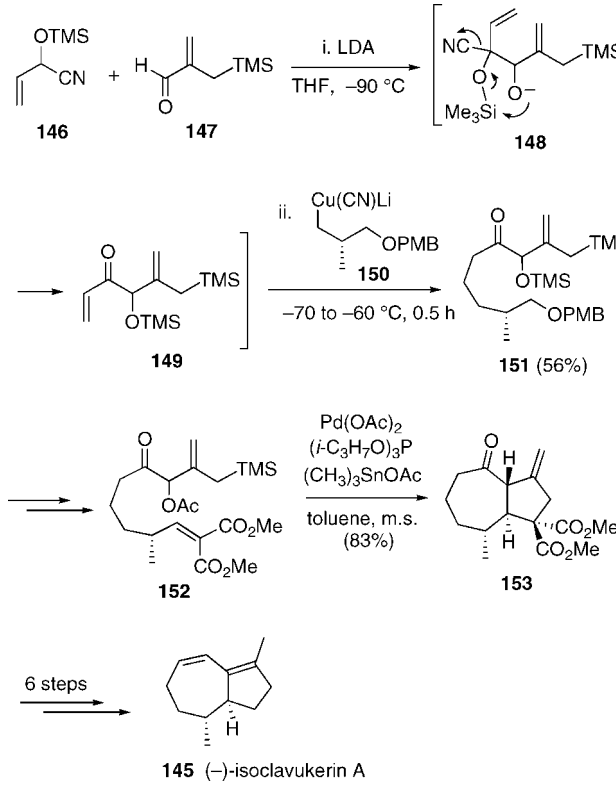
3.2. Cyanohydrin Anion Condensation/Silyl Transfer/Conjugate Addition

The biological activity displayed by the perhydroazulenes, ranging from diuretic and anti-inflammatory to antitumor, combined with the unique bicyclo [5.3.0] system make them

Scheme 24. Synthesis of epi-α-Onocerin Using a Three-Component Nucleophilic Addition on Acylsilane/Brook Rearrangement/Sulfone Elimination, by Corey and Co-workers[64]

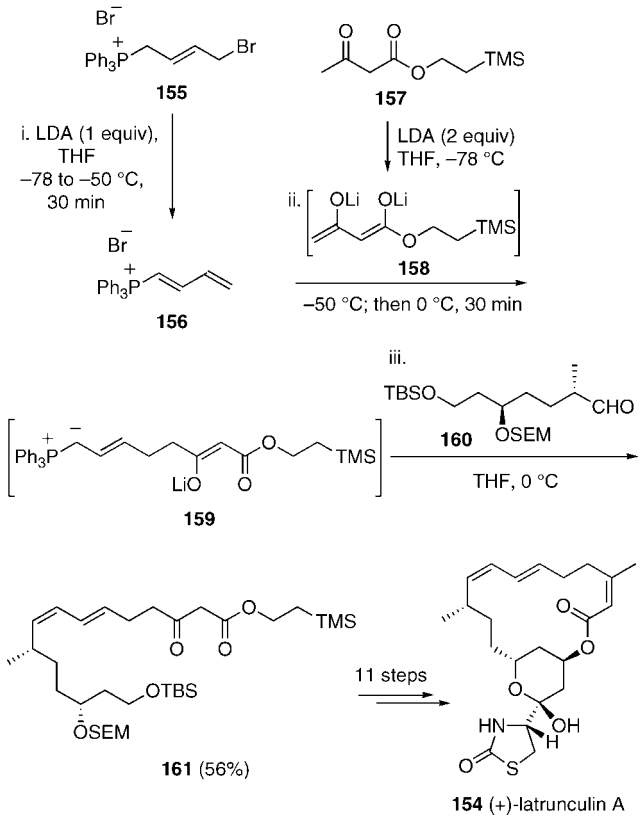


Scheme 25. Synthesis of Isoclavukerin Using a Three-Component Nucleophlic Addition/Cyanohydrin Breakdown/Conjugate Addition, by Trost and Higushi[65]



very attractive synthetic targets. The approach of Trost and Higushi to this class of compounds, exemplified by the total synthesis of isoclavukerin A (**145**, Scheme 25),[65] has the distinctive feature that it allows the simultaneous formation of both the five- and seven-membered rings through a palladium-catalyzed formal [3 + 2]-cyclization as its key step.[66] The crucial substrate for this reaction, malonate **152**,

Scheme 26. Synthesis of Latrunculin Using a Three-Component Nucleophilic Addition/Wittig Olefination on Dienyl Phosphonium Salt, by White and Kawasaki[68]



was derived from key precursor **151**, which in turn was rapidly assembled through an efficient MCR between the silylated cyanohydrin **146**, aldehyde **147**, and the in situ generated organocuprate **150**. In this reaction, initiated by a cyanohydrin anion condensation to give intermediate **148**, the ketone functionality is liberated through a 1,2-silyl transfer/cyanide expulsion sequence. The resulting intermediate, enone **149**, then underwent an in situ 1,4-addition with cyanocuprate **150** to afford the α-siloxyketone MCR product **151.** The latter intermediate was further elaborated into **152**, the required substrate for the palladium-catalyzed cyclization. The product of this formal [3 + 2]-cycloaddition, bicycle **153**, was then converted in six steps into (−)-isoclavukerin A (**145**), a perhydroazulene isolated from *Clavularia koellikeri*.[67]

3.3. Three-Component Wittig Reaction

White and Kawasaki employed a three-component strategy to access an advanced dienyl fragment in their total synthesis of (+)-latrunculin A (**154**, Scheme 26),[68] an ichthyotoxic metabolite of the sponge *Latruncula magnifica*.[69] Their successful strategy hinges on the stereoselective attack of nucleophiles onto butadienyltriphenylphosphonium halide salts to generate *E*-ylides.[70] The latter can be treated in situ with aldehydes to provide acyclic *E*,*Z*-dienes in a highly stereoselective Wittig reaction. Remarkably, *β*-dicarbonyl dianions and α-branched aldehydes are effective partners in this highly convergent three-component coupling approach. Thus, to synthesize (+)-latrunculin A, butadienyltriphenylphosphonium bromide **156** was generated from phosphonium salt **155** and reacted in situ with a Weiler dianion,[71] **158**, to give putative intermediate **159**. Addition of functionalized α-branched aldehyde **160** led to the isolation of *E*,*Z*-diene product **161** accompanied with traces of the *E*,*E* isomer. Following this impressive three-component reaction, both ends of **161** were successfully elaborated into **154** after several additional steps.

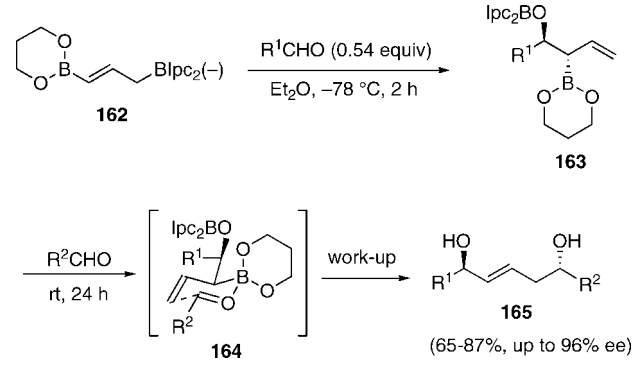


Figure 3. Stereochemical course in the double allylboration of aldehydes with 3-boronyl-allylborane reagent **162**.

3.4. Double Allylation of Aldehydes with Bimetallic Reagents

Bimetallic reagents have interesting potential in the design of multicomponent reactions provided the reactivity of the two metallic centers with electrophiles can be controlled to avoid mixtures of products and allow the sequential addition of two different electrophiles. A tandem double-allylation strategy, based on the (*E*)-3-boronyl allylborane reagent **162**,[72] has been optimized for the synthesis of 1,5-diol products from two different aldehyde substrates (Figure 3).[73] Specifically, reagent **162** undergoes allylation with a limiting amount of a first aldehyde, R^1CHO, and the resulting α-substituted allylic boronate **163** can then add onto a second added aldehyde (R^2CHO). The first allylation with the bis(isopinocampheyl)allylic borane unit is highly enantioselective, and the resulting stereochemistry in **163** controls the fate of the second allylation. Thus, from intermediate **163**, transition structure **164** featuring a pseudoequatorial α-substituent explains the stereocontrolled formation of 1,5-diol **165**. The lower reactivity of **163** compared to **162** and a tight control of reagent stoichiometry help minimize the formation of the double allylation product of the first aldehyde (R^1CHO).

With reagent **166**, the corresponding allylboronate intermediate **167** is thought to favor a transition structure **168** where the α-substituent is positioned in a pseudoaxial orientation in order to escape nonbonding interactions with the bulky tetraphenyl dioxaborolane (Figure 4). This way, a *Z*-configured allylic alcohol unit of opposite configuration is obtained in diol product **169**. This type of steric control with chiral α-substituted allylboronates had been demonstrated before.[74]

Difficulties in subsequently differentiating the two resulting secondary alcohols may limit the potential applications of these reagents when employed as a one-pot three-component process. To address this problem, Roush and co-workers developed a selective monoprotection procedure whereby the allylic alcohol unit of sterically unbiased 1,5-diols is transformed into a triethylsilyl ether.[75] The homoallylic alcohol is left unreacted and can be selectively functionalized.

The usefulness of this powerful tandem allylation/allylation strategy was amply demonstrated by the prepa-

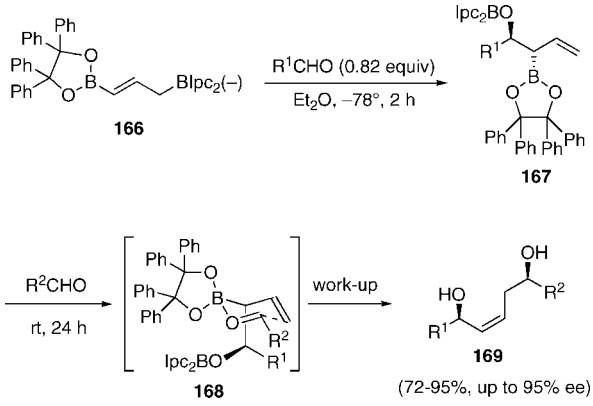


Figure 4. Stereochemical course in the double allylboration of aldehydes with 3-boronyl allylborane reagent **166**.

ration of several examples of both types of 1,5-diols **165** and **169**, and by a number of successful applications to the synthesis of complex natural products. For example, in the construction of the pyran-containing C43−C67 fragment of the complex marine natural product amphidinol 3, **170**,[76] a "one-pot" double allylation was performed with two different acetonide-protected α-chiral aldehydes (Scheme 27).[77a] The first allylation between **166** and aldehyde **171** involved a stereochemically mismatched case of double diastereoselection, which was resolved by the strong stereodirecting power of the bis(isopinocampheyl)boryl units and the optimal choice of protecting group. The desired intermediate **172** was then reacted with the second aldehyde (**173**) to give product **174** in high yield and in good overall stereoselectivity (9:1 dr). Several functional group manipulations and a subsequent cyclization afforded the pyran core **175** of amphidinol 3.[77a]

Reagent **166** was also used in the construction of the C1−C25 fragment of the same natural product, but not in a one-pot protocol because of difficulties in differentiating the secondary alcohols in the desired three-component product.[77b] Reagent **162**, however, was successfully employed to generate one of the requested precursors, **176** (Scheme 28).

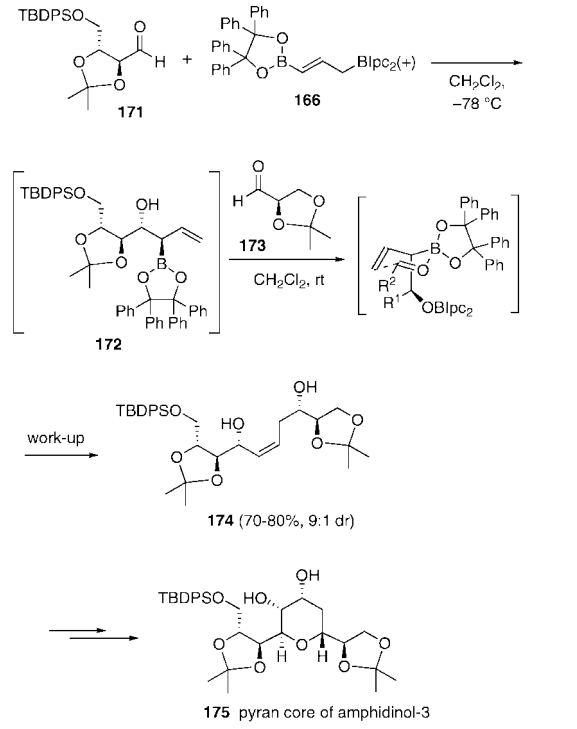
Reagent **162** has also been exploited in the synthesis of fragment C1−C11 of peloruside A[78] (**177**, Scheme 29).[79] To this end, a one-pot successive addition of aldehydes **178** and **179** delivered the desired intermediate **180**, however with a lower enantioselectivity than expected. This lower enantioselectivity is explained by the use of an unusually hindered α,α-disubstituted aldehyde, **178**, in the first addition. An analogue of reagent **162** based on isocaranyl units (instead of isopinocampheyl) provided an increase of enantioselectivity over 95%, albeit with lower yields (40−50%).

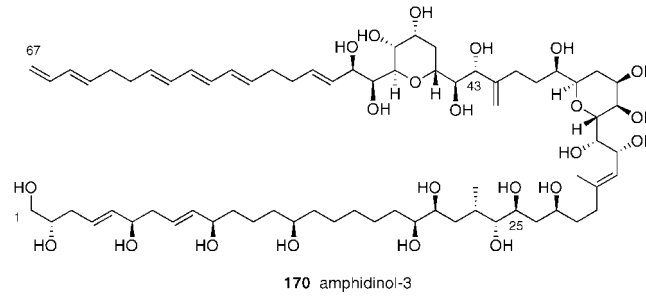
In a very similar way, Crews and co-workers have constructed a C19−C25 fragment of the cytotoxic polyketide amphidinolide B[80] (**181**, Scheme 30) using reagent **166** to establish the desired absolute configuration with very high diastereoselectivity in product **182**.[81] The latter was converted to the C19−C25 fragment **183** in eight additional operations.

3.5. Double Alkenylation of Squarate Followed by Anionic Oxy-Cope Rearrangement

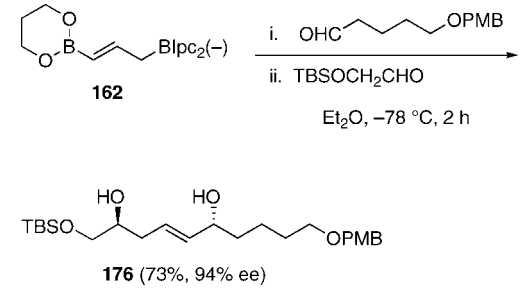
Because of potential chemoselectivity issues, synthons bearing multiple electrophilic sites of comparable reactivity have rarely been used in the context of MCR chemistry. The use of diisopropyl squarate **187**, a symmetrical four-

Scheme 27. Synthesis of the Pyran Core of Amphidinol-3 Using a One-Pot Three-Component Double Allylboration of Two Different Aldehydes, by Flamme and Roush[77a]





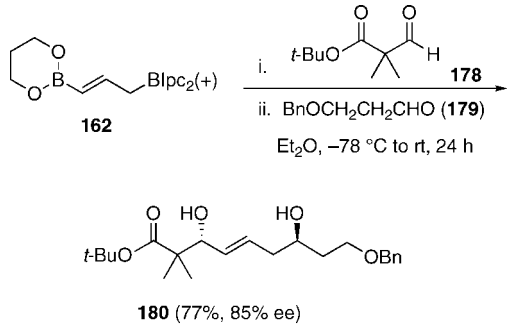
Scheme 28. Synthesis of a Diol Fragment of Amphidinol-3 Using a One-Pot Three-Component Double Allylboration of Two Different Aldehydes, by Roush and Co-workers[77b]

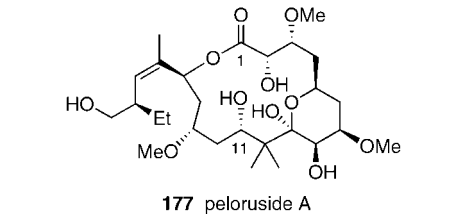


membered ring containing two adjacent ketone functionalities, was described by Paquette and co-workers and defines the standard in this regard. As described below, the double alkenylation of squarate esters was key to forging the fused tricyclic network of triquinane natural products (Scheme 31).[82−84]

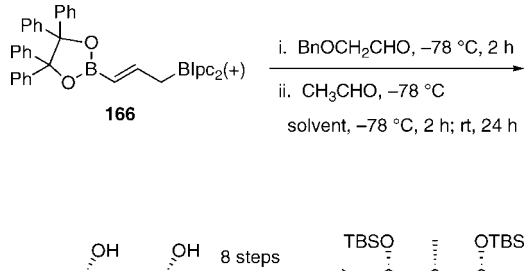
Hypnophilin (**184**, Scheme 31), a potent antibacterial and antitumor agent,[85] was first targeted.[83] Alkenyllithium reagent **188** was reacted with squarate **187** to generate **189** in situ prior to the addition of vinyl lithium. The latter nucleophile may add onto **189** in a *cis* (ketal oxygen-chelation assisted

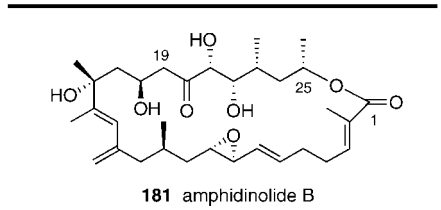
Scheme 29. Synthesis of a Diol Fragment of Peloruside A Using a One-Pot Three-Component Double Allylboration of Two Different Aldehydes, by Owen and Roush[79]



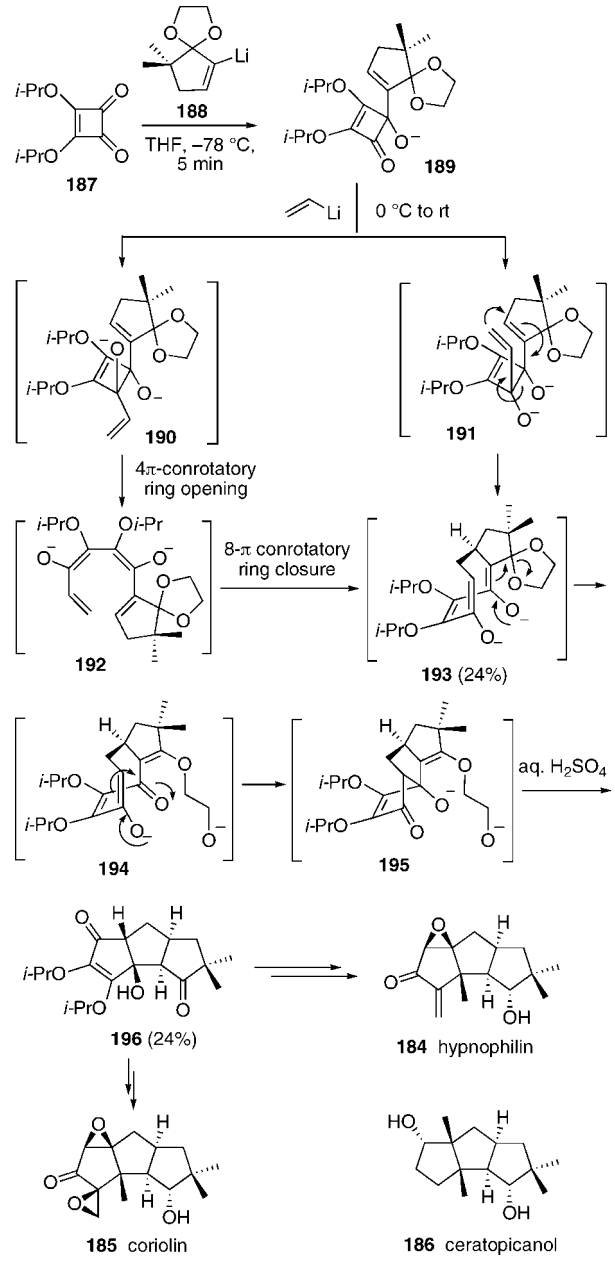


Scheme 30. Synthesis of C19−C25 Fragment of Amphidinolide B Using a One-Pot Three-Component Double Allylboration of Two Different Aldehydes, by Crews and Co-workers[81]





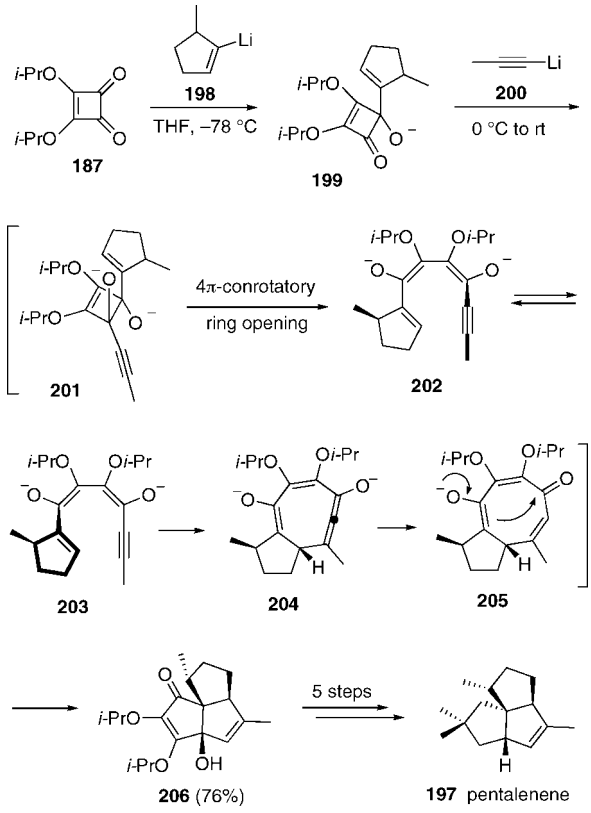
Scheme 31. Synthesis of Hypnophilin and Coriolin Using a Tandem Three-Component Double Alkenylation of Squarate Followed by Anionic oxy-Cope Rearrangement, By Paquette and Co-workers[83]



process) or *trans* (steric control product) fashion, thus allowing two possible competing mechanistic pathways to operate. The *cis*-adduct **191** undergoes a facile dianionic oxy-Cope rearrangement via a boatlike transition state, while the *trans* adduct **190** follows a charge-driven 4π-conrotatory ring-opening/8π-conrotatory ring-closure reaction course through the intermediacy of **192**. It is worth noting the products resulting from these respective reaction pathways become distinguishable when the alkene nucleophiles are substituted at the terminal positions. Regardless of these mechanistic considerations, dienolate cyclooctatriene **193** is a likely common intermediate to both pathways. Then, this unstable intermediate undergoes a regiocontrolled ketone formation (**193** → **194**) directed by the presence of a β-ketal ring, thus paving the way for a final ring contraction event via a transannular aldol reaction to afford **195**. Acidification of the reaction mixture then ensured the efficient removal of ethylene glycol to yield the key intermediate **196**, which was converted into the natural product targets **184**[83] and **185** after a few additional operations.[84] A slight variant of the above strategy enabled the synthesis of ceratopicanol (**186**).[84]

Paquette and Geng also applied this impressive MCR to the synthesis of the angularly fused tricyclic natural product pentalenene **197**,[86] a member of the pentalenone, antibiotic family of fungal metabolites (Scheme 32).[87] In this instance, the second nucleophile is an acetylide, **200**, which added onto intermediate **199** predominantly in a *trans* fashion to initiate the conrotatory cyclobutene ring-opening on **201**. Equilibration between the two helical dienolates **202** and **203** proved facile, but the subsequent electrocyclic ring closure to yield **204** was slow. Presumably, this is due to the presence of the methyl group on the cyclopentene ring, which is

Scheme 32. Synthesis of Pentalenene Using a Tandem Three-Component Double Alkenylation of Squarate Followed by Anionic oxy-Cope Rearrangement, by Paquette and Geng[87]

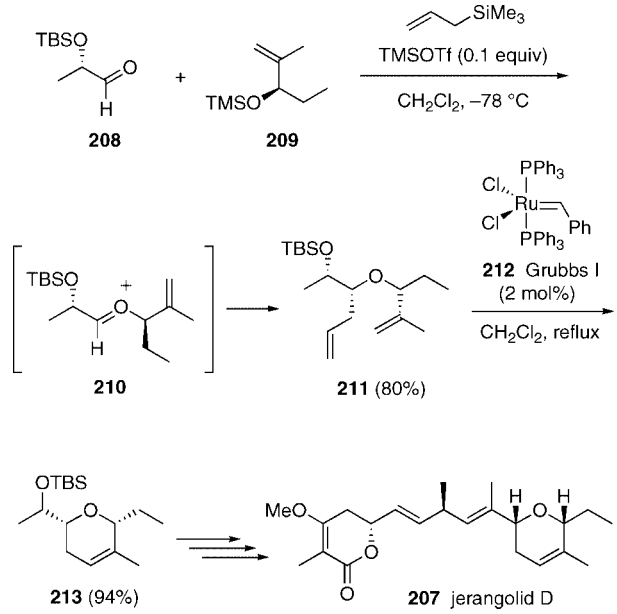


located in the interior of the coil. Also, it should be noted that relief of the strain created by the endocyclic allenolate present in **204** was credited for the regioselective formation of **205**. As per the above example of Scheme 31, a transannular aldol reaction delivered the tricyclic core **206** of the targeted natural product with an excellent yield. The latter MCR adduct was converted into the final target **197** in five more steps.

3.6. Three-Component Oxonium Formation/Allylation

Markó and co-workers developed a three-component Sakurai−Hosomi protocol consisting mechanistically of the addition of allyltrimethylsilane to oxonium ions generated in situ by reaction of aldehydes with trimethylsilyl ethers under catalysis by a Lewis acid.[88] This methodology was applied to the total synthesis of the naturally occurring antifungal agent jerangolid D (**207**, Scheme 33), a secondary metabolite produced by a myxobacterium.[89] Thus, the highly stereoselective three-component condensation between **208**, **209**, and allyltrimethylsilane proceeded via the intermediacy of oxonium intermediate **210** and afforded acyclic ether **211** as a single stereoisomer in very good yield. A ring-closing metathesis with ruthenium alkylidene catalyst **212** yielded the expected dihydropyran **213**. This fragment was further derivatized and coupled to the left-hand unit of the natural product, which was completed in about ten additional steps.[90]

Scheme 33. Synthesis of Jerangolid D Using a Three-Component Oxonium Formation/Allylation, by Pospísil and Markó[90]

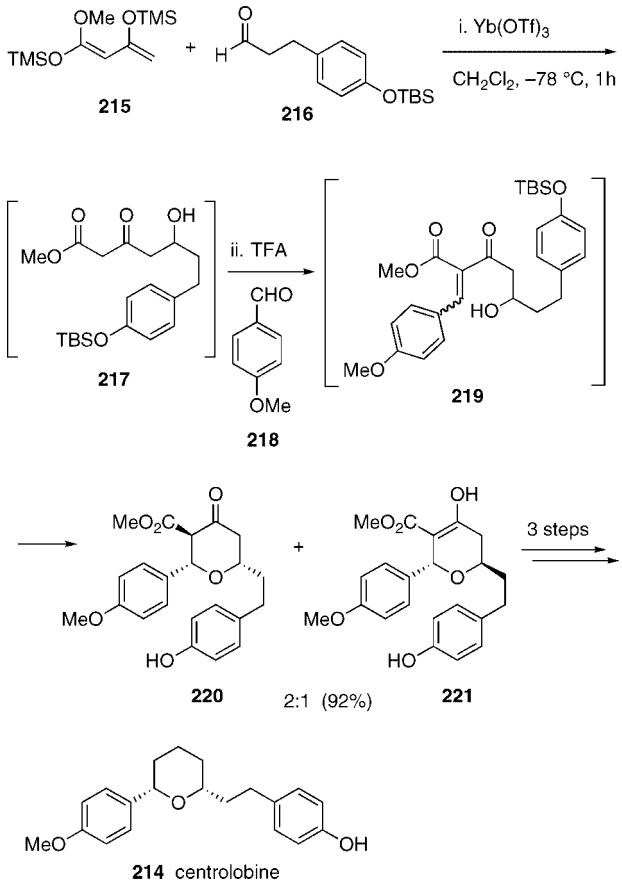


3.7. Tandem Mukaiyama Aldol/Knoevenagel Condensation/oxy-Michael Addition (Maitland−Japp Reaction)

Clarke and Martin have recently revisited the Maitland−Japp reaction, which traditionally involves the reaction of a ketone and two molecules of the same aldehyde to afford polysubstituted tetrahydropyranones under basic conditions.[91] To harness the synthetic potential of this transformation, the authors initiated the use of β-keto-esters as well as bis-silyl enol ethers in lieu of ketones under Lewis acid catalysis.[92] The marked reactivity difference between the β- and γ-carbons of these nucleophiles enabled the sequential addition of two different aldehydes to the reaction mixture and led to a very noticeable improvement. However, the control of the relative stereochemistry still remains a challenge. The nature of the Lewis acids, reaction temperature, and time, as well as the steric demand of the aldehydes or the dianion precursors, are all factors that are known to influence the product distribution (*cis* or *trans* isomers).[92]

The application of this 3-component Mukaiyama aldol/Knoevenagel condensation/1,4-oxy-Michael addition cascade to the racemic synthesis of centrolobine (**214**, Scheme 34), an antiparasitic natural product,[93] was recently reported.[94] Chan's diene (**215**)[95] was first reacted with aldehyde **216** at −78 °C under the catalytic action of ytterbium triflate, which is required for the preferential formation of 2,6-*cis* products. Trifluoroacetic acid (known to significantly increase the rate of the subsequent steps) is added to the resulting aldol product **217**, followed by anisaldehyde (**218**) to give the transient Knoevenagel product **219**. The overall sequence ends with the intramolecular oxy-Michael reaction of **219**, which directly afforded the TBS-deprotected products **220** and **221** in 2:1 ratio in favor of the former. The two products were separated and the minor trans isomer **221** was allowed to re-equilibrate under the above reaction conditions to a 2:1 mixture again, thus boosting the yield of the desired *cis*-product **220**. The latter was converted into centrolobine (**214**) in three straightforward additional steps.

Scheme 34. Synthesis of Centrolobine Using a Three-Component Mukaiyama Aldol/Knoevenagel Condensation/oxy-Michael Addition, by Clarke and Martin[94]



3.8. Grignard Reaction onto Salicylaldehydes Followed by *o*-Quinone Formation and [4 + 2]-Cycloaddition

As reactive intermediates, *ortho*-quinone methides (**223**, Figure 5) are well-suited for the design of cascade reaction processes. They are obtained from benzylic alcohol precursors, **222**, which in turn are generally formed by the *ortho*-hydroxyalkylation of phenols or by nucleophilic additions onto salicylaldehydes. The traditionally harsh conditions employed for the generation of *ortho*-quinone methides from 2-hydroxyalkyl phenols (**222**) have limited the scope of their applications.

To address this issue, Pettus and co-workers have developed a mild and efficient anionic approach to generate *ortho*-quinone

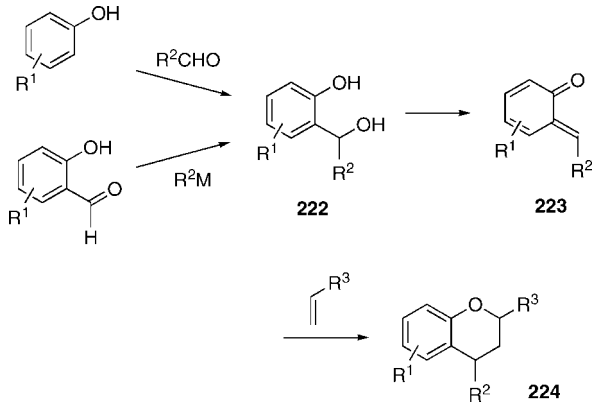
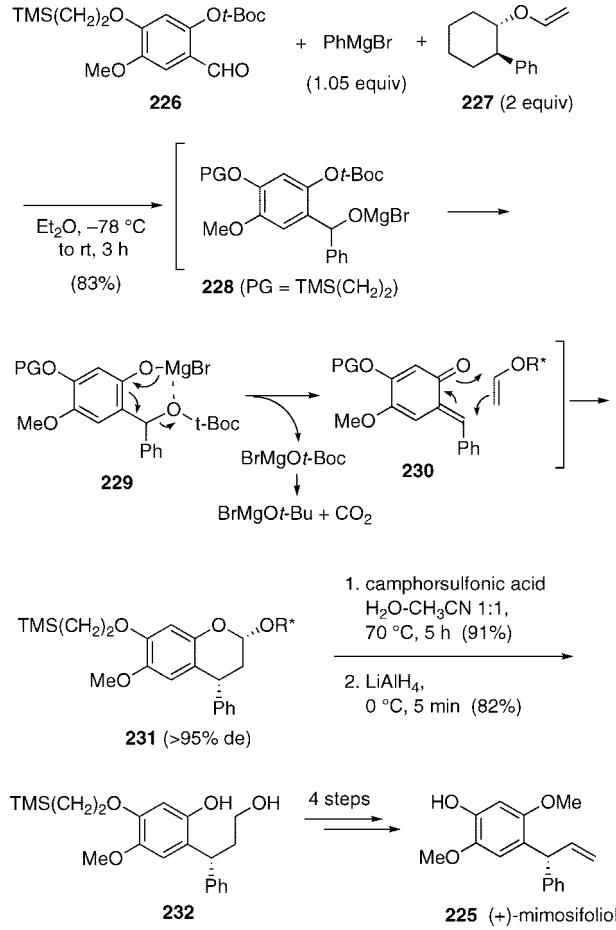


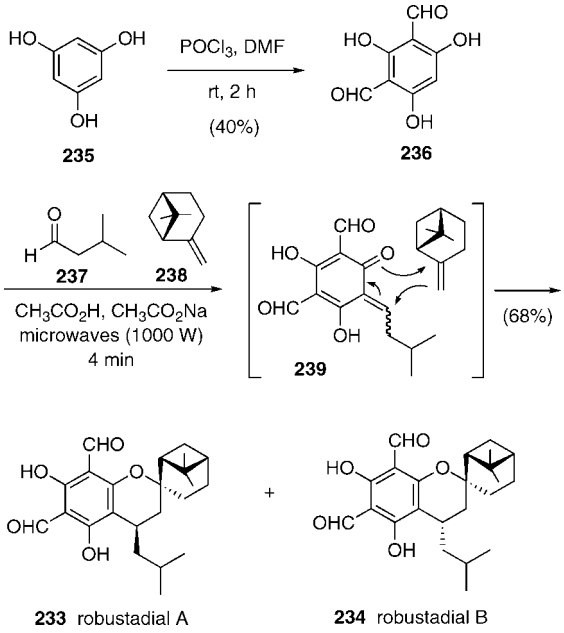
Figure 5. General synthetic routes to *ortho*-quinone methides and their [4 + 2]-cycloaddition with dienophiles.

Scheme 35. Synthesis of (+)-Mimosifoliol Using a Tandem Three-Component Addition of Grignard Reagent to a Salicylaldehyde Followed by *ortho*-Quinone Methide Generation and [4 + 2]-Cycloaddition, by Selenski and Pettus[98]



methides (**223**) at low temperatures. Their subsequent regio- and diastereoselective trapping in [4 + 2]-cycloadditions was optimized with a variety of different electron-rich dienophiles to provide a one-pot synthesis of benzopyran derivatives (e.g., **224**, Figure 5).[96] The use of Grignard reagents and *O*-*t*-Boc-protected salicylaldehydes at −78 °C explains the success of this strategy (see Scheme 35). Following the addition of the Grignard reagent on the aldehyde, the resulting magnesium alkoxide participates in an intramolecular *O*-*t*-Boc transfer process, which is followed by a final β-elimination accompanied with release of carbon dioxide. The latter step, facilitated by the presence of magnesium ions in the reaction mixture, generates the requisite *ortho*-quinone methide. This new and milder process paves the way for the regioselective [4 + 2]-cycloaddition with a variety of electron-rich dienophiles to provide a one-pot synthesis of benzopyran derivatives. The same group also optimized the diastereoselectivity of [4 + 2]-cycloadditions with chiral enol ethers and observed optimal *endo*/*exo* selectivity and enantiofacial selectivity with overall diastereoselectivity excesses of >95% using trans-2-phenyl-1-cyclohexanol vinyl ether (**227**, Scheme 35).[97] The requisite alcohol precursor for the chiral enol ether is commercially available under both enantiomeric forms. To demonstrate the usefulness of this three-component reaction cascade, Selenski and Pettus targeted the total synthesis of a Leguminosae rootwood component, (+)-mimosifoliol (**225**, Scheme 35),[98] which was completed in nine steps and 35% overall yield.[99,100] As discussed above,

Scheme 36. Synthesis of Robustadial A and B Using a Tandem Three-Component *ortho*-Hydroxyalkylation of Phenol Followed by *ortho*-Quinone Methide Generation and [4 + 2]-Cycloaddition, by Bharate and Pal Singh[102]



the key three-component reaction requires an *ortho*-substituted *t*-Boc salicylaldehyde as substrate. Here, trihydroxylated benzaldehyde **226** was treated with phenylmagnesium bromide in the presence of trans-2-phenyl-1-cyclohexanol vinyl ether **227** (Scheme 35). The desired product **231** was obtained as per the mechanistic course explained above, featuring **228**−**230** as putative intermediates. The *ortho*-quinone methide intermediate **230** was trapped by enol ether **227** in a highly regio- and diastereoselective [4 + 2]-cycloaddition. Treatment of the resulting three-component product **231** with camphorsulfonic acid in aqueous conditions afforded a lactol, which was subsequently reduced to provide diol **232**. A concise series of functional group modifications led to synthetic (+)-mimosifoliol (**225**). The formal synthesis of (+)-tolterodine, a related natural product, was also accomplished using a similar multicomponent reaction process.[100]

3.9. *ortho*-Hydroxyalkylation of Phenols Followed by *o*-Quinone Formation and [4 + 2]-Cycloaddition

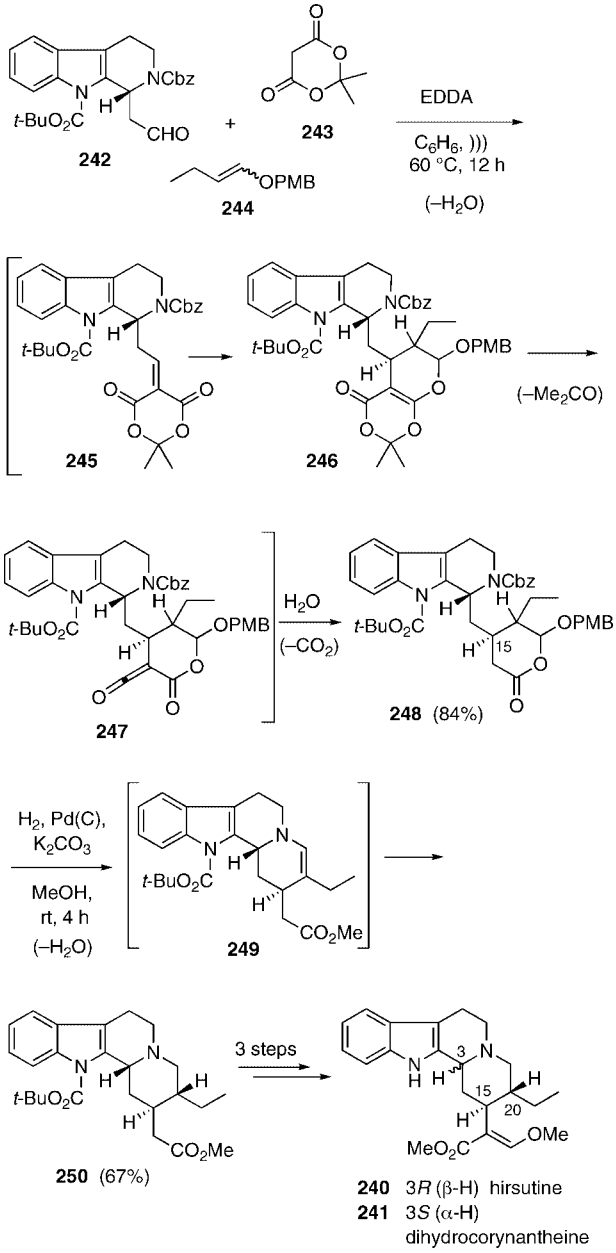
A complementary approach to accessing *ortho*-quinone methides to that discussed in the previous section is discussed below in the context of an application to the synthesis of the antimalarial natural products robustadials A (**233**) and B (**234**)[101] (Scheme 36).[102] This efficient two-step biomimetic synthesis was accomplished using the hetero-Diels−Alder cycloaddition of an *ortho*-quinone methide generated in situ by the *ortho*-hydroxyalkylation of a phenol precursor (Scheme 36).[102] Thus, a diformylation of phloroglucinol (**235**) with the Vilsmeier−Haack reagent afforded phenol derivative **236**. In the presence of (−)-*β*-pinene (**238**), the *ortho*-hydroxyalkylation of **236** with valeraldehyde (**237**) (a Knoevenagel condensation) followed by in situ dehydration afforded the reactive *ortho*-quinone methide intermediate **239**, which underwent a regioselective hetero-Diels−Alder cycloaddition with pinene to provide a separable mixture of targeted natural products **233** and **234**. The use of microwave activation afforded a combined yield of 68%, but conventional heating conditions (80 °C, 2 h) provided a similar outcome. The regioselectivity of the cycloaddition is thought to originate from steric control, with the most hindered heterodiene termini reacting with the pinene's least hindered alkene carbon. The diastereoselectivity (or lack thereof) leading to both **233** and **234** is explained by the *E*/*Z* isomerism of the enone intermediate **239**.

3.10. Domino Knoevenagel Condensation/ Hetero-[4 + 2]-Cycloaddition

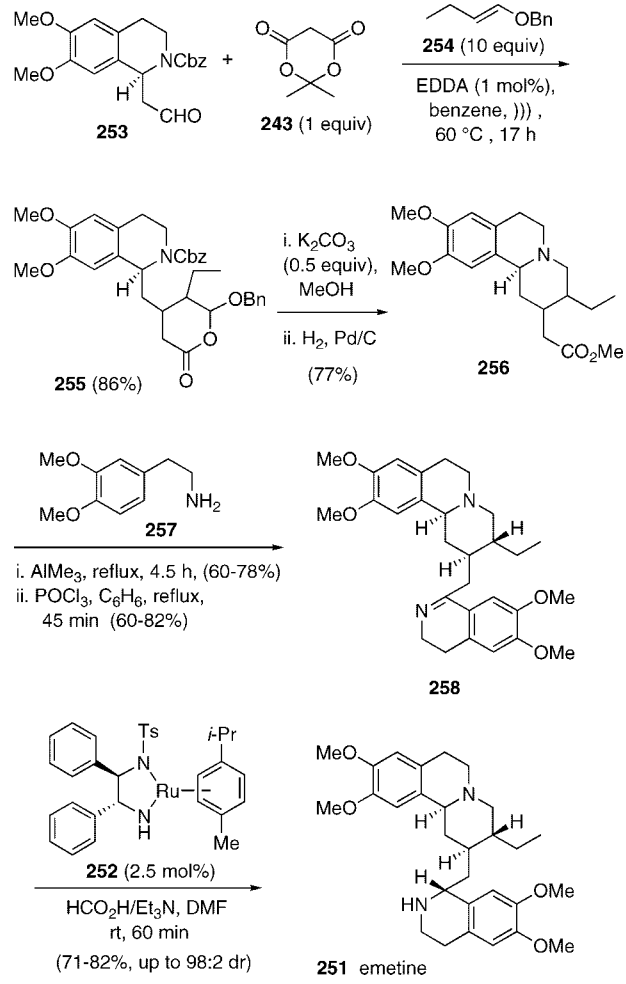
Indole alkaloids are a predominant class of bioactive natural products.[103] In addition to the indole nucleus, they present a wide variety of additional functionalities and complex structural elements. To construct the second piperidine unit and generate two new stereocenters en route to the total biomimetic syntheses of the indole alkaloids hirsutine (**240**) and dihydrocorynantheine (**241**) (Scheme 37),[104] Tietze and Zhou applied a very elegant three-component Knoevenagel/hetero-Diels−Alder reaction previously optimized by the same group and used in the synthesis of a number of other indole alkaloids.[105] This time, optically pure tetrahydro-*β*-carboline carbaldehyde **242** was employed as an advanced precursor. Thus, as exemplified in the total synthesis of hirsutine (**240**) (Scheme 37), a potent inhibitor of the influenza A virus,[106] a one-pot domino Knoevenagel condensation/hetero-Diels−Alder reaction between **242**, Meldrum's acid (**243**), and enol ether **244** afforded lactone **248** with a high degree of stereoselectivity (>20:1 at C15). This three-component process is carried out under sonication and mild acid catalysis and is initiated by a Knoevenagel condensation between **243** and the aldehyde group of **242**, leading to the formation of intermediate **245**. The latter plays the role of 1-oxobutadiene and is trapped with the enol ether (**244**) in a highly face-selective hetero-Diels−Alder reaction to generate intermediate **246**. Under the reaction conditions, the latter rapidly decomposes to lose acetone, presumably giving ketene **247** from a formal retro-[4 + 2] process. This event would be followed by a decarboxylation induced by the reaction of the water produced in the Knoevenagel condensation, affording lactone **248** in a very good yield. The synthesis was completed by another one-pot domino process consisting of methanolysis, cyclic enamine formation, and in situ stereoselective hydrogenation of **249** to give fused bipiperidine **250**. From **250**, cleavage of the *t*-Boc group followed by condensation with methyl formate and treatment with diazomethane provided the desired indole alkaloid hirsutine (**240**). A similar synthetic approach led to C3-epimer **241**, albeit with a lower diastereoselectivity. This very impressive sequence of chemical reactions provides a striking demonstration of the use of multicomponent reactions to rapidly generate complex polycyclic structures in a highly stereoselective fashion.

The asymmetric transfer hydrogenation of imines[107] represents a very useful synthetic tool for the elaboration of optically active isoquinolines, a structural unit often encountered in alkaloid natural products. One such example is emetine (**251**, Scheme 38), the main alkaloid found in the root of *Cephaelis ipecacuanha*.[108] It has been used for centuries as emetic and was subsequently shown to be a potent antiamebic.[109] A concise synthesis of this compound as well as a small library of analogues were reported by Tietze and co-workers.[110] In addition to featuring the Noyori asymmetric transfer hydrogenation with catalyst **252**,[107] this

Scheme 37. Synthesis of Hirsutine and Dihydrocorynantheine Using a Domino Three-Component Knoevenagel/Hetero-[4 + 2] Cycloaddition/Retro-[4 + 2] Fragmentation, by Tietze and Zhou[104]



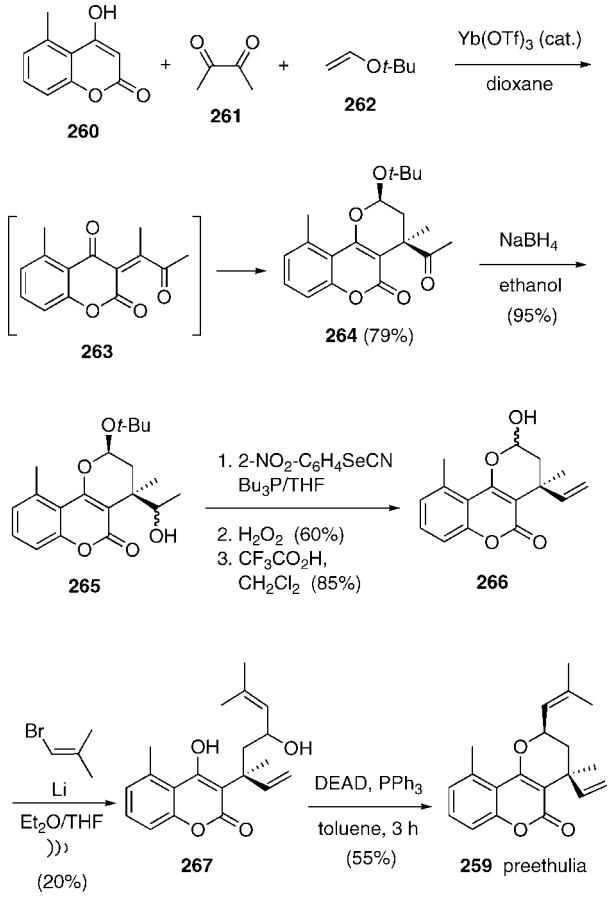
Scheme 38. Synthesis of Emetine Using a Domino Three-Component Knoevenagel/Hetero-[4 + 2]-Cycloaddition/Retro-[4 + 2]-Fragmentation, by Tietze and Co-workers[110]



synthesis makes use of the powerful three-component domino Knoevenagel condensation/hetero-[4 + 2]-reaction sequence previously described (cf. Scheme 37). The optically pure aldehyde **253**, itself made using the asymmetric transfer hydrogenation, was engaged in the domino three-component reaction cascade with Meldrum's acid (**243**) and 3-butenyl benzyl ether **254** to afford lactone **255** in high yield (Scheme 38). The latent aldehyde functionality of **255** was revealed by methanolysis and subsequently allowed to react with the deprotected piperidine unmasked under hydrogenolysis conditions. This sequence of events led to the efficient formation and isolation of the tricyclic framework **256** of the natural product. The ester functionality was then reacted with 2-(3,4-dimethoxyphenyl)ethylamine (**257**), and the resulting amide was converted into cyclic imine **258** using the Bischler−Napieralski reaction protocol.[111] A second asymmetric transfer hydrogenation catalyzed by **252** then completed the synthesis of emetine (**251**) and several analogues thereof.

Preethulia coumarin (**259**, Scheme 39) represents a naturally occurring analogue of ethuliacoumarin, a prenylated polyketide. It possesses powerful anthelmintic and molluscicidal activities.[112] Some analogues have also shown a similar activity profile, which rendered their syntheses rather valuable. The synthesis of (±)-preethulia coumarin by the groups of Appendino, Cravotto, and co-workers[113] started with a variant of the three-component Knoevenagel/hetero Diels−Alder reaction developed by Tietze and co-workers. Thus, 4-hydroxycoumarin (**260**), 2,3-butadione (**261**), and vinyl *t*-butyl ether (**262**) were combined under established reaction conditions to afford the desired MCR adduct **264** in a satisfactory yield (Scheme 39). The ketone was then reduced with $NaBH_4$, and the resulting alcohol **265** was eliminated to establish the required terminal olefin in intermediate **266**. The latter was obtained as an unstable mixture of hemiacetals following cleavage of the *t*-butyl ether with trifluoroacetic acid, and it was immediately submitted to a nucleophilic norprenylation to furnish diol **267**. Finally, an intramolecular Mitsunobu etherification afforded the target molecule **259**.

Scheme 39. Synthesis of Preethulia Using a Three-Component Knoevenagel/Hetero-[4 + 2]-Cycloaddition/Retro-[4 + 2]-Fragmentation, by Appendino et al.[113]



4. Multicomponent Reactions Initiated by a Nucleophilic Addition to Epoxides

4.1. Silyl Dithiane Anion Alkylation/Brook Rearrangement/Dithiane Anion Alkylation

As demonstrated in section 3.1, the Brook rearrangement is readily amenable to the design of multicomponent reactions. On the basis of this concept, Smith and Boldi developed an elegant "linchpin" three-component reaction for the synthesis of polyol chains featuring the union of a silyl dithiane with two different terminal epoxides.[114] This reaction process, first demonstrated by Tietze and co-workers using a single epoxide,[115] features two consecutive one-pot dithiane anion alkylations via intermediacy of a Brook 1,4-rearrangement[60] for generating the second anion in situ (Figure 6).

Smith and co-workers demonstrated the power of this three-component reaction through the efficient syntheses of the A/B and C/D bis-spiroketal units of the spongistatins (**268** and **269**, Figure 7),[116] which are members of a family of highly cytotoxic marine natural products.[117]

One of the most popular synthetic routes to cyclic ethers and ketal derivatives is based on the cyclization of a linear ketodiol precursor, and this approach was also exploited by Smith and co-workers in their synthesis of the A/B fragment **270** (Scheme 40). Thus, treatment of lithiated 2-triethylsilyl dithiane **272** with epoxide fragment **273** led to alkoxide intermediate **274**. The addition of HMPA to the flask, a procedure known to accelerate similar types of 1,4-Brook rearrangements,[118] triggered the transfer of the triethylsilyl (TES) group of **274** from carbon to oxygen, which generates the second dithianyl anion **275**. Addition of epoxide fragment **276** to the latter ultimately afforded polyol derivative **277** after workup. In this solvent-controlled MCR, the sequential addition of HMPA followed by the second epoxide is a crucial operation to ensure that no bisalkylation of the first epoxide is observed, thereby allowing the desired reaction sequence to proceed in a one-pot procedure. Deprotection of the ketone of **277** through mercury(II)-promoted dithiane hydrolysis, concomitant with in situ spiroketalization, provided product **278** as a single isomer. From **278**, a number of standard functional group transformations led to advanced A/B fragment **270**. The C/D fragment **271** was elaborated using a similar linchpin three-component strategy (Scheme 41). The union of the two fragments (**270** and **271**) via a stereoselective aldol reaction led to an advanced intermediate described by Paterson and co-workers,[119] thereby providing a formal total synthesis of spongistatin 1 (**268**).

A large number of macrolide natural products contain long, stereodefined polyol fragments. In their original report on the "linchpin" three-component coupling of silyl dithianes with epoxides,[114] Smith and Boldi prepared a protected 11-carbon fragment related to the 1,3-polyol half of the macrolide roflamycoin. More recently, using a powerful strategy similar to that of the synthesis of the calyculins described above (cf. Schemes 40 and 41), Smith and co-workers reported the preparation of an advanced 18-carbon polyol fragment of the antifungal glycosylated macrolide (+)-rimocidin (**284**, Scheme 42).[120] Sequential coupling of dithianyl unit **279** with epoxides **285** and **286** led to the isolation of masked polyol intermediate **287** accompanied by a small amount of monocoupling product. Intermediate **287** was transformed in four steps to advanced diketone fragment **288**. Although the total synthesis of **284** has not been completed as yet, protected polyol intermediate **288** contains almost all of the required stereochemical and structural elements but for the sugar and polyene units. The same group developed a variant of the three-component linchpin coupling to synthesize naturally occurring alkaloids. To this end, Smith and Kim found that sulfonylaziridines can be employed as the second electrophile in place of an epoxide. The first application of this strategy was directed toward the total synthesis of indolizidine 223AB (**289**, Scheme 43),[121,122] a bicyclic alkaloid isolated from the skin of the neotropical dart-poison frogs of the *Dendrobates* genus.[123] The key three-component operation of the synthesis first involved the opening of epoxide **290** with the anion of **279** to give **291**, followed by the addition of HMPA and aziridine **292** as the second electrophile in the reaction

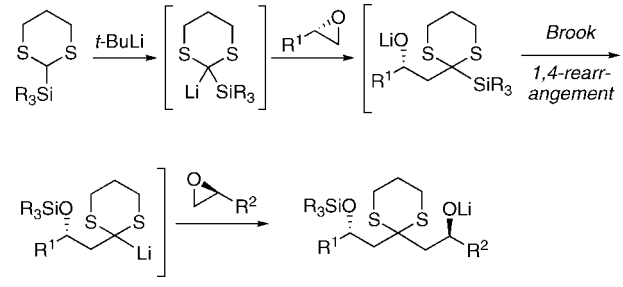


Figure 6. Mechanistic sequence for the three-component alkylation of dithiane anion followed by Brook rearrangement and final dithiane anion alkylation.

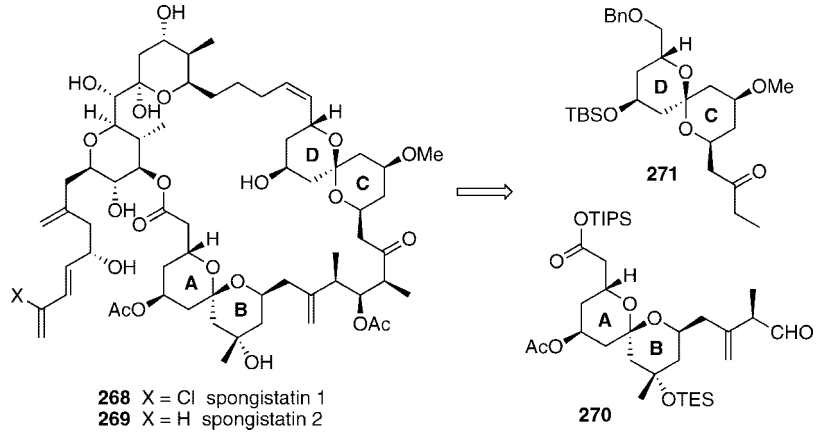
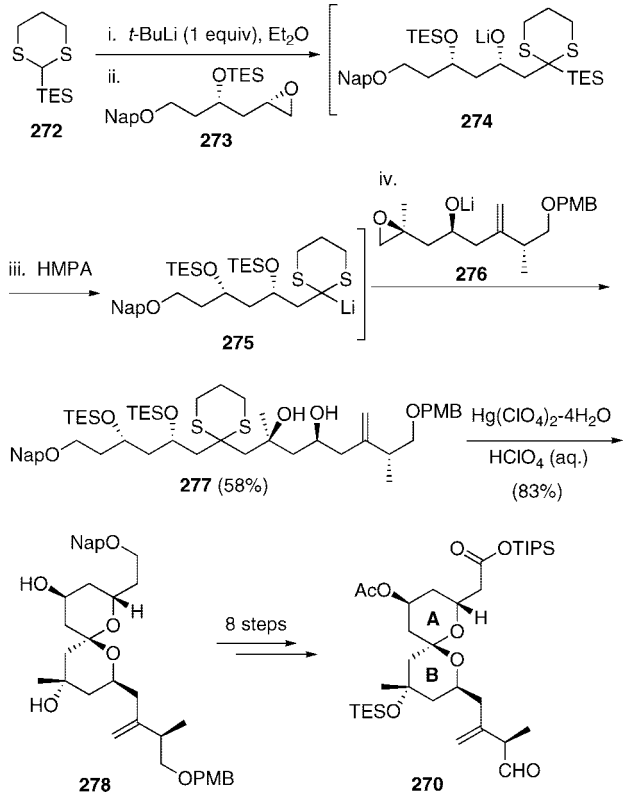
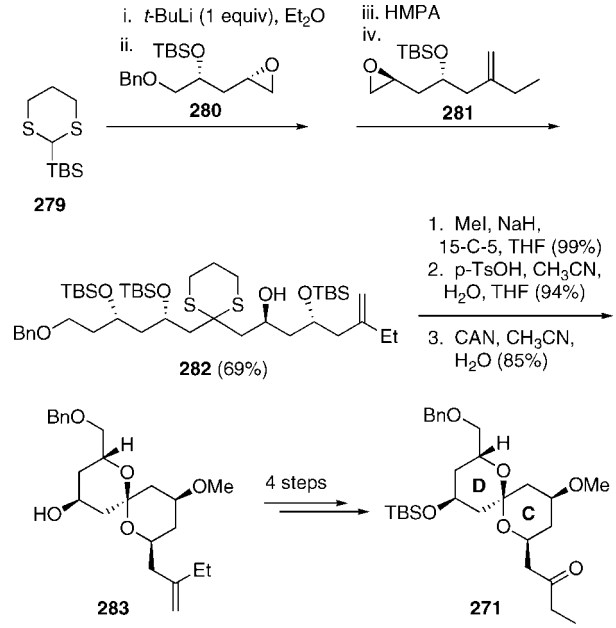


Figure 7. Chemical structures of the spongistatins and spiroketal fragments.

Scheme 40. Synthesis of a Spongistatin Spiroketal A/B Fragment Using a Three-Component Dithianyl Anion Alkylation/Brook Rearrangement/Dithianyl Anion Alkylation, by Smith and Co-workers[116]



Scheme 41. Synthesis of a Spongistatin Spiroketal C/D Fragment Using a Three-Component Dithianyl Anion Alkylation/Brook Rearrangement/Dithianyl Anion Alkylation, by Smith and Co-workers[116]

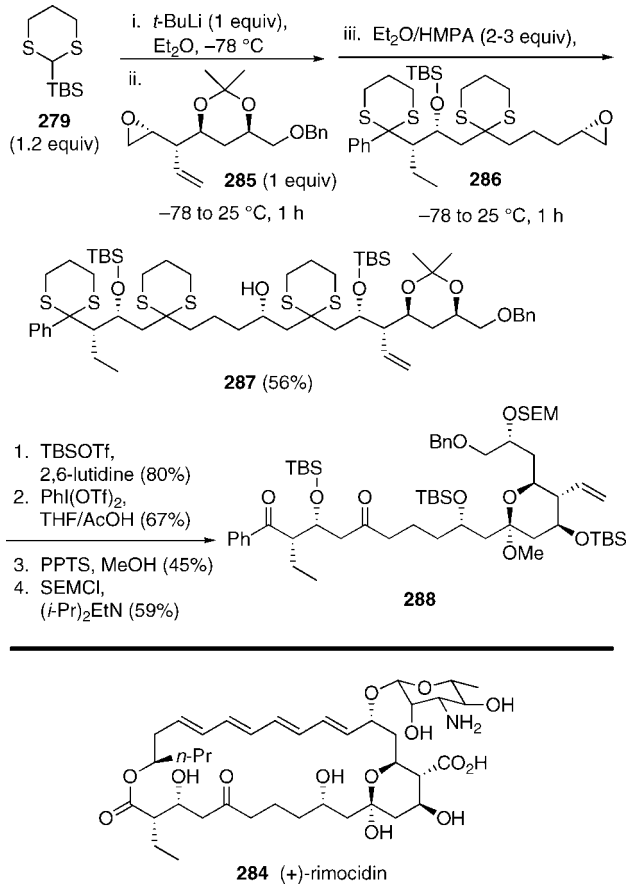


mixture. The double dithiane coupling product **294** was obtained in 56% yield accompanied by a significant amount of monocoupling product **295**. The synthesis was completed in a few steps involving deprotection and mesylation of the two secondary alcohols, followed by a double intramolecular S_N2 displacement to give **297**. Then, the dithiane group was reductively removed to afford the desired natural product, (−)-indolizidine 223AB (**289**). A second illustration of this strategy was reported in the context of the total synthesis of the related alkaloid (−)-205B (**298**, Scheme 44).[124] In this case, however, the Brook rearrangement step on intermediate **300** was triggered by adding aziridine **301** in THF containing 1,2-dimethoxyethane (DME). The use of HMPA or DMPU led to much smaller yields of the three-component product **302**. The remaining steps toward the total synthesis of **298** were similar to those used in the previous synthesis of indolizidine **289** (cf., Scheme 43). To construct the third ring from intermediate **303**, a ring-closing metathesis using the second-generation Grubbs catalyst was called upon. The total synthesis of **298** was subsequently completed in eight additional steps.

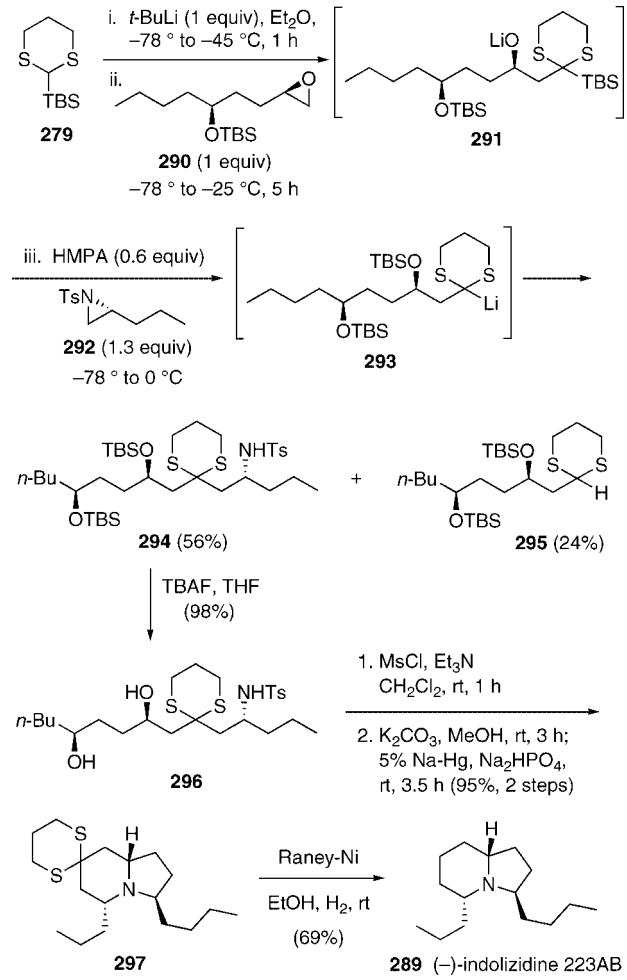
4.2. Anion Relay via Alkoxide Formation/Remote Brook Rearrangement/Dithiane Anion Alkylation

In the original linchpin three-component coupling strategy of Smith co-workers (see previous section), the entire process hinged on the use of 2-silyl-1,3-dithianes for a selective, sequential double alkylation at the same dithianyl carbon via a 1,4-Brook rearrangement. Realizing the potential of this approach for remote carbon-to-oxygen silyl rearrangements, other linchpins were designed where the dithiane fragment acts both as an electrophile in the first fragment union and as a nucleophle during the course of a second coupling. This multicomponent coupling tactic was termed anion-relay chemistry (ARC) and was first designed with a silyldithianyl epoxide linchpin as depicted conceptually in Figure 8.[125]

Scheme 42. Synthesis of (+)-Rimocidin Using a Three-Component Dithianyl Anion Alkylation/Brook Rearrangement/Dithianyl Anion Alkylation, by Smith and Co-workers[120]



Scheme 43. Synthesis of (−)-Indolizidine 223AB Using a Three-Component Dithianyl Anion Alkylation/Brook Rearrangement/Dithianyl Anion Alkylation, by Smith and Kim[121,122]



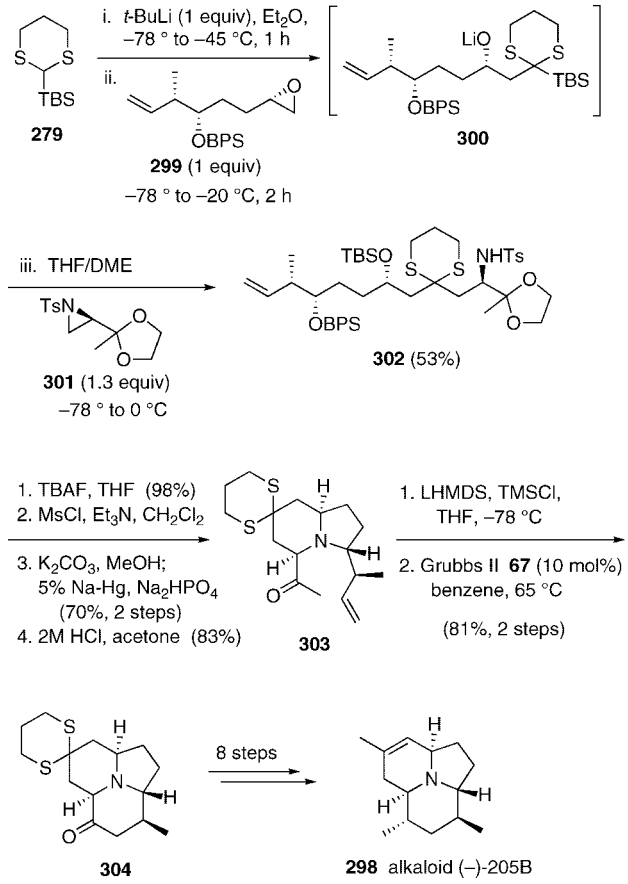
To demonstrate the anion-relay chemistry in the context of complex natural product synthesis, Smith and Kim targeted the southern C1−C25 fragment of spirastrellolide A (**305**, Scheme 45),[126] a unique polyketide isolated from the Caribbean sponge *Spirastrella coccinea*.[127] Spirastrellolide has demonstrated potent activity as an inhibitor of protein phosphatase PP2A. The preparation of the B/C spiroketal unit **312** (C10−C22) of **305** was initiated by the treatment of dithiane fragment **306** with Schlosser's base (*n*-BuLi/KO-*t*-Bu). This deprotonation was followed by addition of known linchpin **307** to provoke the desired nucleophilic epoxide opening giving alkoxide **308** and a subsequent 1,4-Brook rearrangement to unveil a carbanion intermediate, **309**. Addition of epoxide **310** then completed the one-pot, three-component coupling to afford **311** in the excellent yield of 77%. The latter was transformed in a 10-step sequence into spiroketal fragment **312**. It is noteworthy that the remarkable three-component coupling was performed on a scale of five grams.

Continuing on the theme of anion-relay chemistry, Smith and co-workers have hypothesized that the known bifunctional synthon **316**[128] (Scheme 46) should readily participate in a three-component coupling with appropriate electrophiles and nucleophiles. The successful development of this chemistry[129] paved the way to its application to the synthesis and stereochemical assignment of the sesquiterpene (+)-**313** derived from the Caribbean gorgonian coral *Plexaurella grisea*.[130] Toward this goal, skipped diene **314** was treated with Schlosser's base to give a pentadienyl anion, **315**, followed by the addition of the linchpin **316** and prenyl bromide as reaction components (Scheme 46). The desired MCR adduct **319**, bearing all of the natural product's carbon framework, was isolated in 38% yield after hydrolysis of the siloxy group. The mechanistic sequence of events leading to the formation of the MCR adduct **319** is analogous to the ones described above (c.f., Figure 7). On a technical note, the Brook rearrangement in this newer variant proceeds without the need for HMPA as a cosolvent. From **319**, the enantioselective synthesis of the natural product **313** was completed via a Dess−Martin oxidation of the secondary alcohol, CBS reduction of the resulting ketone, and a final acetylation step of the newly created alcohol intermediate **320**.

5. Three-Component Mannich Reactions and Other Imine Addition Reactions

The intermolecular Mannich reaction combines an aldehyde, an amine, and an enolizable carbonyl compound for the one-pot synthesis of beta-amino ketones or esters.[131] It is among the most useful synthetic transformation and has found widespread applications in the "atom economical" synthesis of a number of alkaloid natural products. These efforts are summarized below.

Scheme 44. Synthesis of Alkaloid (−)-205B Using a Three-Component Dithianyl Anion Alkylation/Brook Rearrangement/Dithianyl Anion Alkylation, by Smith and Co-workers[124]



5.1. Direct Mannich Reaction

Direct Mannich reactions may present challenges of chemoselectivity when using two different carbonyl components such as aldehydes and ketones. These problems are circumvented when a preformed enolate is employed (section 5.2) or when one component is a nonenolizable aldehyde. The first report of a proline-catalyzed 3CR coupling of amines, ketones, and aldehydes by List marked the beginning of a flourishing era of organocatalytic Mannich reactions.[132] This direct variant affords syn products, which are not accessible under the conditions described below for directed Mannich reactions with preformed enolates. As such, the two methods nicely complement each other and bring to bear two powerful strategies that can be relied upon for the rapid

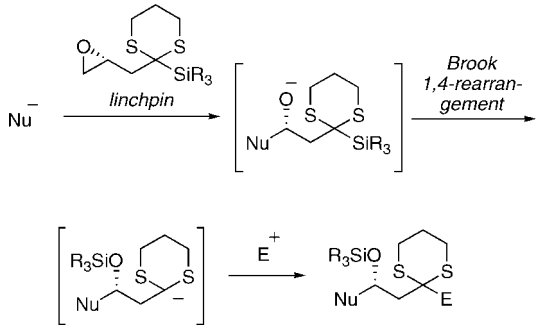
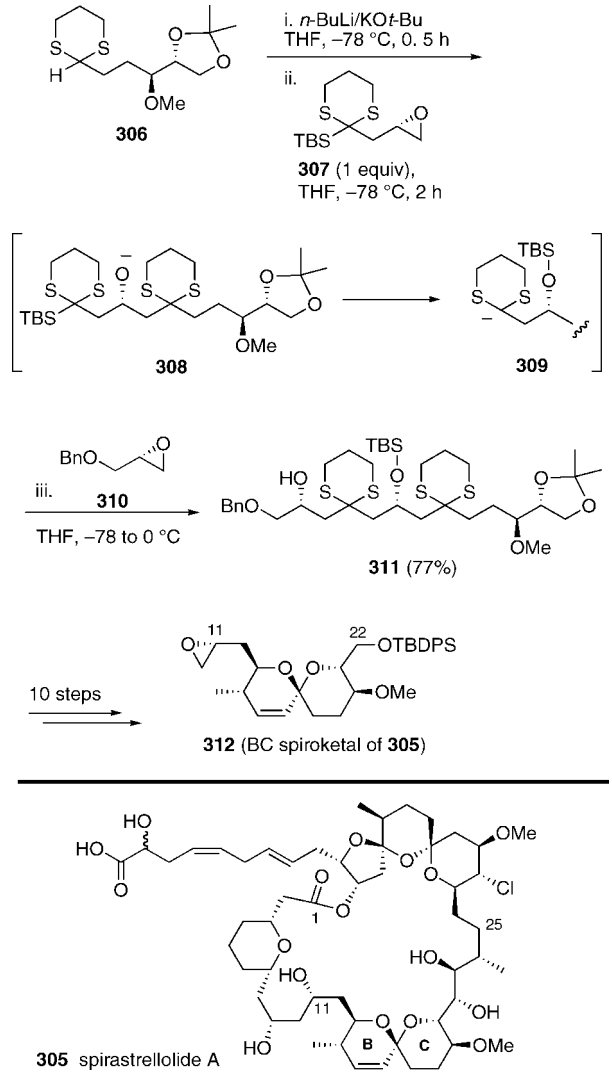


Figure 8. Mechanistic sequence for the three-component anion-relay 3CR via alkoxide formation followed by Brook rearrangement and final dithiane anion trapping.

Scheme 45. Synthesis of the B/C Spiroketal Fragment of Spirastrellolide A Using the Three-Component Anion-Relay Three-Component Reaction via Alkoxide Formation Followed by Brook Rearrangement and Final Dithiane Anion Alkylation, by Smith and Kim[126]

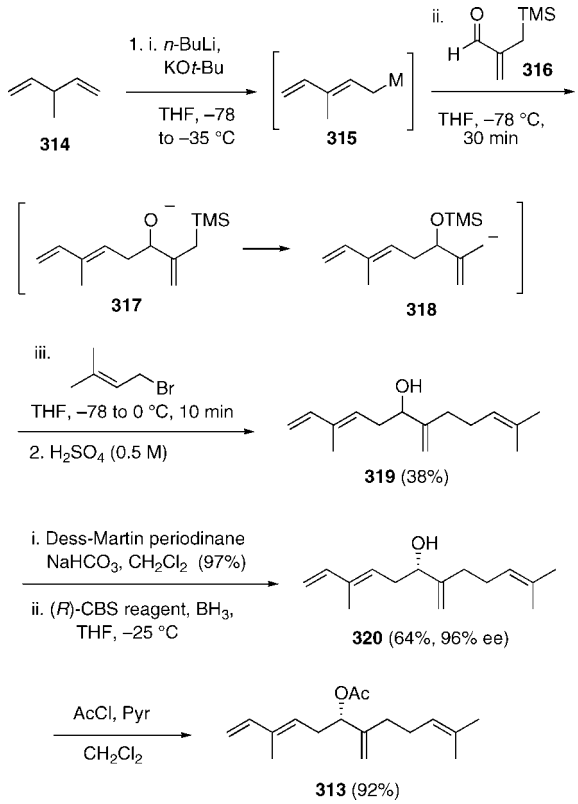


stereoselective assembly of many nitrogen-containing natural products. The version of interest, developed by the Hayashi group, employs anisidine and two different aldehydes and proceeds by way of trapping the reaction product between a nonenolizable aldehyde and anisidine with an in situ generated proline enamine, thus directly affording α-substituted-β-amino aldehydes (Figure 9).[133] A subsequent conversion of the aldehyde functionality into the corresponding alcohols, by nucleophilic addition, is essential to overcome product stability issues.

The overall reaction sequence leads to β-aminoalcohols, which are prevalent in drug candidates, and more importantly in naturally occurring substances. In this regard, the nikkomycin family of antibiotics,[134] examplified by **321** and **322**, were selected to test this impressive direct catalytic enantioselective cross-Mannich reaction.[135] The structure of nikkomycins embed a α-methyl-β-aminoalcohol stereotriad, which was accessed as shown in Scheme 47.

The L-proline-catalyzed enantioselective Mannich reaction involving *p-tert*-butyldimethylsiloxyaniline (a *p*-anisidine surrogate) (**323**), furaldehyde (**324**), and propanal proceeded smoothly to afford **325** in excellent yield and high diastereo-

Scheme 46. Synthesis of a Sesquiterpene Using the Three-Component Anion-Relay Three-Component Reaction via Alkoxide Formation Followed by Brook Rearrangement and Final Allylic Anion Alkylation, by Smith and Co-workers[129]



and enantioselectivity. A subsequent treatment of **325** with 4-methoxyphenyl magnesium bromide (**326**) in the presence of copper iodide afforded a mixture of syn/syn- and syn/anti-diastereomers **327**. The latter isomer was then converted into lactone **328** in several steps.[135] Although no synthesis of any of the nikkomycins was completed, lactone **328** can be considered as a legitimate precursor to both natural products.

5.2. Mannich Reaction with Preformed Enolates

A directed Mannich-type MCR was recently used as a key step for the asymmetric synthesis of the antimalarial alkaloids febrifugine (**329**) and isofebrifugine (**330**) by Kobayashi and co-workers (Scheme 48).[136] The required aldehyde precursor **331** was obtained by a Sn(II)-catalyzed asymmetric aldol reaction.[137] It was then mixed in one pot with *o*-methoxyaniline (**332**) and enol ether **333** to afford the key beta amino ketone **334** in a 2:1 diastereomeric ratio through a Mannich-

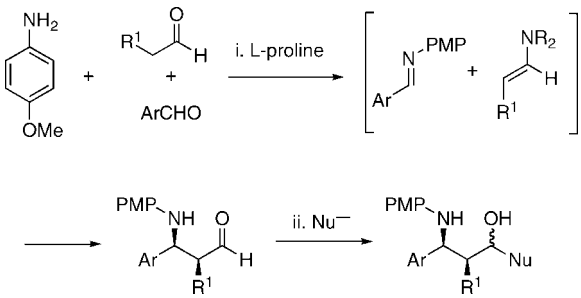
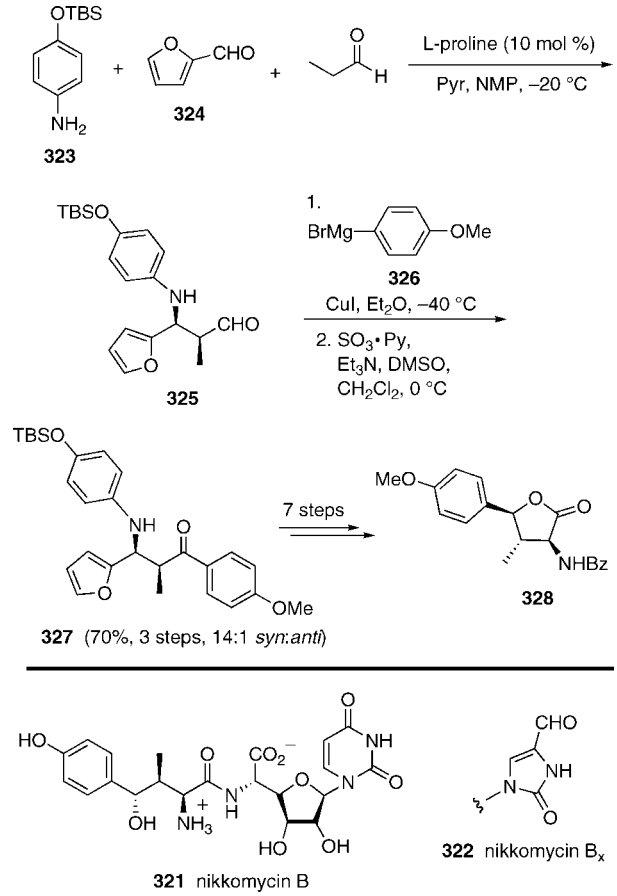


Figure 9. Mechanistic sequence for the direct Mannich three-component reaction.

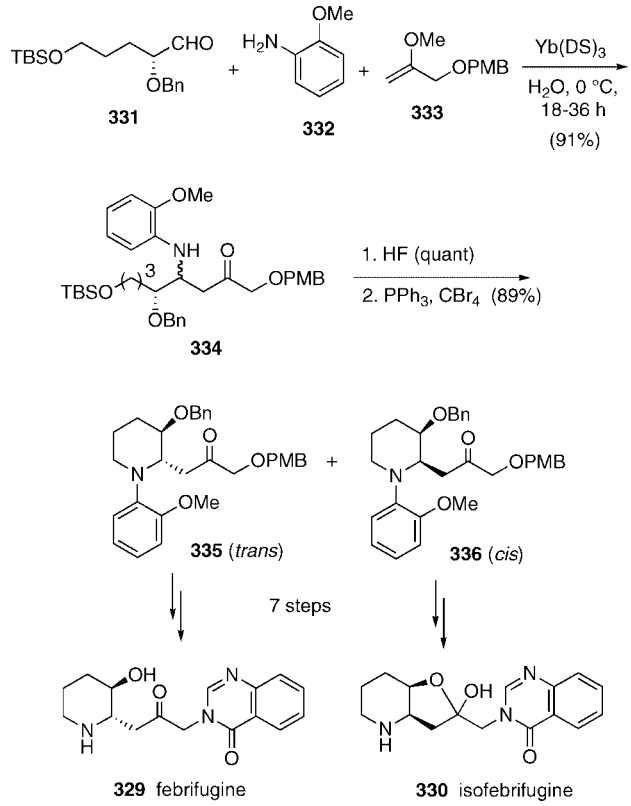
Scheme 47. Approach toward Nikkomycins Using a Direct Three-Component Mannich Reaction, by Hayashi and Co-workers[135]



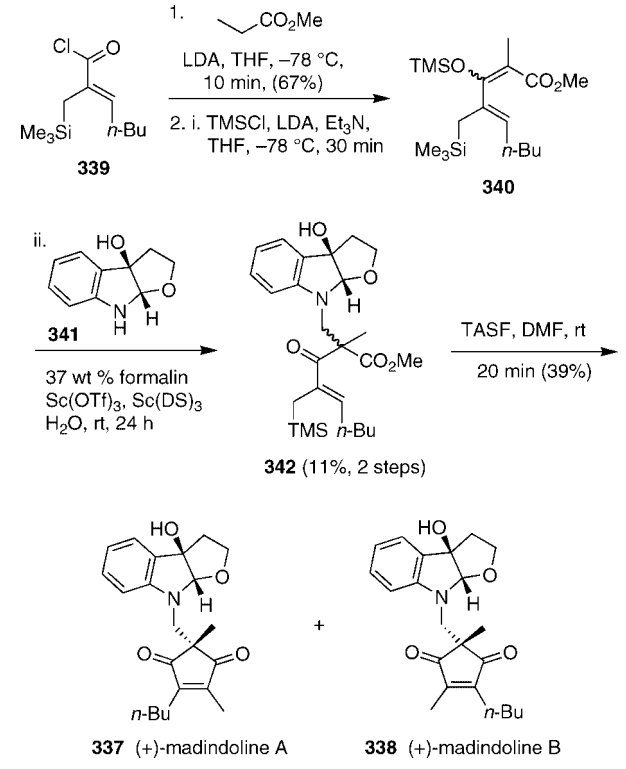
type three-component reaction. This reaction was performed in an aqueous medium, and the use of surfactant such as dodecyl sulfate (DS) was essential. The diastereomeric mixture (**334**) was treated with HF, and the resulting primary alcohol was converted to a bromide, which underwent nucleophilic cyclization to afford piperidines **335** and **336**. The intermediates were then separated and independently elaborated in seven steps into **329** and **330**. The measured optical rotation of these compounds led to the conclusion that they were antipodes of the natural products. A similar synthetic sequence led to the synthesis of the corresponding enantiomers, which were shown to have optical rotation identical to the respective natural products.

Since the isolation of madindolines A and B (**337** and **338**, Scheme 49), which are two inhibitors of interleukin 6 (IL6) signaling,[138] Smith, Omura, and co-workers have spent considerable efforts developing a practical stereoselective synthesis.[139] Recently, they proposed a solution to the challenging construction of the quaternary carbon center based on a three-component Mannich reaction.[140] At the outset, conditions favoring reaction between α-substituted-β-keto esters and 3a-hydroxyfuroindoline-derived iminiums had to be identified. Initial exploratory work established that the former had to be converted to their enol ether equivalents due to their low reactivity. In addition, catalyst screening efforts led to the identification of a mixture of lanthanides ($Sc(OTf)_3$ (10 mol %) and $Sc(DS)_3$ (20 mol %) (DS = tridodecylsulfate)) as an optimal system in aqueous media (so-called Kobayashi conditions).[141,142] With these conditions in mind, the synthesis of madindolines commenced with the

Scheme 48. Synthesis of Febrifugine and Isofebrifugine Using a Three-Component Mannich Reaction with an Enol Ether, by Kobayashi and Co-workers[136]

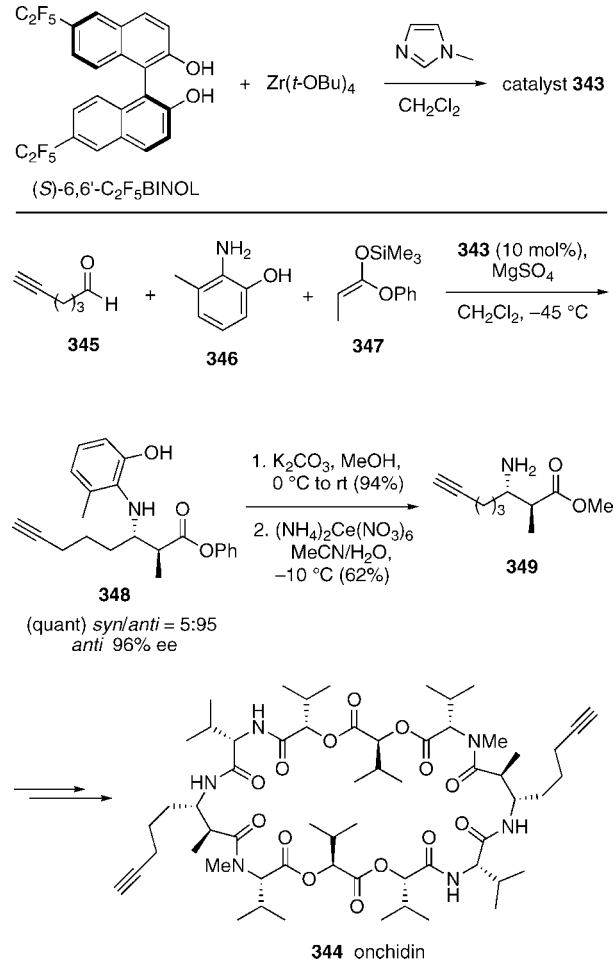


Scheme 49. Synthesis of Madindoline A and B Using a Three-Component Mannich Reaction with a Silyl Enol Ether, by Omura and Co-workers[139]



conversion of acyl chloride **339** into silyl enol ether **340** in two standard synthetic transformations (Scheme 49). Crude product **340** was then engaged in the key MCR involving formaldehyde and optically active (ee >99%) 3a-hydroxy-

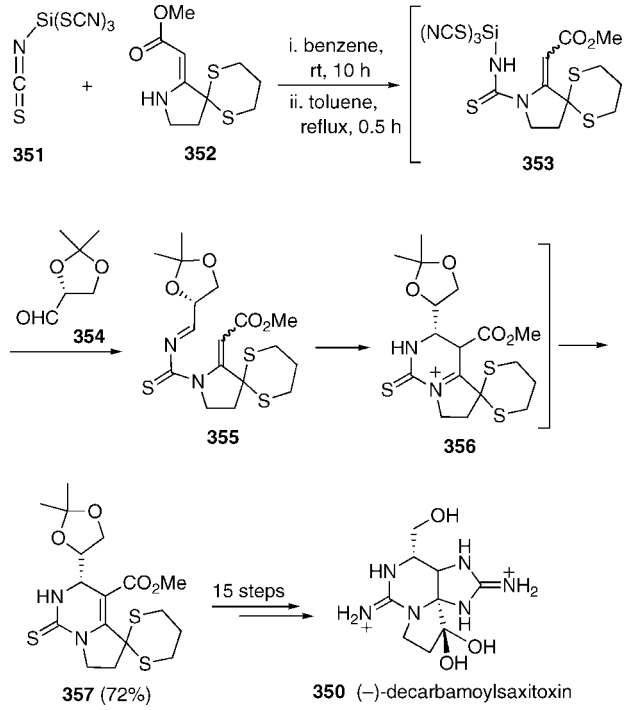
Scheme 50. Synthesis of Onchidin Using a Three-Component Mannich Reaction with a Silyl Enol Ether, by Kobayashi and Co-workers[147]



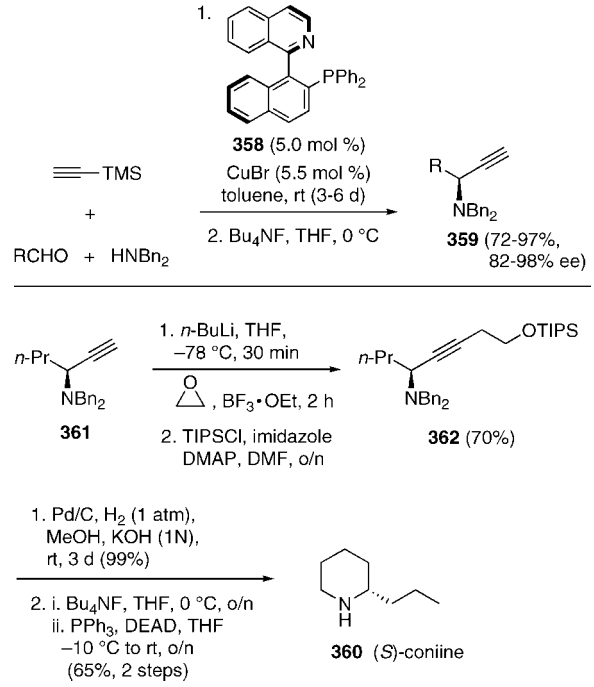
furoindoline (**341**) (easily accessible from tryptophol (3-(2-hydroxyethyl)indole) by Sharpless asymmetric epoxidation[143]) under the conditions described above. The ensuing product **342** was isolated in only 11% as a 1:1 diastereomeric mixture. Presumably, this poor outcome was due to the sensitive nature of **340** under the reaction condition, which was further exacerbated by steric issues that hindered its approach to the micelle-like environment around the Lewis acid. The synthesis was completed by an intramolecular endo allylsilation triggered by the addition of TAS-F, thus affording both madindolines A and B as a separable mixture.

Inspired by the marine depsipeptide natural products,[144] Kobayashi and co-workers have developed a catalytic enantioselective three-component directed Mannich reaction to access anti-α-methyl-β-amino acid units. The reaction is based upon the addition of ketene silyl acetals onto in situ generated imines in the presence of a structurally complex chiral zirconium catalyst, **343** (Scheme 50).[145,146] A notable characteristic of this catalyst is that it can be prepared simply by treatment of a zirconium alkoxide with an electron-deficient BINOL derivative and *N*-methyl imidazole. Although its structure is undetermined, it is isolated as a white powder that possesses superior catalytic properties. Use of this catalyst **343** leads predominantly to the anti-product irrespective of the olefin geometry. Both aromatic and aliphatic aldehydes are tolerated, although in the latter case, a significant erosion of the diastereoselectivity is observed as the steric demand is increased. The application of this

Scheme 51. Synthesis of (−)-Decarbamoylsaxitoxin Using a Three-Component Thiourea Formation/Imine Addition, by Hong and Kishi[149]



Scheme 52. Synthesis of (*S*)-Coniine Using a Three-Component Copper-Catalyzed Alkynylation of in situ Generated Imine, by Gommermann and Knochel[152]



catalytic enantioselective Mannich reaction to the synthesis of the (2*S*,3*S*)-3-amino-2-methyl-7-octynoic acid (AMO) fragments of onchidin, **344**, a cytotoxic natural product isolated from a marine mollusk,[144] was realized (Scheme 50).[147] The key Mannich MCR involved 5-hexynal (**345**), 2-amino-*m*-cresol (**346**), and ketene silyl acetal **347** in the presence of 10 mol % of the catalyst. The desired product **348** was isolated in excellent yield, with high diastereo- and enantioselectivity. A transesterification followed by reductive removal of the amine protecting group afforded amino ester **349**, thus completing the synthesis of a key building block en route to the final target **344**, which was completed in several additional steps.[147]

5.3. Mannich-type Reactions with Other Nucleophiles

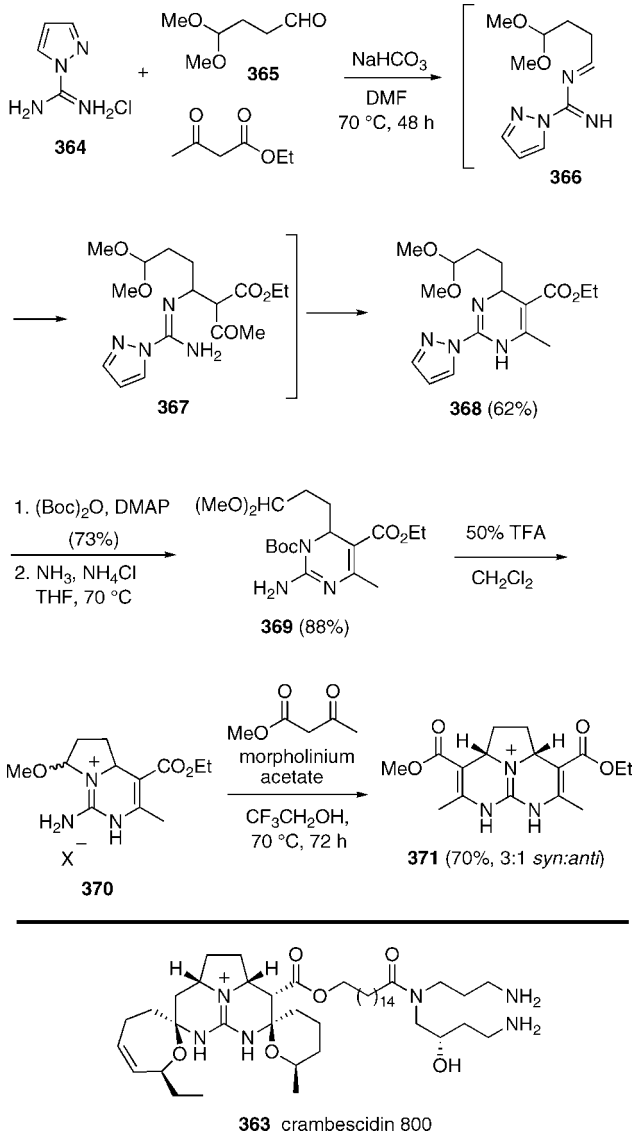
Decarbamoylsaxitoxin (**350**, Scheme 51) was first obtained from saxitoxin by acid hydrolysis and was later isolated as the minor toxic principle of the bivalve *Spondylus butleri* collected at Arumizu bay in Palau.[148] The toxicity of these compounds stems from their ability to block sodium channels. The unique heterocyclic backbone together with the sensitive functionalities embedded within this molecule make it a daring synthetic target. The enantioselective synthesis of the unnatural antipode by Kishi and co-workers was motivated by the controversy surrounding its biological activity (Scheme 51).[149] The key sequence started with a trimolecular cyclization of vinylogous urethane **352**, silicon tetraisothiocyanate (**351**), and (*R*)-glyceraldehyde 2,3-acetonide (**354**). The proposed stepwise mechanism of this elegant MCR features the Mannich-type cyclization of **355**, whose stereochemical outcome can be explained using a simple Felkin−Ahn model. The resulting product **357** was transformed into the synthetic unnatural antipode (−)-**350** using a multistep route. Interestingly, the resulting synthetic sample displayed none of the sodium channel blocking activity of its natural counterpart.

In recent years, there has been a renewed interest in developing new Mannich-type 3CRs to further exploit the rich diversity of readily available aldehydes and amines. In the search for new compatible nucleophiles, terminal alkynes have emerged as an attractive choice. Both the gold- and copper-catalyzed addition of alkynes onto in situ generated imines have been reported.[150−152] However, only the copper catalyzed variant has been applied in natural product synthesis thus far. In this instance, Knochel and co-workers have developed a catalytic asymmetric addition of trimethylsilyl (TMS)−alkynes onto *N*,*N*-dibenzyl imines in the presence of CuBr and QUINAP (**358**) as the chiral ligand (Scheme 52).[152] Although limited in scope of compatible alkynes, this reaction represents a significant improvement over the previous methodology disclosed by the same group.[151] It tolerates a wide range of aldehydes, and the propargylic amine products are obtained in moderate-to-excellent yield and high enantioselectivity. Subsequent removal of the protecting group affords terminal alkynes **359** that can be further derivatized (Scheme 52). For the synthesis of the small piperidine alkaloid coniine (**360**), treatment of **361** with *n*-BuLi was followed by the addition of oxirane to afford intermediate **362** that contained all of the requisite carbon skeleton.[152] The synthesis of this highly toxic alkaloid was completed in three additional standard synthetic manipulations.

5.4. Biginelli Reaction

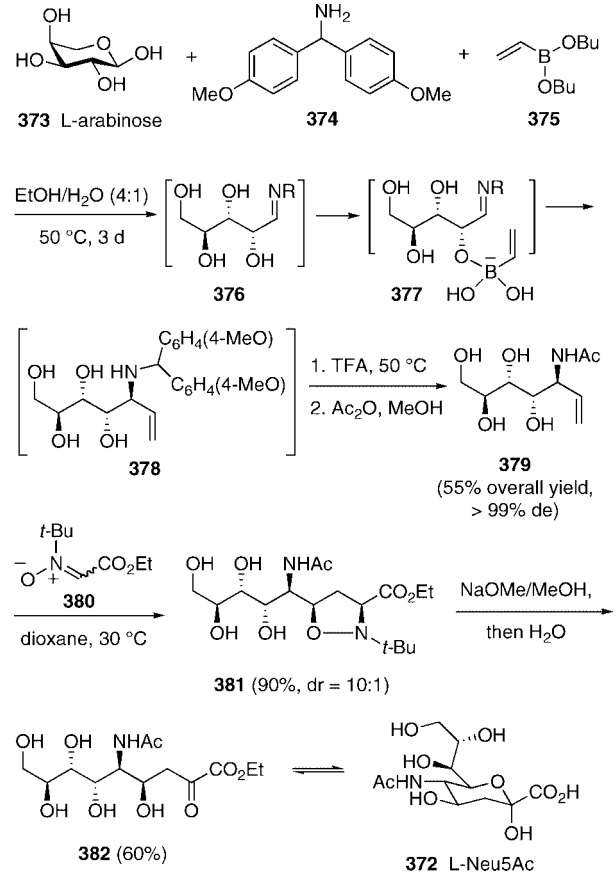
The Biginelli three-component reaction is one of the oldest examples of multicomponent reactions.[153] In recent times, it has been investigated extensively as a simple method to access polysubstituted dihydropyrimidinones from simple components: urea, aldehyde, and β-ketoester.[154] Although the Biginelli reaction was used in the preparation of combinatorial libraries for medicinal chemistry applications, it has

Scheme 53. Approach to the Core of Crambecscidins Using a Biginelli Three-Component Reaction, by Nilsson and Overman[157]



seldom been employed in the context of natural product synthesis. Overman and co-workers have exploited their elegant strategy of tethered Biginelli reactions in the syntheses of complex guanidine-containing alkaloids[155] such as batzelladine and the crambescidins.[156] One of the triazaacenaphthalene cores of batzelladine was assembled with a Biginelli reaction orchestrated as a sequential three-component procedure that required solvent changes between each step. A more recent approach to the core of the crambescidins (e.g., **363**), however, did make use of a one-pot, three-component Biginelli reaction followed by aminolysis, with a final tethered Biginelli reaction to complete the tricyclic core of the desired alkaloid (Scheme 53).[157] Thus, the base-promoted condensation between pyrazole carboxamidine **364**, masked dialdehyde **365**, and ethyl acetoacetate furnished 2-iminodihydropyrimidine **368** by way of a probable mechanism involving intermediates **366** and **367**. Guanidine protection and aminolysis gave **369**, which was treated with a strong acid to induce removal of the *t*-butyl carbamate and acetal formation to yield **370**. The latter was then treated with methyl acetoacetate to provide the advanced tricyclic guanidine intermediate **371** in modest diastereoselectivity. Although no synthesis of a guanidine alkaloid has yet been reported using this impressive Biginelli reaction sequence, it is evident from this compelling example that this powerful three-component reaction is a valuable strategy in natural product synthesis.

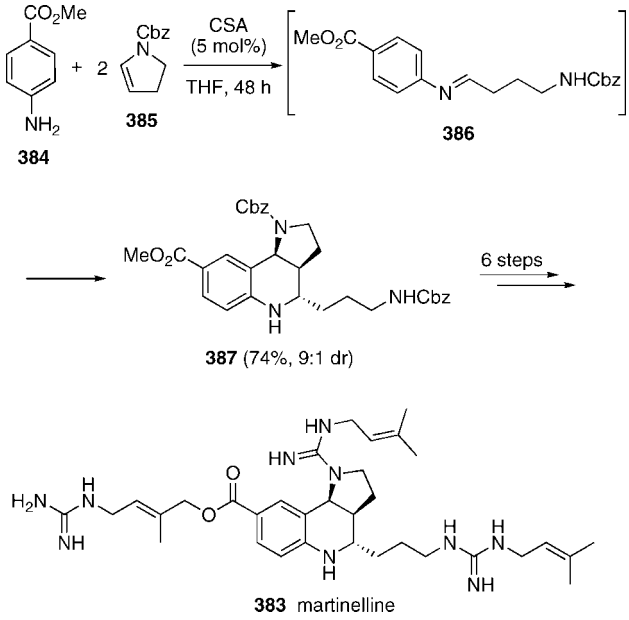
Scheme 54. Synthesis of *N*-Acetylneuraminic Acid Using a Petasis Three-Component Reaction, by Wong and Co-workers[160]



5.5. Petasis Reaction

The sialic acid family of monosaccharide natural products, exemplified by *N*-acetylneuraminic acid (Neu5Ac, **372**, Scheme 54),[158] are key agents in many important biological processes including cell−cell recognition, blood coagulation, and fertilization, and some analogues have reached the market as anti-influenza agents.[159] A key hurdle in this area remains the development of concise, cost-effective, and flexible synthetic routes to sialic acids and analogues thereof. To advance these frontiers, Wong and co-workers disclosed a sequential Petasis three-component condensation/nitrone cycloaddition route.[160] The success of this strategy was contingent upon the successful use of vinylboronic acid, a previously unexplored substrate in the Petasis reaction.[161] As the synthetic plan was put to execution, it was discovered that unveiling the boronic acid functionality in situ from a boronate precursor was critical due to stability issues under the conventional Petasis reaction conditions. Thus, mixing L-arabinose (**373**), amine **374**, and vinyl boronic ester **375** in a water/ethanol cosolvent under prolonged heating conditions yielded the desired Petasis three-component adduct **378** (via the putative intermediates **376** and **377**) (Scheme 54). This product was carried through the deprotection and acetylation steps without any purification to afford **379** in moderate yield and excellent diastereoselectivity. The dipolar

Scheme 55. Synthesis of Martinelline Using a Povarov Three-Component Reaction, by Powell and Batey[163]



cycloaddition involving **379** and nitrone **380** proceeded smoothly to afford **381** in high yield. The high diastereoselectivity observed in this reaction is attributed to the use of a bulky *t*-Bu substituent, which locked the nitrone predominantly in the *Z*-conformation. An efficient base-mediated fragmentation of the N−O bond and hydrolysis of the resulting imine completed a concise synthesis of L-Neu5Ac (**372**). A similar strategy also allowed the synthesis of D-Neu5Gc and other truncated and elongated sialic acid analogues, thus highlighting the flexibility of this MCR approach.

5.6. Povarov Three-Component Reaction

The antibiotic and G-protein coupled receptor ligand martinelline (**383**, Scheme 55) was isolated from the root extracts of the *Martinella iquitosensis*.[162] The retrosynthesis of this alkaloid by Batey and co-workers[163] recognized that the unprecedented hexahydropyrrolo[3,2-c]quinoline core could be synthesized using a three-component Povarov hetero Diels−Alder reaction.[164] For this synthetic strategy to be successful, however, reaction conditions that favor the *exo* approach of the dienophile over the *endo* approach had to be found. For this purpose, a variety of protic acids were tested, and it was found that the reaction was best performed in the presence of camphorsulfonic acid (CSA). Indeed, a mixture of 4-aminobenzoate **384** and *N*-Cbz 2-pyrroline (**385**) were stirred at room temperature in the presence of catalytic CSA to afford the aromatic imine intermediate **386**, which then underwent a [4 + 2]-cycloaddition and rearomatization to produce *exo* cyclo-adduct **387** as the major isomer (Scheme 55). The *N*-Cbz 2-pyrroline served both as an aldehyde equivalent and a dienophile in the present context, thus providing another example of an "A + B + B" MCR. The Diels−Alder adduct **387** already bore all the requisite functionalities for the successful completion of the synthesis of martinelline (**383**), which was successfully achieved in six additional steps.

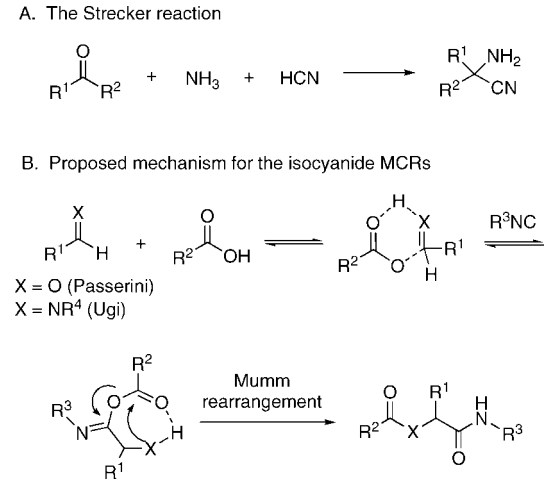


Figure 10. Mechanistic sequence of isocyanide-based multicomponent reactions for amino acid and peptide synthesis.

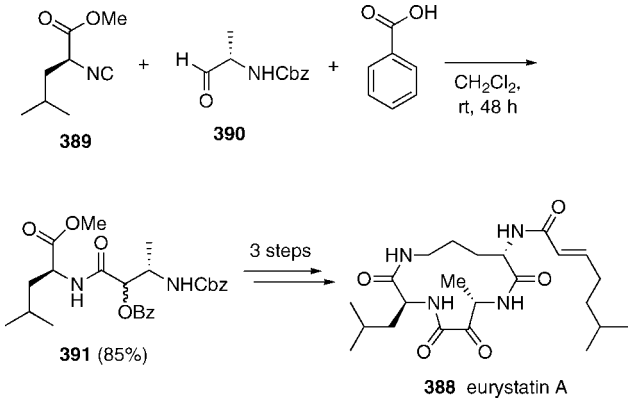
6. Multicomponent Reactions Based on Isocyanides

Synthetic peptides and their analogues have played major roles in the context of biological research and therapeutic applications. This is due in large part to the development of powerful methods and reagents for direct amide coupling,[165] as well as the invention of solid-supported synthesis.[166] Despite these advances, new avenues for the rapid elaboration of these biopolymers are still being explored. One emerging concept in this area is the development of MCRs. While the application of MCRs is still in its infancy, it has already delivered three of the most powerful and common tools for the synthesis of amino acids, peptides, and peptoids, be it cyclic or linear. The Strecker amino acid synthesis is of historical importance in chemistry as it represents one of the early examples of MCRs.[167] Coincidentally, this reaction addressed the formation of some of nature's fundamental building blocks: amino acids. Indeed, in 1850, Strecker demonstrated that α-amino cyanides could be obtained from simple and easily accessible materials such as ammonia, carbonyl compounds, and hydrogen cyanide (Figure 10A). This reaction process has been utilized for the synthesis of natural and unnatural amino acids and many asymmetric variants are now available.[168]

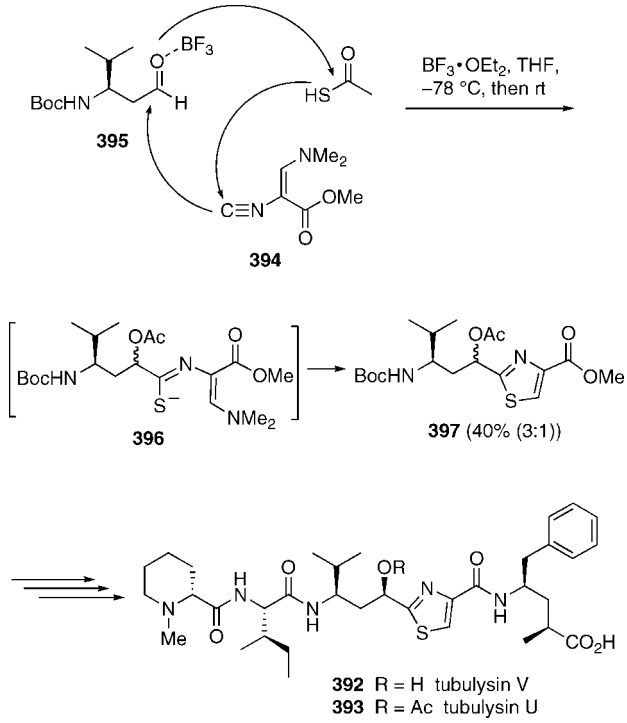
6.1. Passerini Reaction

Isocyanides, formal divalent carbon functionalities (R−N═C), are ideal candidates for the development of MCRs. Their reaction with carbonyls and imines, through an α-addition process, generates a zwitterionic nitrilium intermediate, which is then trapped by a nucleophile. The resulting double α-addition adduct is unstable and rapidly undergoes the Mumm rearrangement to afford the final product (Figure 10B). The venerable three-component Passerini reaction is the first MCR based on this type of molecular process.[169] It addresses the formation of α-acyloxycarboxamides, which constitute a class of very versatile synthons in organic chemistry. In the present context, this reaction was utilized by Schmidt and collaborators for the elaboration of intermediate **391**,[170] a key fragment for the synthesis of the prolyl endopeptidase inhibitor eurystatin A (**388**) (Scheme 56).[171] The initial α-addition adduct from the reaction of methyl (*S*)-2-isocyano-4-methylpentanoate (**389**) and protected (*S*)-alaninal (**390**) further reacted with benzoic acid to furnish

Scheme 56. Synthesis of Eurystatin Using a Passerini Three-Component Reaction, by Schmidt and Weinbrenner[170]



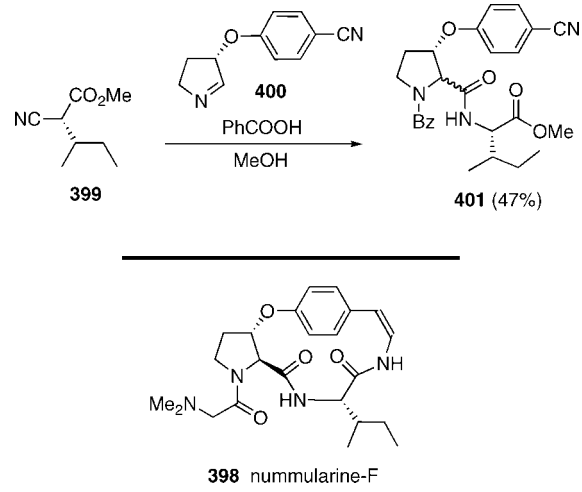
Scheme 57. Synthesis of Tubulysin V and U Using a Passerini-Type Three-Component Reaction, by Dömling et al.[175]



391 as a diastereomeric mixture. The stereochemistry of the resulting benzoyl protected alcohol was inconsequent since the latter functionality is oxidized during the course of the synthesis using pyridinium dichromate to afford the α-oxoamide in the final target. In general, however, in isocyanide MCRs, the control of the newly created stereogenic center is problematic and the separation of diastereomeric mixtures cannot be avoided. However, recent reports on catalytic asymmetric variants of this reaction present interesting developments.[172]

Inspired by the 2-(α-acyloxy(hydroxyl)alkyl)thiazole amino acids encountered in the tubulysins, a class of tubulin cytoskeleton-degrading natural products[173] (e.g., **392** and **393**, Scheme 57) that also incorporate a rich array of nonribosomal amino acids, Dömling and co-workers have developed a three-component Lewis acid-catalyzed Passerini-type reaction.[174] This de novo thiazole synthesis involved the simultaneous addition of Schöllkopf's isonitrile (**394**) and thioacetic acid to a solution of L-*N*-Boc homovaline aldehyde (**395**) preactivated by BF_3 etherate (Scheme 57).[175] The

Scheme 58. Approach to Nummularine-F Using a Ugi Three-Component Reaction, by Joullié and Co-workers[177]



reaction is best carried out at −78 °C under an atmosphere of nitrogen, as higher temperatures or prolonged time (>2 h) resulted in significant formation of byproduct. In addition to the known versatility of isocyanides (dual electrophilic and nucleophilic character), Schöllkopf's isonitrile also contains a leaving group (Me_2N^-), which served to reinstate the unsaturation following the Michael addition step on intermediate **396**. The desired Passerini adduct **397** was isolated in only 40% yield as a 3:1 mixture of diastereomers. In general terms, this 3CR is low yielding and the control of the newly created stereocenter still remains an unsolved issue. Nonetheless, precursor **397** led to the first total syntheses of tubulysins V and U after several additional steps.[175]

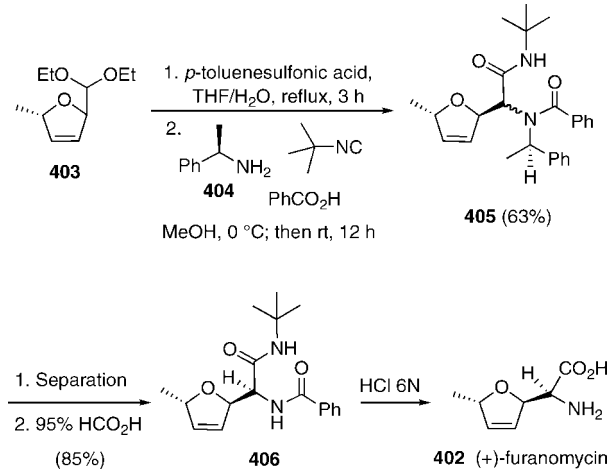
6.2. Ugi Three- And Four-Component Reactions

The Ugi reaction stands as a powerful method for the synthesis of peptide fragments, although the development of an efficient asymmetric variant still remains an active area of research. Despite this apparent limitation, the Ugi reaction has found widespread applications in combinatorial synthesis.[176] The reaction combines an amine, aldehyde, carboxylic acid, and isocyanide in one pot to afford α-acylaminoamide-containing compounds through a mechanism similar to the Passerini reaction (Figure 10). The applications of this powerful MCR in target-oriented synthesis are discussed in this section.

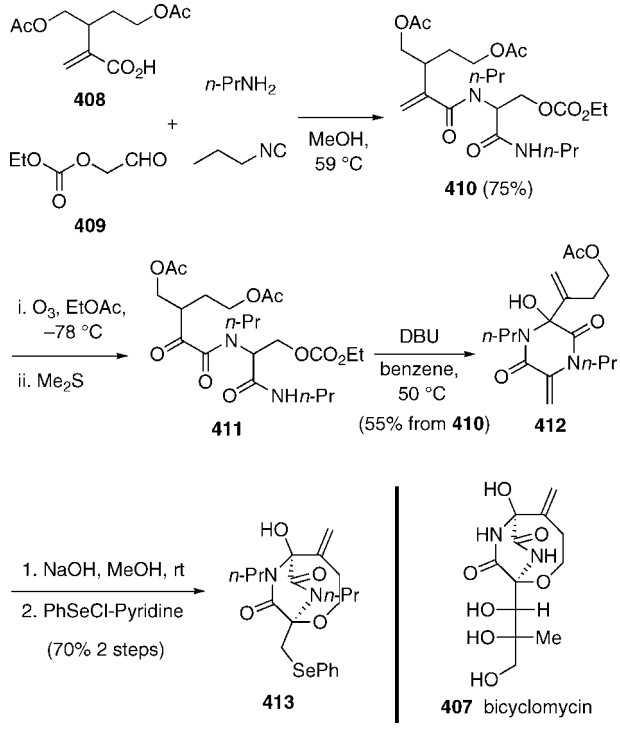
Joullié and collaborators have devised a potential route to the 14-membered cyclopeptide alkaloid nummularine-F (**398**, Scheme 58) based on a three-component Ugi reaction where the imine component was preformed.[177] The homochiral isocyanide **399**, prepared in two steps from L-isoleucine methyl ester salt, was mixed in one pot with cyclic imine **400** and benzoic acid to furnish a separable mixture of diastereomers **401** in moderate yield. Although further attempts to transform the latter compound to the final target failed, the expediency of this MCR approach is remarkable. The synthesis of **398** was eventually completed through an alternative strategy.[178]

The potent amino acid antibiotic furanomycin (**402**, Scheme 59), isolated from *Streptomyces threomyceticus*,[179] was also synthesized by Joullié and co-workers using a four-component Ugi reaction as the key step.[180] Enantiopure acetal **403** and α-methyl benzylamine (**404**) were mixed in metha-

Scheme 59. Synthesis of Furanomycin Using a Ugi Four-Component Reaction, by Joullié and Co-workers[180]



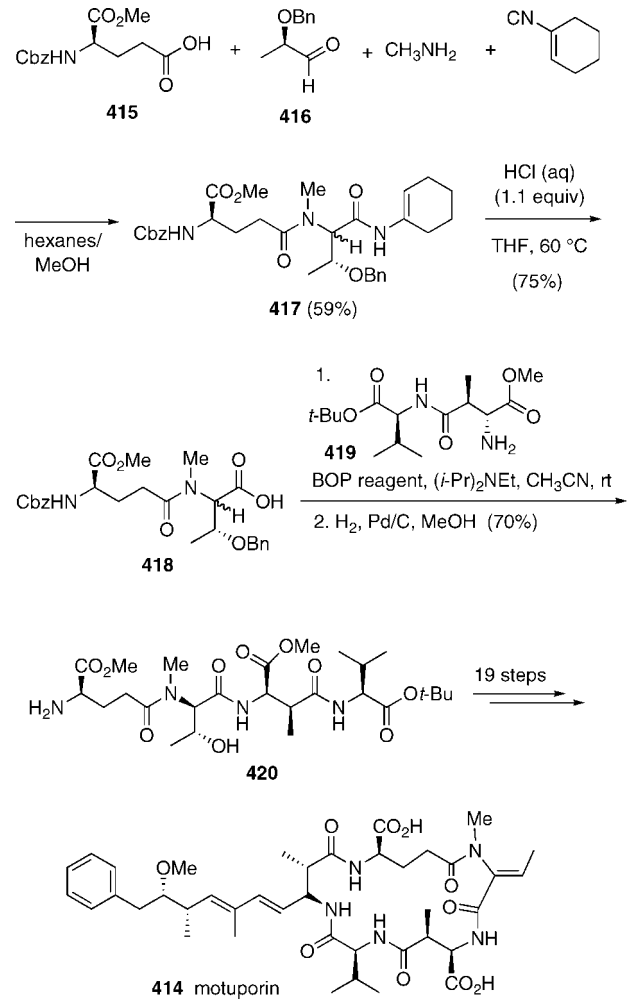
Scheme 60. Synthesis of Bicyclomycin Using a Ugi Four-Component Reaction, by Fukuyama and Co-workers[181]



nol in the presence of *tert*-butyl isocyanide and benzoic acid to afford a separable diastereomeric mixture of the Ugi 4CR product **405**. Debenzylation using formic acid, aimed at preserving the double bond, followed by acid hydrolysis of the secondary amides of **406** afforded the target molecule, (+)-furanomycin (**402**).

At an early stage of their synthetic studies, Fukuyama and co-workers relied upon a four-component Ugi reaction to quickly assemble the highly functionalized intermediate **410** en route to the cyclic core of bicyclomycin (**407**, Scheme 60),[181] an antibiotic natural product active against gram-negative bacteria.[182] This key intermediate **410**, obtained from α,β-unsaturated carboxylic acid **408**, *n*-propylamine, glycolaldehyde ethyl carbonate (**409**), and *n*-propyl isocyanide was then submitted to ozonolysis to afford the α-keto amide **411**. Treatment of the latter compound with DBU resulted in the efficient formation of piperazinedione **412** through a double elimination/nucleophilic cyclization process. Hydrolysis of

Scheme 61. Synthesis of Motuporin Using a Ugi Four-Component Reaction, by Bauer and Armstrong[183]

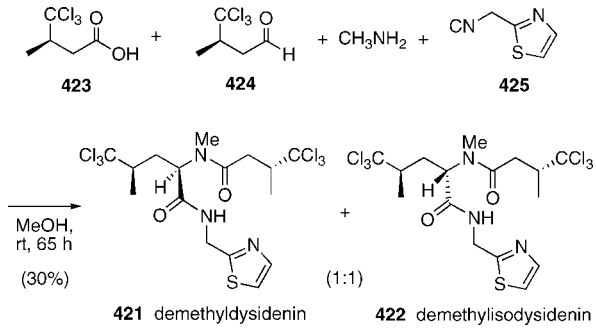


the acetates followed by oxidative cyclization promoted by phenylselenyl chloride terminated the construction of the cyclic core of the natural product. Although no total synthesis of bicyclomycin was completed, chain elongation from product **413** should provide a feasible route.

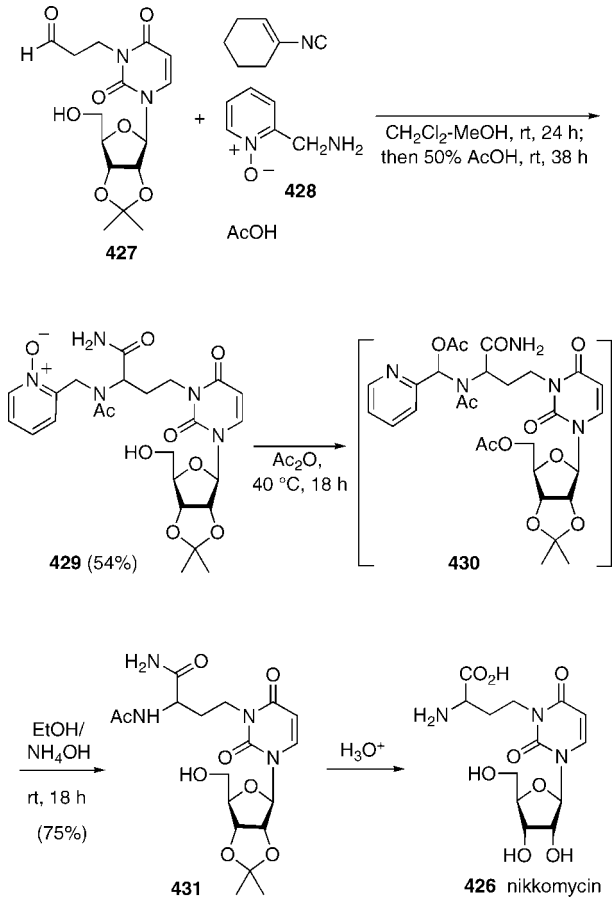
Oftentimes, the Ugi four-component reaction can offer an interesting alternative to the difficult amide coupling between secondary amines and carboxylic acids. Guided by this premise, Armstrong and co-workers efficiently synthesized the N-methylated dipeptide **417** en route to motuporin (**414**),[183] an inhibitor of protein phosphatases (Scheme 61).[184] The synthesis started with a four-component Ugi condensation involving protected glutamic acid (**415**), aldehyde **416**, methylamine, and cyclohexenyl isocyanide. The resulting dipeptide product **417** was first hydrolyzed to **418**, then coupled with amine **419**. Tripeptide **420** was obtained, and it led to the desired macrocyclic natural product after several more steps.

The synthesis of the polychlorinated antihypertensive natural products (+)-demethyldysidenin (**421**) and its C5 epimer (−)-demethylisodysidenin (**422**) was reported by Williard and co-workers (Scheme 62).[185] The key carboxylic acid **423** and the related aldehyde **424** were synthesized from β-methylglutaric acid. These key components were then reacted in one pot with methylamine and isocyanide **425** to afford the two diastereomeric natural products as a separable mixture.

Scheme 62. Synthesis of Demethyldysidenins Using a Ugi Four-Component Reaction, by De Laszlo and Williard[185]



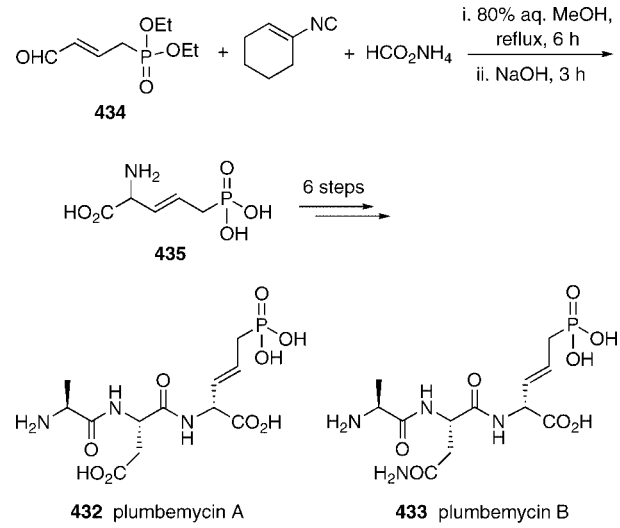
Scheme 63. Synthesis of Nikkomycin Using a Ugi Four-Component Reaction, by Tsuchida and Co-workers[186a]



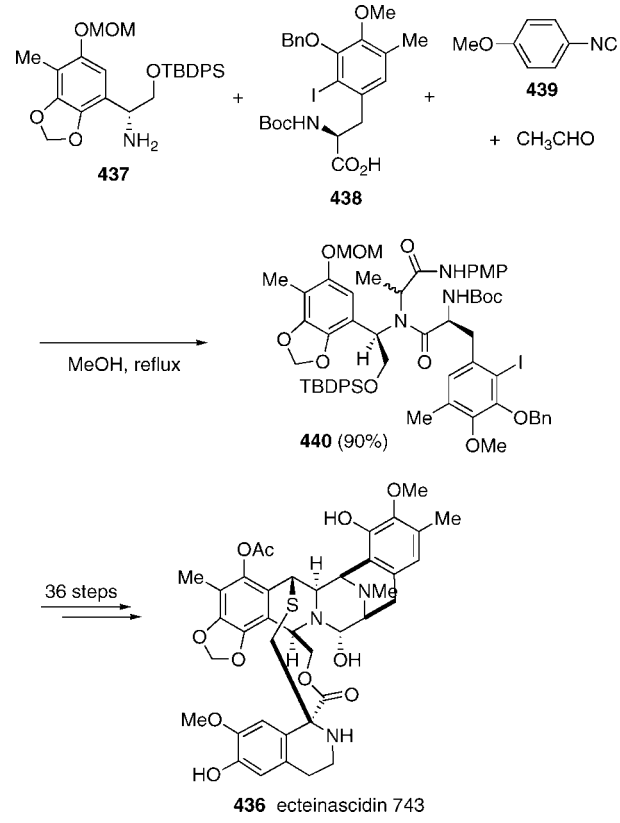
The naturally occurring nucleoside antibiotic nikkomycin (**426**) was synthesized on a large scale by Tsuchida and co-workers using a four-component Ugi condensation as the key step (Scheme 63).[186a] To this end, the aldehyde **427** was mixed in one pot with cyclohexenyl isocyanide, acetic acid, and (2-picolyl-1-oxide)amine (**428**) to afford the Ugi reaction adduct, which was deprotected in situ under mild conditions to afford primary amide **429**. Treatment of the latter compound with acetic anhydride triggered a rearrangement (to aminal **430**) that significantly facilitated the removal of the acetamide substituent to give product **431**. Then, hydrolysis under strong acid completed this efficient synthetic sequence aimed at assembling nikkomycin. A synthesis of isowillardiine was accomplished in a similar manner.[186b]

The Ugi four-component reaction was used by Natchev as a key step to assemble the antibiotic plumbemycin A (**432**) and B (**433**) (Scheme 64).[187] To this end, the unusual amino

Scheme 64. Synthesis of Plumbemycins Using a Ugi Four-Component Reaction, by Natchev[187]



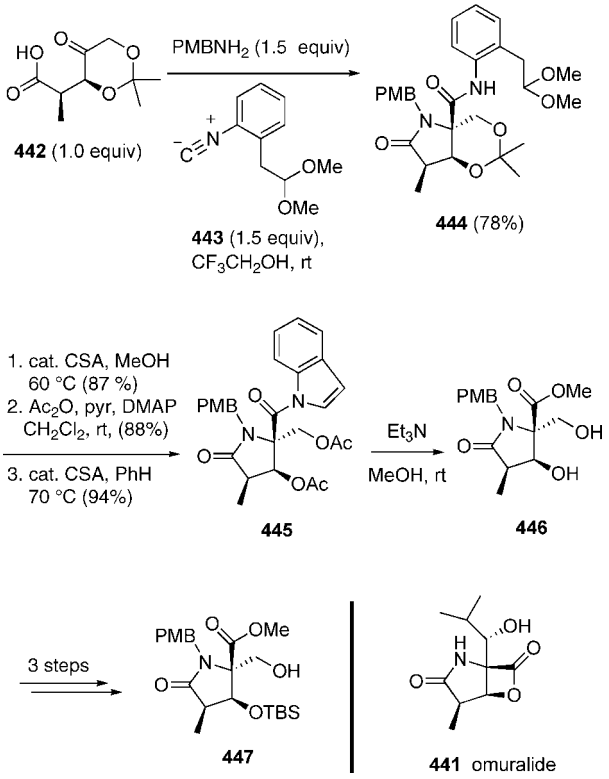
Scheme 65. Synthesis of Ecteinascidin 743 Using a Ugi Four-Component Reaction, by Fukuyama and Co-workers[189]



carboxylic acid 3,4-didehydro-5-phosphono-D-norvaline (**435**) was produced by the Ugi 4CR involving aldehyde **434**, ammonium formate, and cyclohexyl isonitrile. The resulting product **435** was further transformed to the desired peptides through a sequence of routine transformations.

Ecteinascidin 743 (**436**, Scheme 65) represents a powerful antitumor agent, which was recently approved in Europe for the treatment of soft tissue sarcomas. This complex polyazacyclic, polyaromatic compound was isolated from the marine tunicate, *Ecteinascidia turbinate*.[188] A total synthesis of this natural product, which featured an Ugi four-component reaction as pivotal step, was reported by Fukuyama and co-workers.[189] The highly decorated arylglycinol derivative **437** was obtained via an asymmetric Mannich-type reaction[190]

Scheme 66. Synthesis of Omuralide Using a Ugi Three-Component Reaction, by Kobayashi and Co-workers[193]



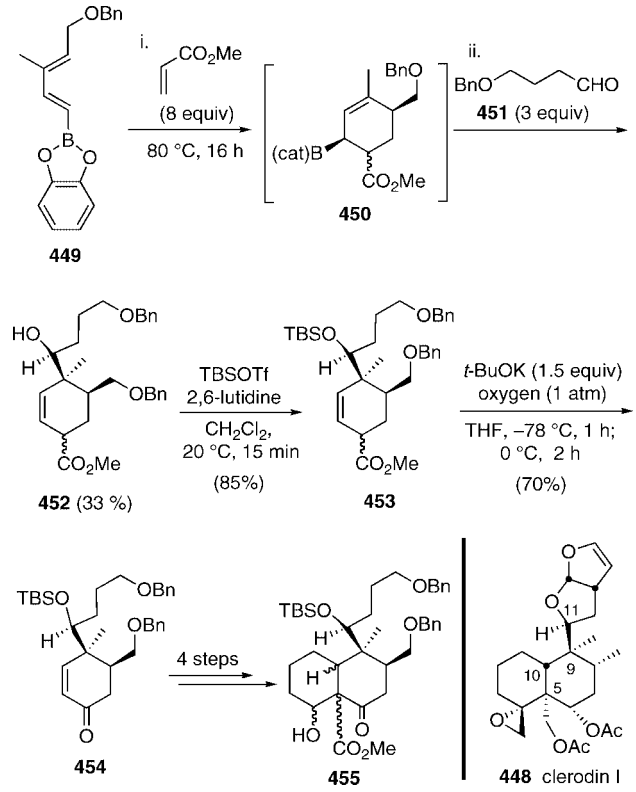
and was engaged in a mulicomponent condensation process involving the protected amino acid **438**, *p*-methoxyphenyl isocyanide (**439**), and acetaldehyde to afford the dipeptide **440** in high yield. The latter compound embedded all the necessary carbon atoms for the elaboration of the upper fragment. The synthesis of **436** was eventually completed in a total of about 36 steps.

Since the clinical validation of the proteasome as an oncology target,[191] compounds capable of inhibiting this important protein degradation machinery have come under intense scrutiny. Omuralide (**441**, Scheme 66) is a lactacystin derived natural product[192] that has been prominently featured in these efforts in recent years. A stereocontrolled Ugi three-component reaction to its γ-lactam unit was recently achieved by Kobayashi and co-workers and is described in Scheme 66.[193] A highlight of this synthesis is the introduction of 1-isocyano-2-(2,2-dimethoxyethyl)benzene, **443**, as a differentiating element between the two amides created by the above MCR. Thus, mixing **443** with chiral ketoacid **442** and *p*-methoxybenzylamine in trifluoroethanol at room temperature delivered the desired Ugi reaction product **444** in excellent yield as a single diastereomer. Protecting-group interplay followed by the conversion of the exo secondary amide into the corresponding *N*-acyl indole **445** rendered this functionality labile enough that it could be converted into a methyl ester, **446**, without opening the lactam ring. Again, protecting group and functional group manipulations yielded **447**, a known intermediate in a previous total synthesis of the desired natural product **441**.[194]

7. Multicomponent Reactions Initiated by [4 + 2]-Cycloadditions

The power and versatility of the Diels−Alder reaction as a synthetic tool to assemble natural products is well-established.[195]

Scheme 67. Approach to the Core of Clerodin Using a Three-Component Diels−Alder Cycloaddition/Allylboration, by Lallemand and Co-workers[197]

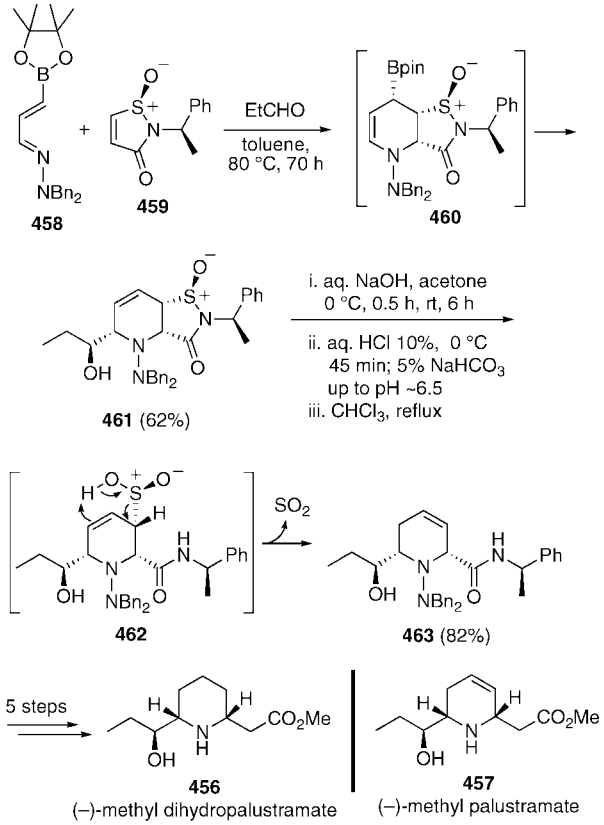


Its use as an important mechanistic step in multicomponent reaction strategies was elegantly demonstrated in previous sections with the work of Tietze and Batey (sections 3.10 and 5.6, respectively). Provided the [4 + 2]-cycloaddition step unmasks a suitable functionality with the use of an appropriately designed diene or dienophile, Diels−Alder reactions can also be exploited as the first stage of multicomponent reaction cascades. This section describes a number of efficient MCRs initiated by a [4 + 2]-cycloaddition.

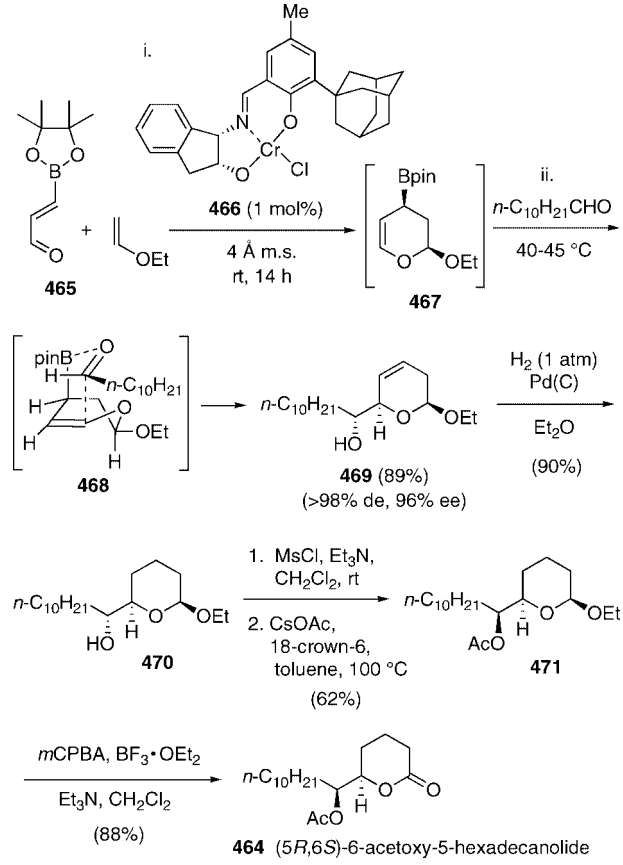
7.1. Tandem [4 + 2]-Cycloaddition/Allylboration

By virtue of its seven contiguous stereogenic centers, including two quaternary centers, and the presence of very sensitive functionalities such as the exocyclic epoxide and the acetal unit, clerodin 1 (**448**, Scheme 67) represents one of the most complex diterpenoids isolated.[196] It constitutes a very appealing and challenging synthetic target, which indeed has so far eluded total synthesis despite the fact that its structure has been known for more than 70 years. One promising synthetic approach to this interesting target was disclosed by Lallemand and co-workers.[197] Although a synthesis of clerodin has not yet been completed using this approach, the elegant [4 + 2]-cycloaddition/allylboration MCR strategy to the construction of the decalin core warrants discussion. Previous work from this group had established that the furo[2,3-b]furan bicyclic system could be constructed from a simple 1,4-diol containing substrate.[198] A simplified and attractive solution to the challenging construction of the C9 and C11 stereogenic centers was then devised based on the group's improved variant of a three-component reaction first reported by Vaultier and co-workers.[199] This multicomponent reaction merges two extremely powerful synthetic transformations, namely, the Diels−Alder cycloaddition and the allylboration reactions, and delivers α-hydroxyalkyl

Scheme 68. Synthesis of Methyl Dihydropalustramate Using a Three-Component Aza-[4 + 2]-Cycloaddition/Allylboration, by Touré and Hall[201]



Scheme 69. Synthesis of (5*R*,6*S*)-6-Acetoxy-5-Hexadecanolide Using a Three-Component Hetero-[4 + 2]-Cycloaddition/Allylboration, by Gao and Hall[206]



cyclohexyl units as shown in Scheme 67. Upon heating, 4-borono-1,3-diene **449** underwent a stereoselective Diels−Alder reaction with methyl acrylate, thereby unmasking the cyclic allylboronate intermediate **450**, which condensed with γ-benzyloxy butanal (**451**) to afford the highly functionalized α-hydroxyalkyl cyclohexene **452** as a single diastereomer, albeit in low yield. This advanced intermediate bears all the necessary functionalities for the rapid elaboration of both ring systems of clerodin 1. Protection of the secondary alcohol of **452** as its silyl ether followed by treatment of the resulting product **453**, with potassium *t*-butoxide as base in the presence of oxygen, provided enone **454**. From the latter, several transformations led to an advanced intermediate (**455**) featuring the decalin core of the clerodanes.[197]

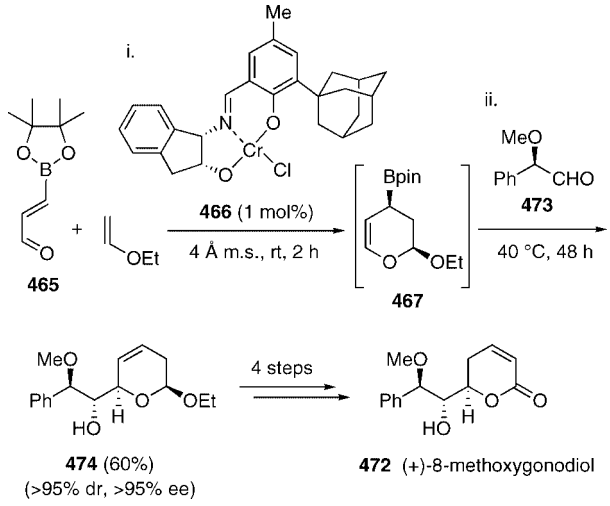
7.2. Tandem aza-[4 + 2]-Cycloaddition/Allylboration

The stereocontrolled synthesis of α-hydroxyalkylated piperidines, a motif frequently encountered in natural products, represents a difficult synthetic challenge that was tackled by Hall and co-workers using the aza-variant of the Vaultier−Lallemand three-component reaction.[200] One interesting feature of this reaction is the use of hydrazines as masked amines, which allows the hetero-Diels−Alder reaction to operate on a normal electron-demand manifold. Touré and Hall recently applied this powerful MCR to the asymmetric synthesis of methyl (−)-dihydropalustramate (**456**),[201] a degradation product and postulated biosynthetic precursor of (−)-palustrine (Scheme 68).[202] This synthesis featured the thermal reaction of a mixture of 1-dibenzylamino-1-aza-4-boronodiene (**458**), Waldner's chiral dienophile **459**,[203] and propionaldehyde in toluene for three days. Through the intermediacy of cycloadduct **460**, the tandem [4 + 2]/allylboration adduct **461** was isolated as a single regioisomer and diastereomer in good yield. The latter compound was then treated with sodium hydroxide followed by acidification to afford the corresponding sulfinic acid intermediate (**462**), which fragmented in refluxing chloroform to give amide **463** in good yield through a retro-sulfinyl-ene rearrangement.[204] The completion of the synthesis of **456** included a one-carbon homologation and the hydrogenolytic cleavage of the N−N bond to reveal the saturated piperidine moiety. A total synthesis of methyl palustramate (**457**) was reported using the same strategy and a novel hydrazine unit allowing a chemoselective N−N bond cleavage that left the alkene intact.[205]

7.3. Tandem oxa-[4 + 2]-Cycloaddition/Allylboration

On the basis of the previous work of this group on the three-component aza-[4 + 2]/allylboration strategy to construct polysubstituted piperidines,[200] Gao and Hall developed a catalytic enantioselective variant[206] of the corresponding oxygeneous process to construct α-hydroxyalkylated pyrans from 3-boronoacrolein.[207] This variant of the Vaultier−Lallemand one-pot, three-component reaction was successfully applied to a concise total synthesis of (5*R*,6*S*)-6-acetoxy-5-hexadecanolide (**464**, Scheme 69), the oviposition attractant pheromone of the female *Culex* mosquito[208] capable of transmitting the West Nile virus. In this work, 3-boronoacrolein pinacolate (**465**) was found to be a very effective and versatile heterodiene in Jacobsen's enantioselective inverse electron demand hetero-[4 + 2] reaction with

Scheme 70. Synthesis of (+)-8-Methoxygonodiol Using a Three-Component Hetero-[4 + 2]-Cycloaddition/ Allylboration, by Carboni and Co-workers[210]

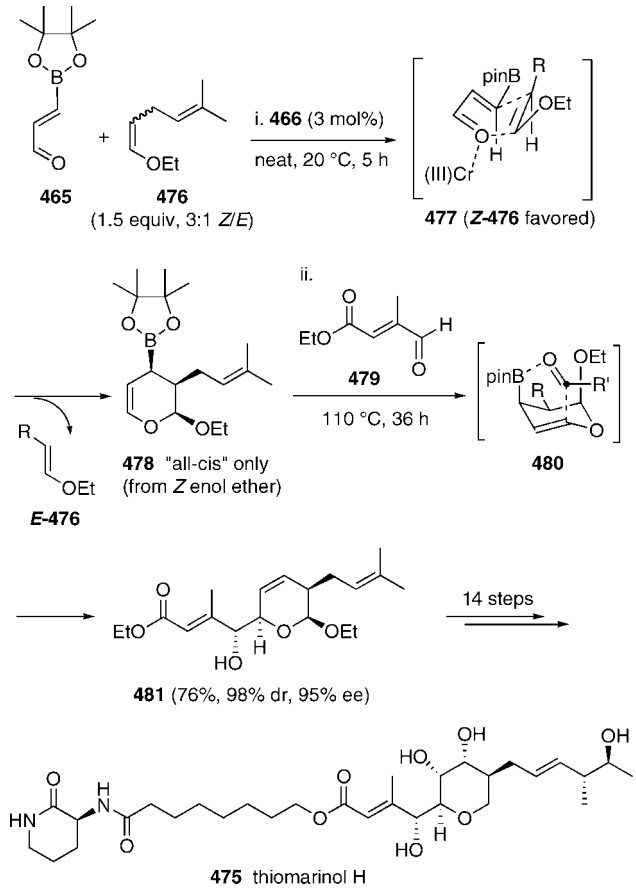


enol ethers, catalyzed by the tridentate (Schiff base) chromium complex **466**.[209] The reaction between **465** and ethyl vinyl ether, used as solvent, unmasked the cyclic allylboronate **467** in high enantioselectiviy (96% ee) using an exceptionally low catalyst loading (1 mol% of **466**). Following the cycloaddition step, intermediate **467** was further transformed by simple addition of undecanal and gentle heating to provide the α-hydroxyalkyl dihydropyran **469** as final product of this one-pot sequential MCR. The allylboration occurred at a slightly elevated temperature (40−50 °C) and afforded **469** as a single diastereomer consistent with the expected chairlike Zimmerman−Traxler transition structure (**468**). The relative facility of the hetero-[4 + 2]-cycloaddition step compared to the allylboration was crucial in suppressing the potential "self-allylboration" between **467** and **465**, and thus ensured the feasibility of this MCR. To complete the synthesis of lactone **464**, the pyran intermediate **470** was obtained from the hydrogenation of **469** and the acetylation of the secondary alcohol by inversion of configuration afforded **471**. Oxidation of the acetal led to the desired mosquito pheromone **464** after only seven total steps from commercial 3,3-diethoxy-1-propyne.

Carboni and co-workers extended the application of this three-component hetero-[4 + 2]-cycloaddition/allylboration to the use of chiral α-substituted aldehydes.[210] Thus, use of aldehyde **473** in a double-diastereoselective MCR led to product **474** as a single stereoisomer (Scheme 70). Four more steps were needed to complete a synthesis of 8-methoxygonodiol (**472**), a natural analogue of the cytotoxic, antitumor natural product gonodiol.[211]

Hall and co-workers reported a more complex example of the same three-component reaction strategy in their concise and highly efficient total synthesis of a member of the thiomarinol family (**475**, Scheme 71) of potent antibiotics,[212] which are related to the pseudomonic acids and the commercial topical antibacterial agent mupirocin.[213] The key MCR step of this synthesis hinged on the preparation of the dihydropyran intermediate **481** and called for an isomerically pure *Z*-configured disubstituted enol ether (Scheme 71). This was not possible, however, and a 3:1 *Z*/*E* mixture of **476** had to be used in the inverse electron demand hetero-Diels−Alder reaction. Fortunately, the authors found that the cycloaddition between **465** and **476** proceeds in high enantioselectivity to give cyclic dihydropyranyl boronate **478** in

Scheme 71. Synthesis of Thiomarinol Using a Three-Component Hetero-[4 + 2]-Cycloaddition/ Allylboration, by Gao and Hall[212]

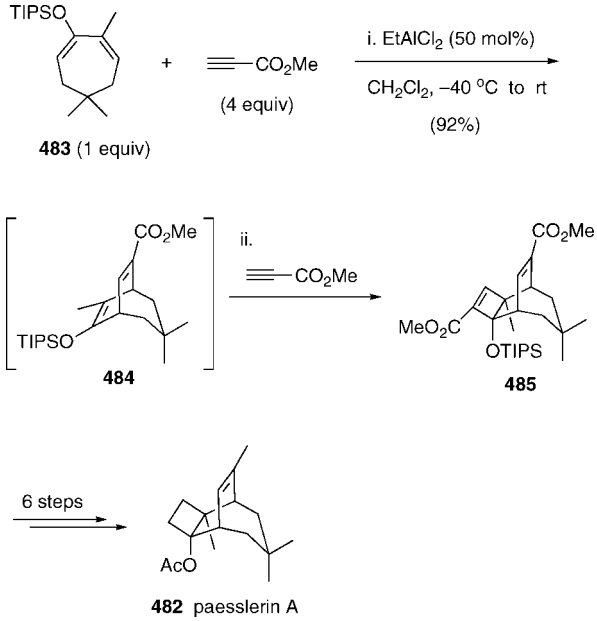


excellent diastereo- and enantioselectivity. Interestingly, the large chiral catalyst **466** promotes the cycloaddition of the requisite Z enol ether **476** faster than that of the corresponding *E* isomer, thus affording cyclic allylboronate **478** as sole product. The latter added stereoselectively to unsaturated aldehyde **479** via transition structure **480** in a "one-pot" sequential process that gave the desired 2-hydroxyalkyl dihydropyran product **481** in good yield. The remarkable selectivity of this tandem reaction allowed an expedient enantioselective synthesis of the potent antibiotic thiomarinol H. To this end, the exocyclic *gem*-dimethylated trisubstituted alkene of **481** was transformed chemoselectively to elaborate the right-hand side chain via a Julia−Kocienski olefination. Overall, the synthesis of **475** was completed in 15 steps and 22% overall yield from **465**.

7.4. Tandem [4 + 2]-Cycloaddition/[2 + 2]-Cycloaddition

Ihara and co-workers have developed a hard Lewis acid-catalyzed Michael aldol-like [2 + 2]-cycloaddition methodology to access polysubstituted cyclobutanes.[214] An interesting extension of this work highlighted a novel three-component reaction based on sequential [4 + 2]/[2 + 2]-cycloadditions.[215] This multicomponent reaction is of the "A + B + B" type because the second and third components are identical. Precisely, acrylates or methyl propiolate can serve both as dienophiles for the Diels−Alder cycloaddition with siloxybutadienes and as acceptors in a subsequent Michael aldol-like [2 + 2]-cycloaddition with the intermediate cycloadduct. Overall, bicyclo[4.2.0]octane products are

Scheme 72. Synthesis of Paesslerin a Using a Tandem Three-Component [4 + 2]/[2 + 2]-Cycloaddition, by Ihara and Coworkers[215]



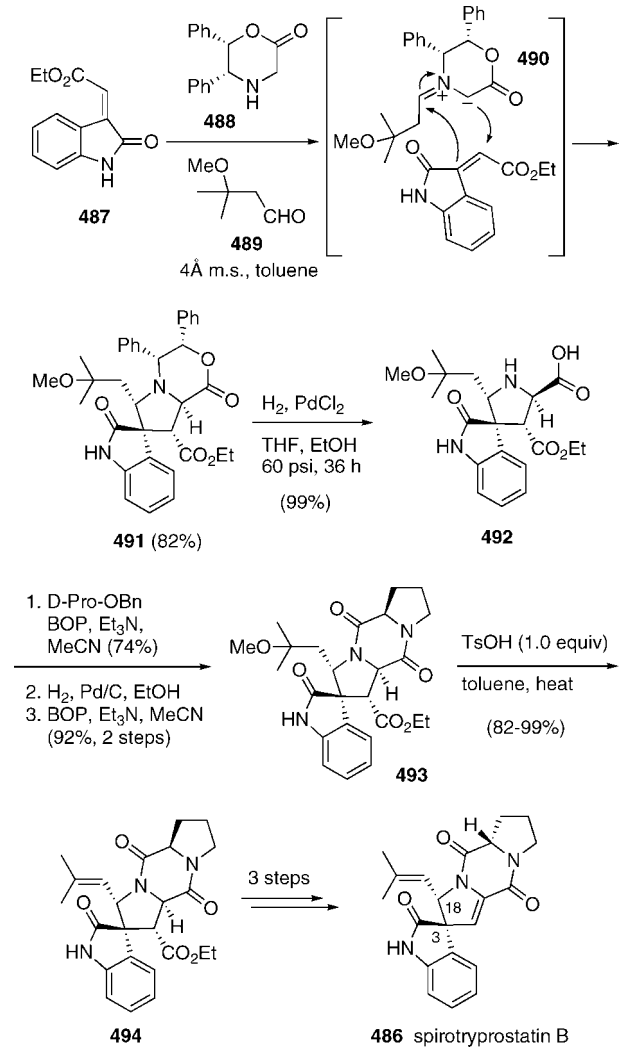
obtained. The carefully optimized process was applied to the total synthesis of the cytotoxic sesquiterpene paesslerin A (**482**, Scheme 72).[215] The paesslerins are marine natural products isolated from soft coral *Alcyonium paessleri*,[216] and they possess a novel tricyclic 2,8,8,10-tetramethyltricyclo[4.3.2.0]undecane skeleton. A preliminary study showed that they exhibit moderate toxicity against human tumor cell lines.[216] Ihara and co-workers' synthesis of paesslerin A featured as a key step the cascade [4 + 2]/[2 + 2]-multicomponent cycloaddition between cyclic seven-membered siloxydiene **483** and an excess of methyl propiolate. The "A + B + B" MCR product **485** was obtained via bicycle **484** in excellent yield (92%) and with complete diastereoselectivity. A series of functional group manipulations that included a deoxygenation and a decarboxylation was executed, and the proposed structure of paesslerin A (**482**) was reached in 34% overall yield (for eight steps). Although the structure of the synthetic material was unambiguously ascertained by X-ray crystallographic analyses, NMR spectroscopic data of the synthetic material differed from those reported for the natural product, thus pointing to the need for a structural revision of natural paesslerin.

8. Multicomponent Reactions Based on [3 + 2]- and [3 + 3]-Dipolar Cycloadditions

8.1. Three-Component in situ Azomethine Ylide Formation and [3 + 2]-Cycloaddition

The scarcity, interesting biological profile,[217] and intriguing molecular architecture have brought the spirotryprostatin natural products to the forefront of synthetic activities. A concise route to spirotryprostatin B (**486**) via an asymmetric three-component 1,3-dipolar cycloaddition has been reported by Williams and co-workers.[218] The essence of their strategy is captured in Scheme 73. Azomethine ylide **490** was generated in situ by reacting 3-methoxy-3-methyl butanal (**489**) and chiral 5,6-diphenylmorpholin-2-one (**488**). Aldehyde **489** served as a veiled prenyl unit and circumvented chemoselectivity issues that might have arisen in subsequent

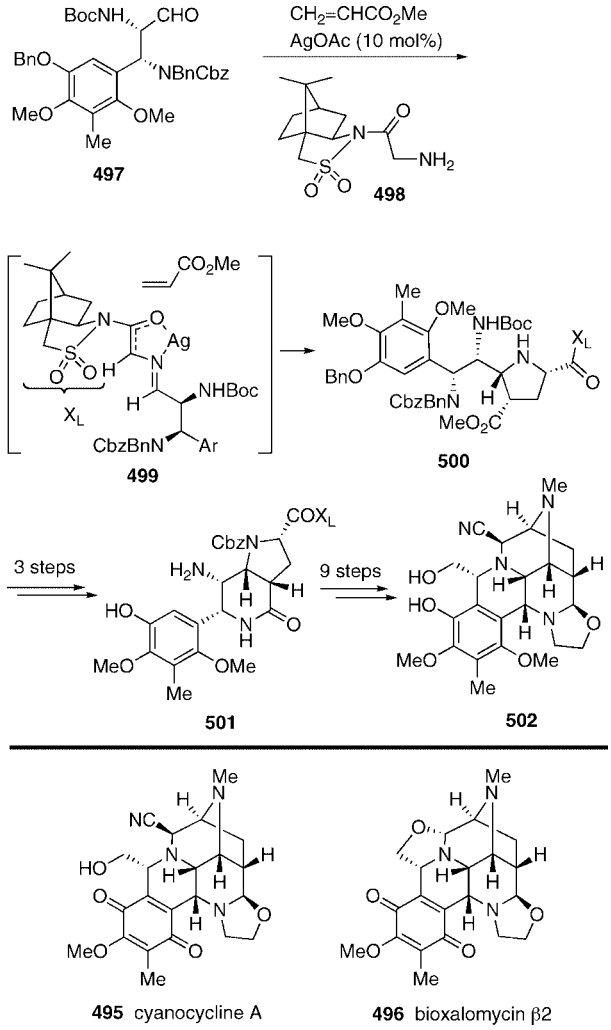
Scheme 73. Synthesis of Spirotryprostatin B Using in situ Azomethine Ylide Formation Followed by [3 + 2]-Cycloaddition, by Williams and Co-workers[218]



steps. It addition, its bulky nature favors the formation of *E*-azomethine ylides, which lead to the correct C18 stereochemistry.[219] The cycloaddition of in situ formed **490** with oxindolydene **487** furnished cycloadduct **491** in very good yield. Remarkably, this reaction proceeded with a high degree of regio- and stereoselectivity, delivering the desired product via the *exo* transition state, which is a feature associated with this subclass of dipolarophiles.[218,219] Three bonds and four contiguous stereocenters are created in this single synthetic operation, albeit only the C3 and C18 stereocenters are retained in the final product. Reductive removal of the dibenzyl unit from **491** revealed the requisite amino acid functionality of **492** required for the construction of the diketopiperazine core, which was accomplished via two consecutive amidations with D-proline benzyl ester. With intermediate **493** in hand, the clean generation of the prenyl side chain required the use of TsOH in refluxing benzene, thus affording **494**. The synthesis of the natural product was accomplished in three additional steps. A similar reaction strategy was also utilized by the Williams group in their successful synthesis of spirotryprostatin A.[220]

The 1,3-dipolar cycloaddition between azomethine ylides and dipolarophiles provides a convenient access to highly decorated pyrrolidines. However, reactivity and stereocontrol issues plague the use of acyclic dipolarophiles in these

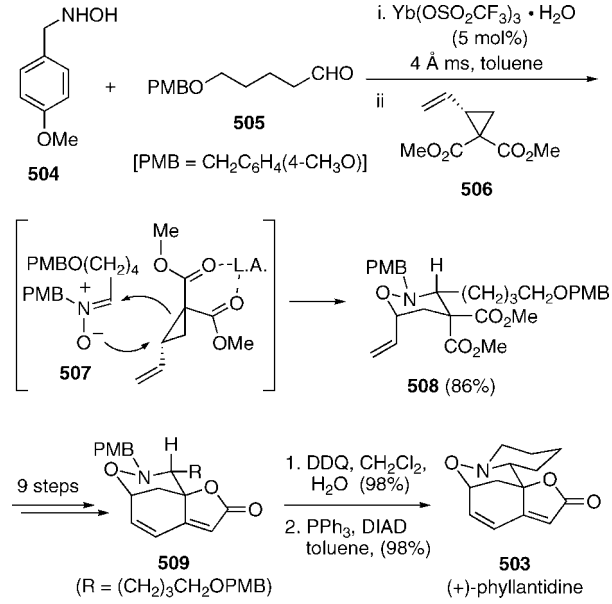
Scheme 74. Formal Syntheses of Cyanocycline A and Bioxalomycin β2 Using in situ Azomethine Ylide Formation Followed by [3 + 2]-Cycloaddition, by Kaniskan and Garner[222a]



reactions. The recent efforts by Garner and co-workers, which resulted in the development of two stereocomplementary [3 + 2]-cycloaddition reactions termed [C + NC + CC] couplings, have unlocked new synthetic opportunities in this arena.[221] Notable advances include the use of silver (*endo* product) or copper (*exo* product) catalysts in combination with a chiral auxiliary to ensure a high level of stereocontrol. The efficiency of the silver-catalyzed variant is highlighted below in the formal total syntheses of cyanocycline A (**495**, Scheme 74) and bioxalomycin β2 (**496**),[222a] two complex natural products capable of eliciting a host of biological responses.[223]

As depicted in Scheme 74, the preparation of known intermediate **502** hinges on a remarkably effective three-component cycloaddition of the differentially protected diamino aldehyde **497**, which was prepared in several steps. This key aldehyde was reacted with glycylsulfam **498** and methyl acrylate (used as solvent) in the presence of a catalytic amount of silver acetate to deliver the highly functionalized MCR adduct **500** in an *endo* selective manner via the in situ formed activated dipole **499**. Already, this intermediate bears all the functional groups required to forge the ring systems present in the targeted natural products. Its elaboration into **502**, a known precursor for both natural products **495** and **496**,[222b−f] was accomplished in 12 steps via **501** and

Scheme 75. Synthesis of (+)-Phyllantidine Using in situ Nitrone Formation Followed by [3 + 3]-Cycloaddition with 1,1-Cyclopropane Diesters, by Carson and Kerr[226]



consisted, for the most part, of protecting group manipulations. Other key reactions en route to **502** include a Pictet-Spengler cyclization to form the tetrahydroisoquinoline core, a Strecker annulation approach to the bridged bicyclic ring system, and a Pelletier oxazolidine synthesis.

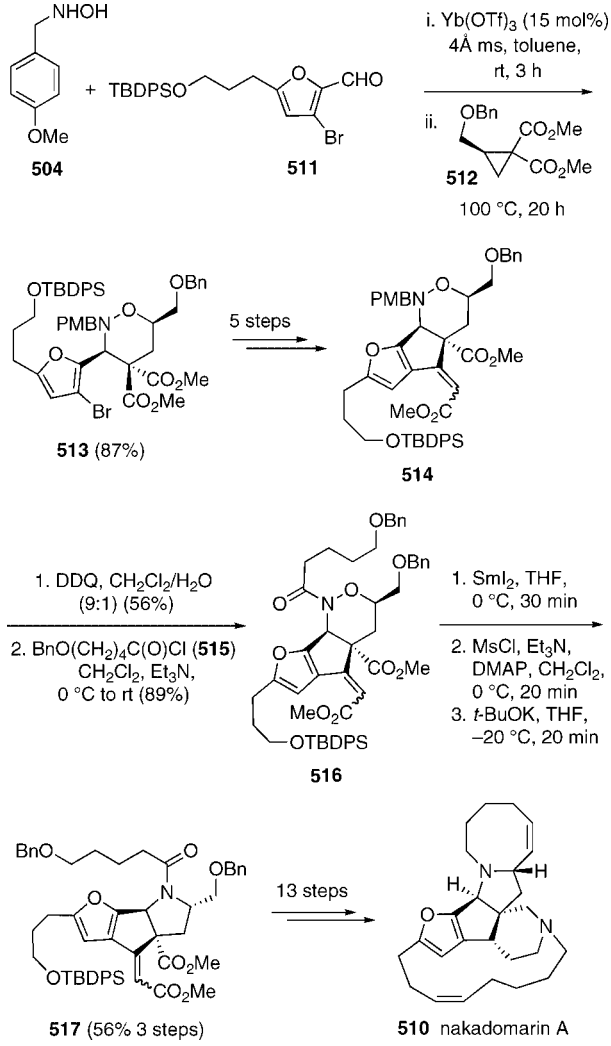
8.2. Three-Component in situ Nitrone Formation and [3 + 3]-Cycloaddition with 1,1-Cyclopropane Diesters

Kerr and co-workers have reported a highly diastereoselective ytterbium triflate-catalyzed cycloaddition process involving nitrones and 1,1-cyclopropane diesters.[224] The nitrone component can be preformed or generated in situ by reacting aldehydes with hydroxylamines prior to the addition of the cyclopropane component with similar efficacy. This new MCR delivers functionalized tetrahydro-1,2-oxazines bearing 3,6-*cis* substituents. Two applications of this process in natural product synthesis have been reported thus far.

First, (+)-phyllantidine (**503**, Scheme 75), a tetrahydro-1,2-oxazine containing natural product closely related to the securinega class of GABA agonistic alkaloids[225] was assembled in 12 steps.[226] At the outset, attempts to forge a bicyclic core directly using nitrone cycloaddition chemistry failed. Subsequently, a linear approach was implemented (Scheme 75). This sequence was initiated by first allowing PMB-protected hydroxylamine **504** to react with aldehyde **505** in toluene in the presence of 5 mol % of $Yb(OTf)_3$ and 4 Å molecular sieves. The in situ formation of nitrone **507** was allowed to proceed to completion prior to the introduction of homochiral cyclopropane **506** to the reaction mixture. The MCR adduct **508** was obtained as the major diastereomer (12:1, *cis*/*trans* ratio), and interestingly, in only 80% ee (i.e., with erosion of enantiomeric purity). Oxazine **508** was elaborated into advanced intermediate **509** in nine steps, then the PMB groups were simultaneously removed by DDQ treatment followed by ring closure using Mitsunobu conditions to afford the final target **503**.

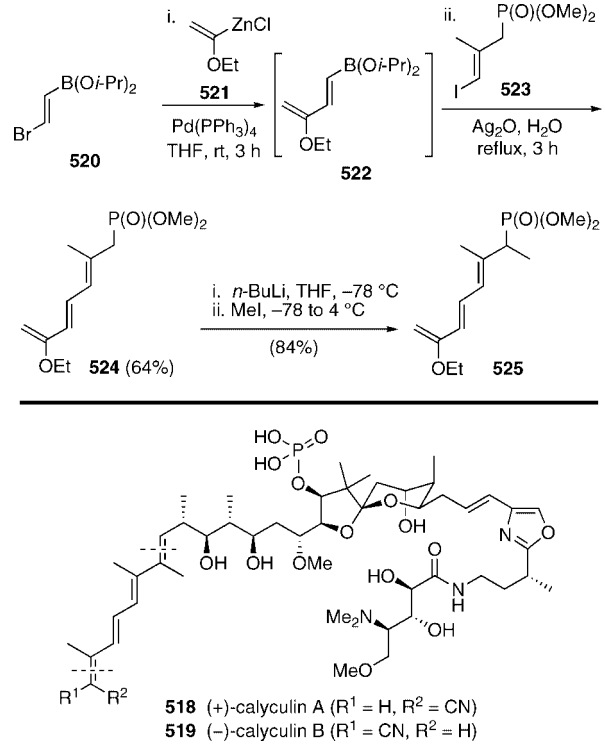
The oxazine cycloadducts can also serve as precursors to stereodefined γ-amino alcohols, which can be cyclized to produce pyrrolidines. The caveat is that both the N—O bond

Scheme 76. Synthesis of Nakadomarin A Using in situ Nitrone Formation Followed by [3 + 3]-Cycloaddition with 1,1-Cyclopropane Diesters, by Young and Kerr[227]



cleavage and the subsequent cyclization steps require significant functional group manipulations, as observed during the synthesis of nakadomarin A by Young and Kerr (**510**, Scheme 76).[227] This recently isolated alkaloid belongs to the manzamine family and has been reported to induce a host of biological responses encompassing anticancer, antibacterial, and antifungal activities.[228] For the synthesis of nakadomarin A, furaldehyde **511** was prepared in five steps then reacted with hydroxylamine **504** and cyclopropane **512** (ee > 97%) (Scheme 76). The three-component reaction afforded the adduct **513** in excellent yield and high regio- and stereocontrol as per a mechanism and transition state similar to that of Scheme 75. This oxazine product was converted into the tricyclic system **514** in five steps. The PMB ether of **514** was then removed and the N—O bond was activated by acylation using acyl chloride **515**. The SmI_2 mediated N—O fragmentation of **516** delivered a key γ-amino alcohol, which, due to stability issues, was quickly transformed into pyrroline **517** in two additional steps. Overall, the conversion of **514** into **517** required 5 steps, and the elaboration of the latter intermediate into the final target **510** was accomplished in 13 additional steps including the reduction of the pyrrolidine amide inherited from the N—O activation process, as well as ring-closing metathesis chemistry for closure of the large and medium rings.

Scheme 77. Synthesis of a Calyculin Fragment Using a Three-Component Negishi/Suzuki Cross-Coupling, by Smith and Co-workers[231]



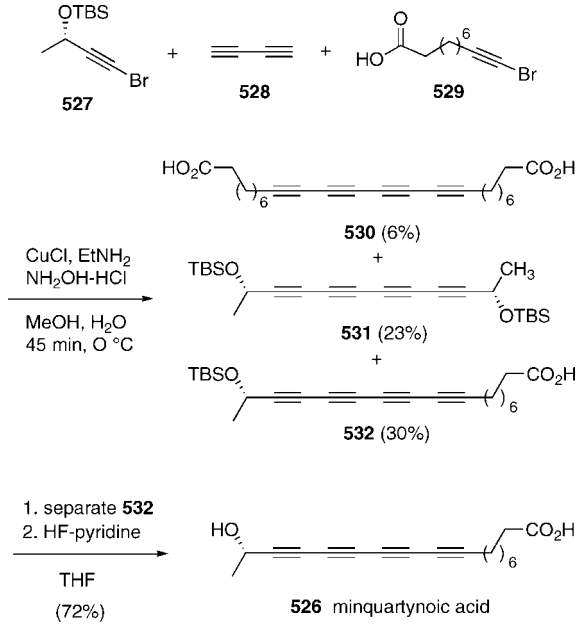
9. Multicomponent Reactions Centered on Transition Metal Catalysis

One clear area with enormous potential for the development of new multicomponent reactions is the use of transition metal-catalyzed processes with simple unsaturated and halogenated substrates.[229] Provided that such MCRs are compatible with the oxygenated and nitrogen-containing functionalities ubiquitous to so many natural products, they could overpower the current toolbox of MCRs and their rather limited mechanistic diversity. The following section describes several examples that were successfully applied in the synthesis of natural products.

9.1. Multiple Cross-Coupling Strategies

The coupling of three of more suitable and compatible partners is perhaps one of the most obvious applications of transition metal catalysis in the design of MCRs. Polyene units are a common structural feature of several classes of natural products. To access polyene compounds, any effective multicomponent reaction strategy has to provide effective control of the geometry of individual double bonds. The calyculins, a class of potent and highly selective serine—threonine phosphatase inhibitors,[230] present a conjugated tetraene unit as part of their structure that is also characterized by a complex array of rings and functional groups (Scheme 77). To elaborate the tetraene unit in their total synthesis of (+)-calyculin A (**518**) and (−)-calyculin B (**519**),[231] Smith and co-workers have applied a simple but efficient one-pot, three-component cross-coupling[232] reaction between fragments **520**, **521**, and **523** in order to reach the desired triene product **524** (Scheme 77). The use of such a cross-coupling strategy is advantageous over classical methods like Wittig olefinations because it does not entail issues of *E*/*Z* stereocontrol, thus avoiding tedious separations at a later stage. Here, the

Scheme 78. Synthesis of Minquartynoic Acid Using a Three-Component Cadiot−Chodkiewicz Double Cross-Coupling, by Gung and Co-workers[236]

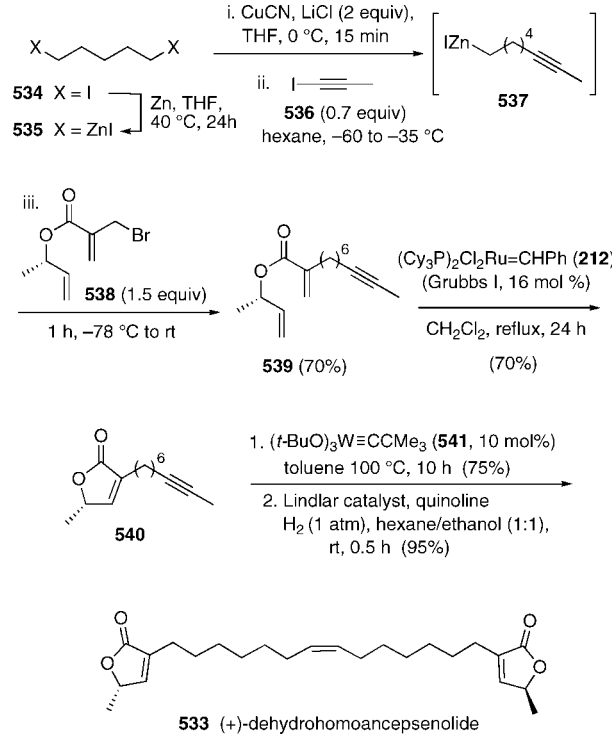


three alkenyl components were prepared in advance with the requisite double-bond geometry. Thus, Negishi coupling between **520** and **521** affords dienylboronate **522**, which is then treated in situ with alkenyl iodide **523** under Kishi's mild conditions for Suzuki−Miyaura cross-coupling using silver oxide as promoter.[233] The sensitive, isolated trienyl phosphonate **524** was methylated to afford the desired triene synthon **525**. The latter was eventually coupled to an advanced aldehyde fragment through a Horner−Emmons−Wadsworth olefination. Triene **525** also embeds an enol ether as a masked ketone that was eventually elaborated onto the required unsaturated nitrile required toward completing the total syntheses of calyculins A and B.[231]

Minquartynoic acid (**526**, Scheme 78) was isolated from the bark of *Minquartia guianensis* and represents a promising lead compound for cancer and AIDS therapy.[234] Gung and co-workers reported the synthesis of this molecule using a three-component Cadiot−Chodkiewicz coupling reaction[235] as the pivotal step (Scheme 78).[236] In this three-component reaction, diyne **528** was utilized as a bidirectional synthon and was coupled successively with bromoalkynes **527** and **529** under Cu(I) catalysis to afford a separable mixture of all possible cross-coupling products including the symmetrical tetracetylenes **530** and **531** and the desired unsymmetrical one, **532**, albeit in low yield. Despite this shortcoming, this synthesis highlighted the practical appeal of MCRs, as all attempts to assemble the target molecule using linear two-component couplings delivered unstable intermediates. The desired molecule **526** was obtained following removal of the silyl ether protecting group of **532**.

Fürstner and co-workers relied on a three-component Knochel-type[237] coupling to achieve the synthesis of (+)-dehydrohomoancepsenolide (**533**, Scheme 79),[238] a secondary metabolite isolated from the gorgonian octocoral *Pterogorgia citrina* collected off the west coast of Puerto Rico.[239] The requisite heterobimetallic intermediate was generated in situ by insertion of activated zinc into both C−I bonds of 1,5-diiodopentane (**534**) to give **535** followed by transmetalation with 1 equiv of Cu(I). Consecutive addition of 1-iodo-1-

Scheme 79. Synthesis of Dehydrohomoancepselenolide Using a Three-Component Cross-Coupling/Alkylation, by Dierkes and Fürstner[238]

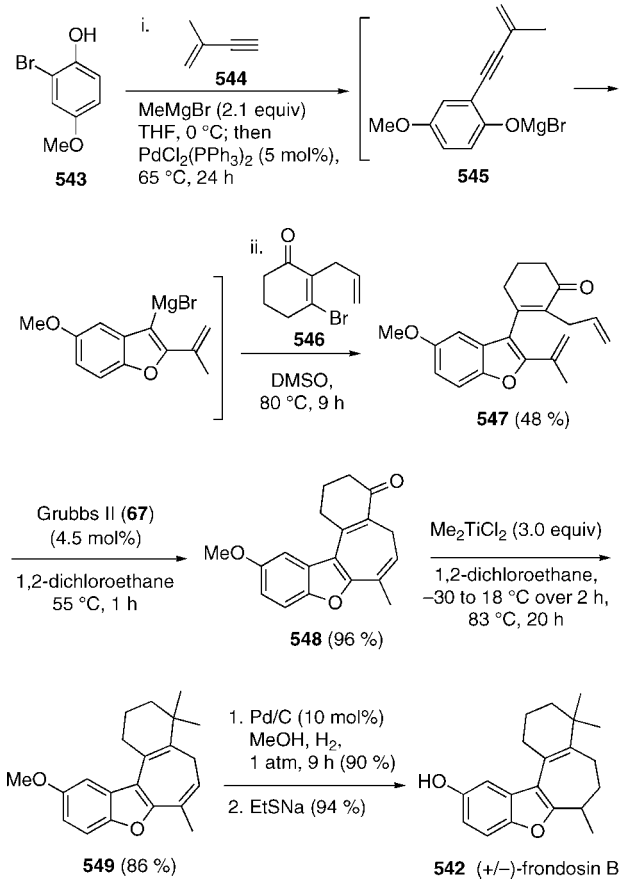


propyne (**536**) to give intermediate **537** and unsaturated ester **538** resulted in the double nucleophilic displacement to afford the crucial three-component adduct **539** in good yield. With this key intermediate in hand, alkene metathesis methodologies were called upon for the completion of the synthesis, a rather bold strategy because it required two selective catalysts to differentiate between π-systems. These chemoselective transformations were carried out using the first-generation Grubbs catalyst **212**,[240] providing butenolide **540**, followed by use of the Schrock alkylidyne complex **541**,[241] which afforded target **533** in very good yield after hydrogenation using Lindlar's catalyst.

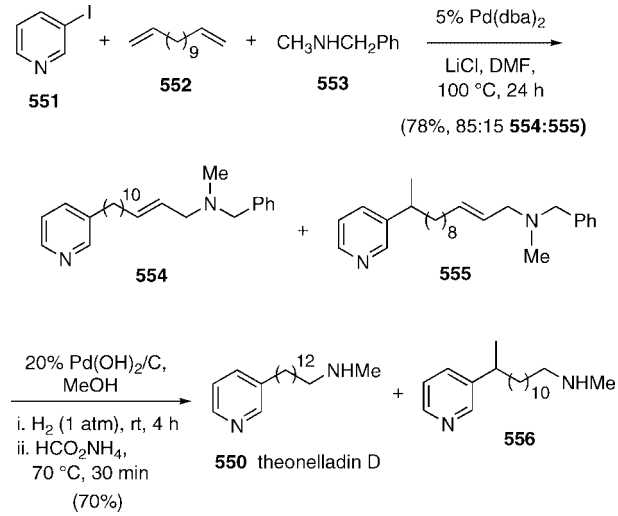
A concise palladium-catalyzed three-component route to (±)-frondosin B (**542**, Scheme 80), a known IL-8 receptor antagonist isolated from a marine sponge *Dysidea frondosa*,[242] was described by Flynn and co-workers.[243] The synthetic venture started with the brominated phenol **543**, which was then mixed with 2-methyl butenyne **544** in the presence of 2.1 equiv of methyl magnesium bromide. The latter reagent served as a base, priming both reactants for a Sonogashira-type coupling that produced **545** in situ. A tandem heteroannulative coupling of **545** with cyclohexene bromide **546** afforded MCR adduct **547**. The latter was engaged in a ring-closing metathesis event to afford the tricyclic core **548** in only four synthetic operations from commercially available starting materials. Conversion of the ketone functionality embedded within **548** into *gem*-dimethyl was accomplished using Reetz' Me_2TiCl_2 reagent,[244] providing intermediate **549**. Hydrogenation of the trisubstituted olefin of **549** and cleavage of the methyl ether completed the synthesis of the natural product in only six steps, which constitutes a considerable improvement over the previously published routes.

Theonelladins and niphatesine C (**558**) are members of a rapidly growing class of 3-substituted pyridine alkaloids that are known to display important biological activities.[245] For

Scheme 80. Synthesis of Frondosin B Using a Palladium-Catalyzed Three-Component Cross-Coupling Process, by Flynn and Co-workers[243]

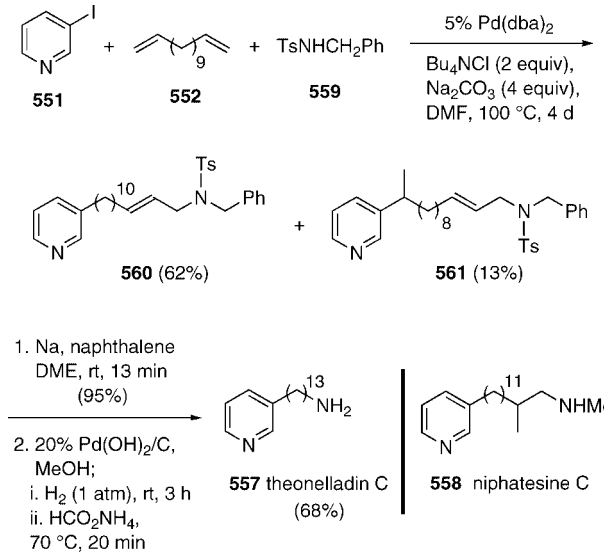


Scheme 81. Synthesis of Theonelladin D Using a Palladium-Catalyzed Three-Component Hetero-Cross-Coupling Reaction, by Larock and Co-workers[246]



instance, theonelladins C (**557**, Scheme 82) and D (**550**, Scheme 81) have shown antileukemic and antineoplastic properties. These interesting biological properties have fueled the development of new synthetic methods aimed at rapidly assembling these natural compounds and analogues thereof. Within this context, Larock's three-component cross-coupling reaction involving halopyridines, dienes, and amines stands as a powerful method because of its versatility.[246] For the synthesis of **550**, 3-iodopyridine (**551**) was mixed in one pot

Scheme 82. Synthesis of Theonelladin C and Niphatesine C Using a Palladium-Catalyzed Three-Component Hetero-Cross-Coupling Reaction, by Larock and Co-workers[246]

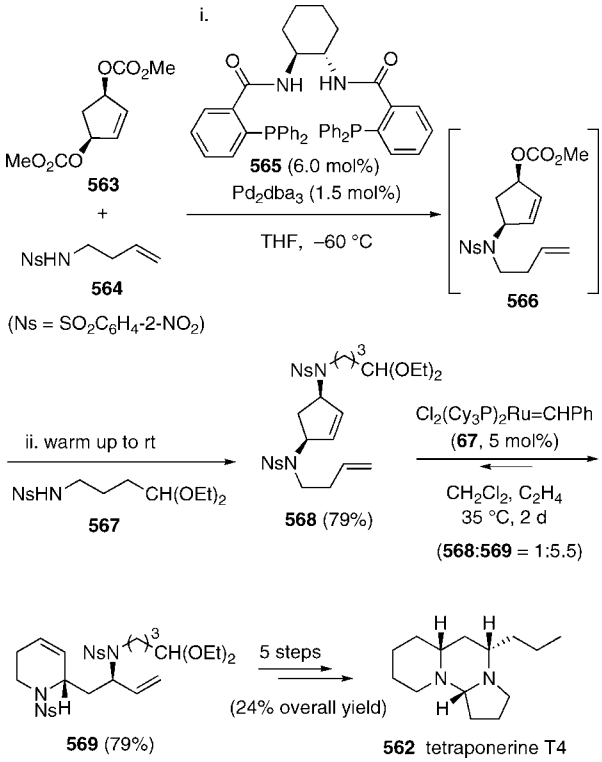


with 1,12-tridecadiene (**552**) and *N*-benzyl methylamine (**553**) under palladium catalysis to afford the key intermediate **554** and a small amount of an inseparable impurity, **555** (Scheme 81). A one-pot, stepwise hydrogenation of the double bond followed by debenzylation then afforded the natural product (**550**) and its branched isomer **556** as an inseparable mixture. One minor limitation of this multicomponent chemistry lies in the fact that it is mainly compatible with secondary amines. Thus, for the synthesis of **557**, protected amines were employed (Scheme 82).[246] Unfortunately, dibenzylamine did not prove to be a good nucleophile, thereby forcing the authors to resort to an amine bearing different protecting groups. Thus, the palladium-catalyzed coupling process between 3-iodopyridine (**551**), 1,12-tridecadiene (**552**), and *N*-benzyl tosylamide (**559**) produced a separable mixture of isomers **560** and **561**. The pure major isomer **560** was then subjected to a detosylation and one-pot hydrogenation/debenzylation, and afforded theonelladin C (**557**). The synthesis of **550** was revisited using this strategy, and the use of *N*-methyl tosylamide allowed its preparation as a single isomer. A similar synthetic strategy also led to the synthesis of niphatesine C (**558**).[246]

9.2. Double Allylic Amination

Symmetrically substituted cyclopentenes have proven to be very good substrates in allylic substitution chemistry.[247] This chemistry was elegantly exploited by Blechert and Stragies for the synthesis of the nerve poisoning tetraponerines natural products exemplified by tetraponerine T4 (**562**, Scheme 83),[248] which was isolated from the New Guinean ant *Tetraponera sp*.[249] The desymmetrization of dicarbonate **563** was initiated by the addition of 1 equiv of *N*-(3-butenyl)nosylamide **564** under palladium catalysis in the presence of Trost's chiral diphosphine ligand **565** (Scheme 83).[250] When the first allylic substitution was completed, the reaction was warmed up and the resulting intermediate **566** was treated in situ with 1 equiv of nosylated amine **567**. The product **568** resulting from this double substitution reaction was submitted to a tandem intramolecular ROM/RCM to furnish the key precursor **569**. The latter was transformed into the desired natural product **562** following

Scheme 83. Synthesis of Tetraponerines Using a Three-Component Double Allylic Amination, by Stragies and Blechert[248]



a sequence of redox transformations and a final acid-catalyzed aminal formation.

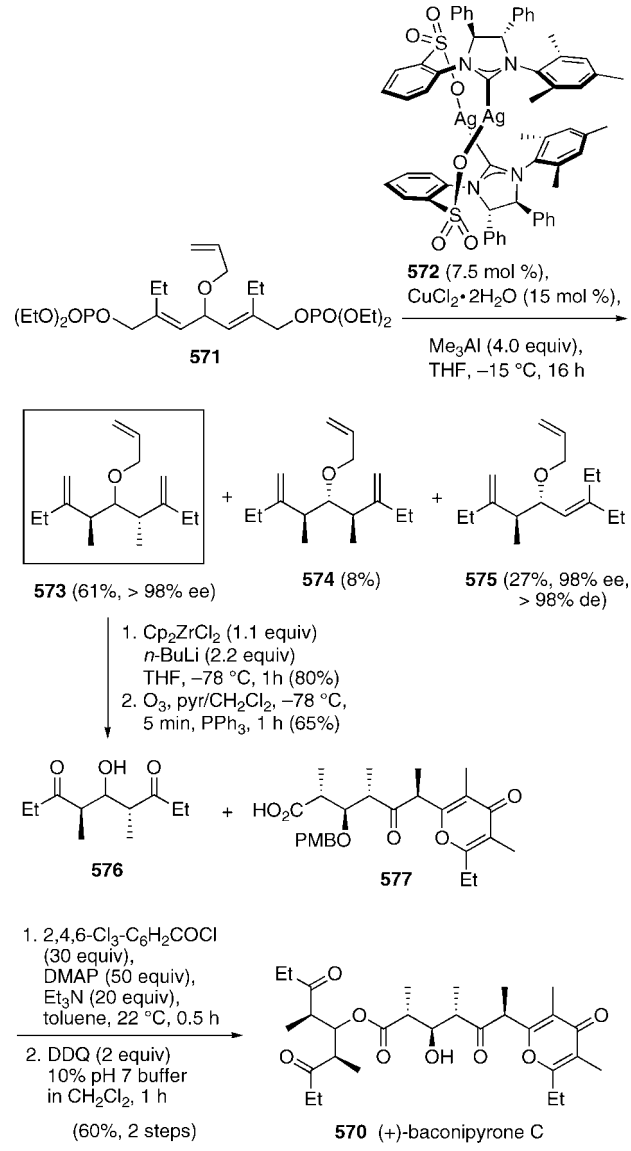
9.3. Double Allylic Alkylation

En route to baconipyrone C (**570**, Scheme 84), a polypropionate from the pulmonate *siphonaria baconi*,[251] Hoveyda and co-workers developed a new catalytic double asymmetric allylic alkylation (AAA) to secure the two stereocenters embedded within the pseudo-C_2-symmetric diketone **576**.[252] Their efforts, summarized in Scheme 84, required the preparation of bis(allylic phosphate) **571**. Treatment of **571** with $CuCl_2 \cdot 2H_2O$ (15.0 mol %), chiral silver carbene **572** (7.5 mol %), and $AlMe_3$ (4.0 equivalent) in THF afforded the desired three-component adduct **573** in 61% yield and over 98% ee, along with separable byproducts **574** and **575**. Two noteworthy advances in this catalytic enantioselective "A + B + B" MCR are the use of the more Lewis acidic $AlMe_3$ and the ability of **572** to override the influence of adjacent stereocenters in the second allylation to form **573**. The MCR product **573** was then converted into the diketone **576** by a zirconocene-mediated removal of the allyl protecting group and ozonolysis reaction sequence. The union of **576** with fragment **577** followed by the removal of the PMB protecting group completed the total synthesis of **570**.

9.4. Others

Acetoxyodontoschismenol (**578**, Scheme 85), a dolabellane diterpenoid, was isolated from the liverwort *Odontoschisma denudatum* and displayed moderate growth-inhibitory activity on a series of plant pathogenic fungi.[253] The challenging construction of the *trans* bicyclic [9.3.0] system, a common feature to this class of terpenes, was addressed by Whitby and Baldwin.[254] The authors' approach hinged on a three-component zirconocene-induced cocyclization,[255] carbenoid

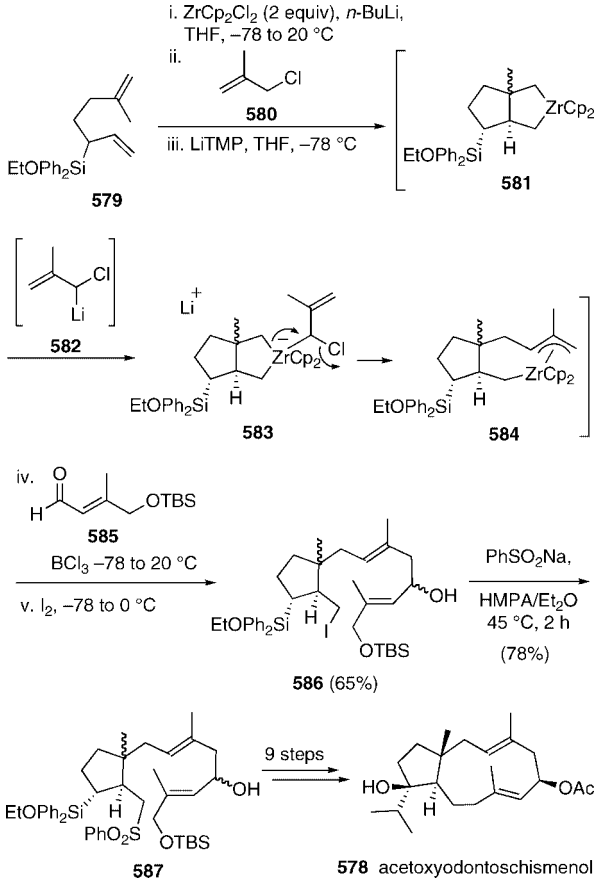
Scheme 84. Synthesis of (+)-Baconipyrone C Using a Three-Component Double Allylic Alkylation, by Gillingham and Hoveyda[252]



insertion, and electrophilic addition, and it culminated in the total synthesis of racemic acetoxyodontoschismenol (**578**) as illustrated in Scheme 85. The dibutylzirconocene generated in situ from zirconocene dichloride was reacted with diene **579** at room temperature to furnish a transient zirconacyclopentane **581**, which was trapped with the carbenoid **582** resulting from the treatment of methallyl chloride (**580**) and lithium 2,2,4,4-tetramethylpiperidine. This operation afforded the putative allylzirconium species **584** via **583**, and it was further elaborated by the addition of aldehyde **585** in the presence of boron trichloride. Cleavage of the carbon−zirconium bond with iodine then furnished the final MCR-adduct **586** as a mixture of all four diastereomers in moderate yield. The unstable iodide **586** was then rapidly converted to sulfone **587** by reaction with sodium benzenesulfinate. The total synthesis of **578** was completed in nine additional steps from **587** using a sequence of routine transformations.

Lignans are aromatic polyols and polyethers that may comprise one or more other distinct structural elements such as cycloalkanes or heterocycles. A palladium-catalyzed three-component reaction approach to furanoid lignan derivatives

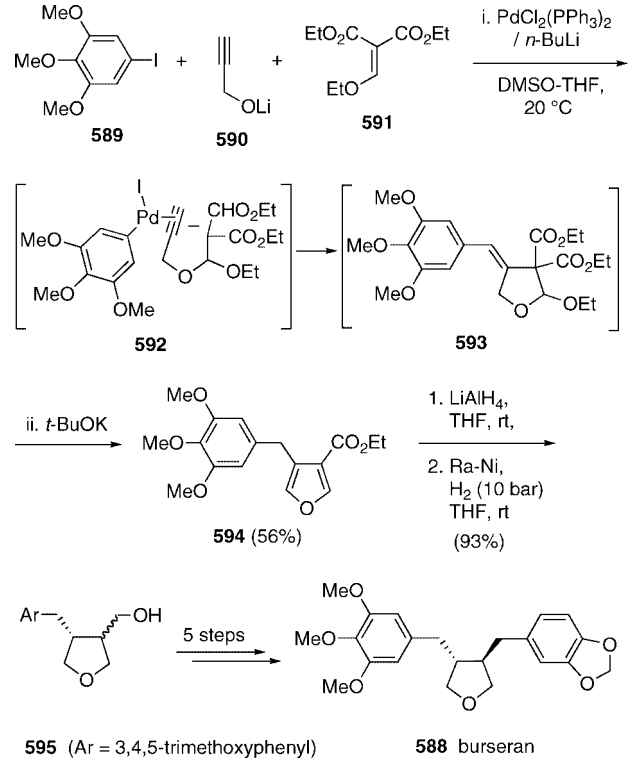
Scheme 85. Synthesis of Acetoxyodontoschismenol Using a Three-Component Zirconocene Induced Co-Cyclization/ Carbenoid Insertion/Electrophilic Trapping, by Baldwin and Whitby[254]



was reported by Balme and co-workers.[256] From this reaction, initiated by a conjugate addition of alkoxides to electron-deficient alkenes, the desired functionalized furans are isolated in good yield following a Wacker-type cyclization process. This interesting MCR was applied to the formal synthesis, in racemic form, of the antitumor lignan burseran (**588**, Scheme 86).[257] To this end, an equimolar mixture of 3,4,5-trimethoxy phenyl iodide (**589**), lithium propargyl alkoxide (**590**), and diethyl ethoxymethylene malonate (**591**) were stirred at room temperature in the presence of a palladium catalyst. Then, to the resulting intermediate **593**, formed via cyclization of **592** and reductive elimination, was added potassium *t*-butoxide. The ensuing base-promoted decarboxylative aromatization afforded the tetrahydrofuran MCR adduct **594** in good yield. The ester was first reduced and the furan ring was hydrogenated with Raney nickel to furnish a diastereomeric mixture of products **595** in high yield. Further synthetic manipulations then provided a known precursor to the natural product and secured a formal synthesis of burseran that relies on the work of Hanessian and Léger.[258]

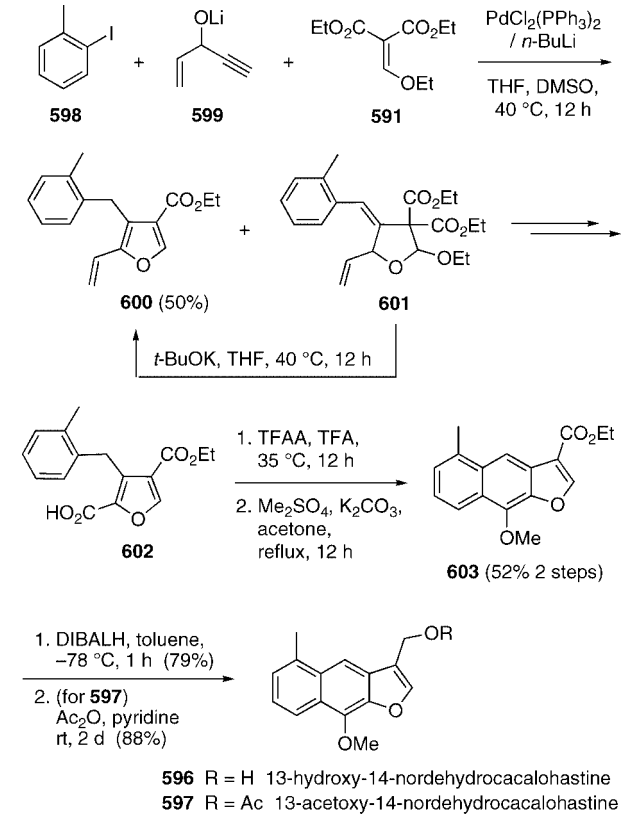
Balme's three-component furan synthesis[256] was utilized by Morimoto and co-workers to complete the synthesis of 13-hydroxy-14-nordehydrocacalohastine (**596**, Scheme 87) and 13-acetoxy-14-nordehydrocacalohastine (**597**),[259] two modified furanoeremophilane-type sesquiterpenes capable of preventing membrane lipid peroxidation.[260] As illustrated in Scheme 87, the lithium alkoxide of 1-penten-4-yn-ol (**599**), malonate **591**, and 2-iodotoluene (**598**) were stirred in a THF−DMSO solvent mixture in the presence of Pd(0)

Scheme 86. Synthesis of Burseran Using a Three-Component Heteroatom Conjugate Addition/ Wacker-Type Cyclization, by Balme and Co-workers[257]

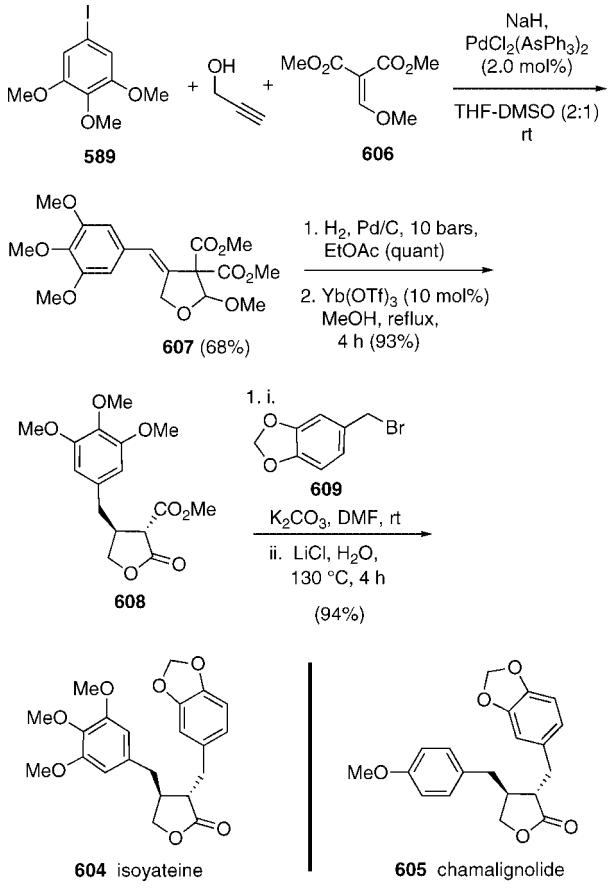


obtained by in situ reduction of $PdCl_2(PPh_3)_2$ with *n*-butyl lithium.[259] This highly chemoselective reaction directly afforded the desired furan product **600** along with its

Scheme 87. Synthesis of Nordehydrocacalohastine Using a Three-Component Heteroatom Conjugate Addition/ Wacker-type Cyclization, by Morimoto and Co-workers[259]



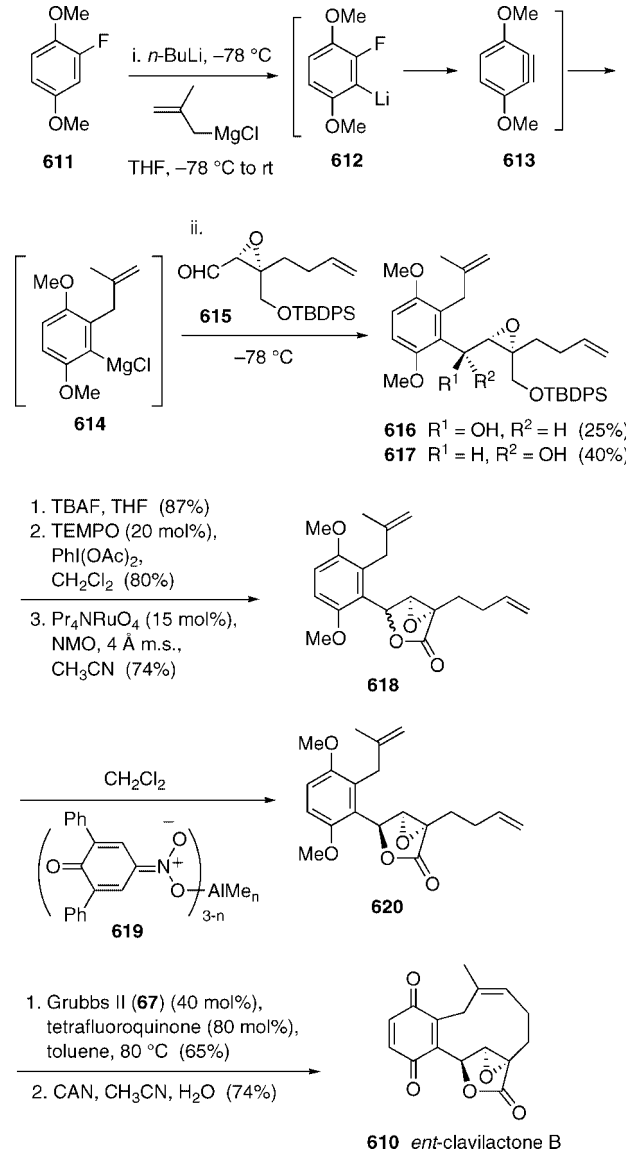
Scheme 88. Synthesis of Isoyateine and Chamalignolide Using a Three-Component Heteroatom Conjugate Addition/Wacker-type Cyclization, by Balme and Co-workers[261]



precursor **601** via the previously described reaction mechanism (c.f. Scheme 86). It is worth noting that recovered **601** could be converted into **600** by simple treatment with potassium *tert*-butoxide. The pendant furan alkene side chain in **600** was then converted into the corresponding carboxylic acid **602** in two steps, thus setting the stage for an intramolecular Friedel−Crafts cyclization that afforded product **603** to complete the efficient construction of the tricyclic core of the natural products. Simple functional group manipulations then delivered targets **596** and **597** in two steps.

Again, a slight variant of this methodology was utilized by Balme and co-workers to access the bis-3,4-dibenzylated tetrahydrofuran lignans isoyateine (**604**) and chamalignolide (**605**) (Scheme 88).[261] In this instance, benzylidene tetrahydrofuran **607** was submitted to hydrogenolytic conditions followed by a formal alkoxydecarbonylation catalyzed by ytterbium triflate to furnish lactone **608** in excellent yield. This reaction is proposed to proceed through a ring fragmentation/ring closure with a participation of adventitious water. A one-pot enolate alkylation with **609** under mild conditions, followed by a Krapcho dealkoxycarbonylation, afforded isoyateine **604** as a *cis*/*trans* mixture of isomers (15:85, respectively), which could be further enriched by treatment with DBU. A similar strategy led to chamalignolide, **605**.

Scheme 89. Synthesis of Clavilactone B Using a Benzyne-Mediated Three-Component Coupling, by Barrett and Co-workers[263]

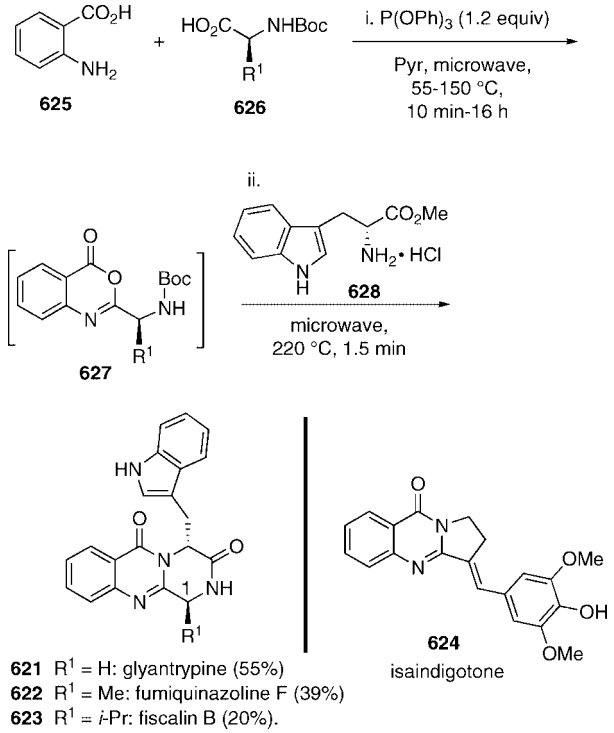


10. Miscellaneous

10.1. Benzyne-Mediated Three-Component Coupling

The clavilactone natural products exhibit antibacterial and antifungal activities.[262] In addition, some family members are potent inhibitors of kinases,[262c] an important class of enzymes involved in cellular signaling. A recent synthesis of *ent*-clavilactone B (**610**, Scheme 89) by Barrett and co-workers exploited the rich chemistry of benzynes.[263] These ephemeral and highly reactive species are easily generated by dehydrohalogenation of benzene rings and can be subjected to Grignard addition to afford an *ortho*-metalated arene intermediate that can be trapped with various electrophiles. For the synthesis of **610**, fluoroarene **611** was identified as the best benzyne precursor. Its treatment with *n*-BuLi at −78 °C generated the lithiated intermediate **612** (Scheme 89). At this point, methylallyl magnesium chloride was added, and the reaction mixture was warmed up to room temperature, which was necessary for the generation of benzyne **613** and its subsequent combination with the added

Scheme 90. Synthesis of Quinazolinone Alkaloids Using a Multicomponent Polycondensation of Aminoacids, by Liu and Co-workers[266]



Grignard reagent to provide **614**. Upon cooling to −78 °C, aldehyde **615** was added and the 1,2-addition was allowed to proceed. Overall, the three-component benzyne coupling afforded the crowded tetrasubstituted benzene core as a 1.6:1 mixture in favor of the undesired diastereomer **617**. This mixture was converted into lactone **618** in two steps. At this point, an aluminum-catalyzed epimerization of the benzylic stereocenter (with complex **619**) cleanly converted the major undesired diastereomer into lactone **620**. The synthesis of **610** was completed in two additional steps from **620**.

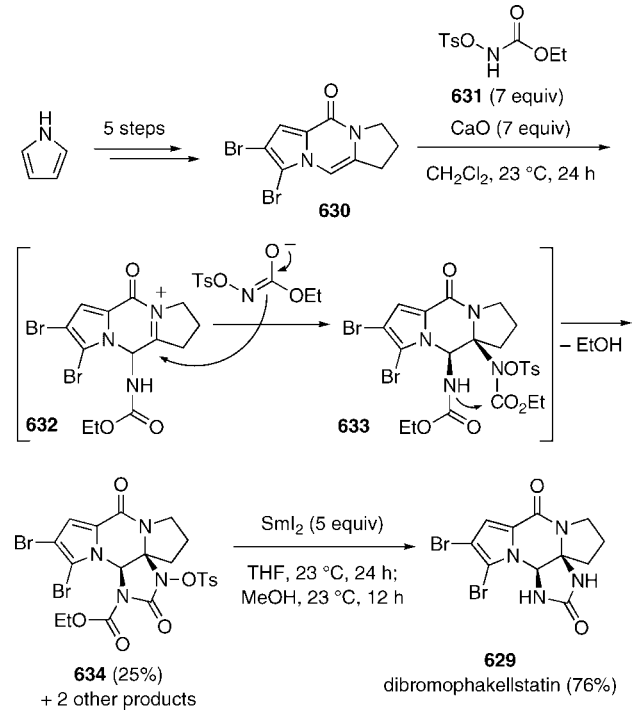
10.2. Multicomponent Polycondensation of Amino Acids

Liu and co-workers have developed a novel microwave-assisted, three-component coupling involving differently protected amino acids to access quinazolin-4-ones,[264] a motif encountered in the cytotoxic quinazoline alkaloids exemplified by glyantrypine (**621**), fumiquinazoline F (**622**), and fiscalin B (**623**) (Scheme 90).[265] These tripeptide natural products differ only at the C1 position and were assembled in only one step by Liu and co-workers.[266] Heating anthranilic acid (**625**) with the appropriate N-Boc protected amino acids (**626**) in pyridine in the presence of triphenyl phosphite yielded the corresponding benzoxazin-4-ones (**627**). Subsequent addition of tryptophan methylester (**628**) followed by a short microwave irradiation then provided the respective natural products (**621**−**623**) in low-to-moderate yields. Minor modifications to this methodology also enabled the synthesis of isaindigotone (**624**) and a number of other related alkaloids (Scheme 90).[267]

10.3. Three-Component Multiple Functionalization with Ethyl-*N*-Tosyloxycarbamate

A unique three-component reaction of the A + B + B type was utilized by Lindel and co-workers in their synthesis

Scheme 91. Synthesis of Dibromophakellstatin Using a Three-Component Double Functionalization of Ethyl-*N*-tosyloxycarbamate, by Lindel and Co-workers[268]



of *rac*-dibromophakellstatin, **629** (Scheme 91),[268] a cytotoxic tetracyclic pyrrole−imidazole alkaloid isolated from the marine sponge *Phakellia mauritiana*.[269] The imidazolidinone ring of **629** was constructed from key intermediate **630**, which can be accessed in five steps from pyrrole. To this end, **630** was treated in the presence of calcium oxide with a large excess of the reagent ethyl-*N*-tosyloxycarbamate, $EtO_2CNHOTs$ (**631**), which acts both as a source of electrophilic nitrene and as a dipolar carbamoyl component.[270] The initial nucleophilic addition step between the enamide of **630** and **631** is thought to produce acyliminium intermediate **632**. A nucleophilic *syn* attack of the anion of **631** on **632** would provide **633**, which would undergo an intramolecular condensation to provide the desired MCR product **634** in low yield. Key to the feasibility of this three-component reaction is the relatively slow decomposition (by α-elimination) of the corresponding anion of **631**), thereby allowing its use both as an electrophilic nitrene equivalent and as an N-nucleophile in a one-pot reaction process. In the last step of this concise synthesis, a samarium diiodide-promoted reduction with ethanolic workup afforded the alkaloid target **629**.

An enantioselective synthesis of this target was also reported by the authors using the same three-component reaction strategy described above and hydroxyproline as a temporary stereodirecting group.[271]

11. Conclusion

In recent years, atom-economy, tandem/cascade reactions, and protecting group free strategies have been advocated as overarching goals in contemporary organic synthesis. Arguably, the concept of multicomponent reactions compares favorably with these trend-setting concepts. As illustrated in this review, it is clear from the variety of natural products described that MCR strategies are far reaching and demonstrate a broad scope of applications. Many of the examples

have successfully combined elegance and brevity in the conquest of complex natural products. By relying on retrosynthetic schemes inspired by MCRs, new and oftentimes nonobvious disconnections are revealed. This is in essence the hallmark of MCRs: provide the shortest path possible to complex structural motifs by optimizing convergency at every possible step. An apparent contradiction emanating from this review, however, is that the current repertoire of available MCRs is still rather limited, and many of those MCRs are in fact closely related on a mechanistic standpoint. It is hoped that the burgeoning of transition metal-catalyzed MCRs will translate into new applications in natural product syntheses and provide, in the near term, a potential solution to expanding the scope of mechanistic diversity on display in this review.

Natural product synthesis is the yardstick by which progress is often measured in organic synthesis. By this analysis, we hope that we have painted an accurate picture of the advances made in the field of MCR chemistry, and we hope this review has made a convincing case for the need to develop new MCR processes and expand the realm of their applications in natural product synthesis.

12. Note Added in Proof

Recently, Smith and co-workers utilized their anion-relay chemistry (ARC), described in section 4, this time using 2-TBS-1,3-dithiane and two different epoxides to construct the eastern hemisphere of (−)-2-epi-peloruside A, an unnatural analogue of (+)-peloruside A epimeric at the C2 position.[272] A recent pair of publications described an efficient three-component Passerini sequence to provide a convenient solution to the difficult construction of the alpha-keto beta amino carboxamide unit embedded within cyclotheonamide C.[273,274] Kobayashi and co-workers have reported the application of a three-component Ugi reaction using a convertible isocyanide developed in their laboratory, and described earlier for the synthesis of omuralide (Scheme 66) to achieve first the racemic synthesis of the natural product dysibetaine,[275] then an enantiocontrolled synthesis.[276] Using a variant of the benzyne-mediated multicomponent chemistry described in section 10.1, Barrett and co-workers have developed a concise total synthesis of the antibacterial marine natural product dehydroaltenuene B.[277]

13. Abbreviations

MCR	multicomponent reaction
3CR	three-component reaction
Ac	acetyl
ALB	Al−Li bis(binaphthoxide)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOP	benzotriazole-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (Castro's reagent)
BPS	*tert*-butyldiphenyl silyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cat	catecholate
CBS	Corey−Bakshi−Shibata oxazaborolidine
Cbz	carboxybenzyl
cod	cyclooctadiene
Cp	cyclopentadienyl
CSA	camphorsulfonic acid
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethylazodicarboxylate
DHF	3,4-dihydrofuran
DIAD	diisopropylazodicarboxylate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropyleneurea
DMSO	dimethylsulfoxide
Dppb	diphenylphosphinobutane
DMAP	1,1-dimethylaminopyridine
DS	dodecyl sulfate
EDDA	ethylenediamine-*N*,*N*′-diacetic acid
HMPA	hexamethylphosphoramide
Ipc	isopinocampheyl
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
mCPBA	*meta*-chloroperoxybenzoic acid
MOM	methoxymethyl
Ms	methanesulfonyl
Nap	naphthylmethyl
NMO	*N*-methylpyridine-*N*-oxide
Ns	nosyl (4-nitrobenzenesulfonyl)
PG	prostaglandin
Pin	pinacolate
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
PPTS	pyridinium *p*-toluenesulfonate
pyr	pyridine
RCM	ring-closing metathesis
ROM	ring-opening metathesis
SEM	trimethylsilylethoxymethyl
TAS-F	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAF	tetra-*n*-butyl ammonium fluoride
TBDPS	*tert*-butyl diphenylsilyl
TBS	*tert*-butyl dimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
TEOC	2-(trimethylsilyl)ethoxycarbonyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
TFE	trifluoroethanol
TIPS	*tri*-isopropylsilyl
TMP	tetramethylpiperidinyl
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
Ts	*p*-toluenesulfonyl

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