Novel Syntheses of Bridge-Containing Organic Compounds

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1. Introduction

Bridge-containing segments exist in numerous natural products and active pharmaceutical ingredients (API) and intermediates, creating more structural complexity. In addition, bridge-containing segments make the molecules structurally less flexible compared to their homologous counterparts. Accordingly, installation of the bridge segment(s) onto the existing ring system makes it more challenging and interesting for synthetic organic chemists, and much effort has been made to develop new cyclization technologies.

Among the variety of methods documented in the literature, the Diels−Alder (DA) reaction[1] is the most commonly used method for the construction of carbo- and heterocyclic compounds. A cyclic diene is required if the intermolecular DA reaction is involved in the synthesis of bridge-containing organic compounds (Scheme 1, eq 1). The intramolecular DA (IMDA) reaction has been classified into two categories by Shea, type 1-IMDA (Scheme 1, eq 2) and type 2-IMDA (Scheme 1, eq 3).[1f,2] The dienophile in the type 2-IMDA reaction is joined at the 2 position of the diene. This type 2-IMDA reaction is distinguished by the fact that a strained bridgehead double bond is formed in the cycloaddition step. It is well known that DA reactions occur usually at elevated temperature. However, in the presence of Lewis-acid catalyst some reactions can be carried out at relatively low temperature.[3]

The [*n* + *m*] dipolar cycloaddition reactions have been found in many useful organic syntheses to access bridge-

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Wenyi Zhao was born in Shenyang, China, and received his B.S. and M.S. degrees from Lanzhou University, and Ph.D. degree from Nanjing University, China. He spent two years at the Institute of Chemistry, Chinese Academy of Sciences, as Postdoctoral Associate. In 1995, he joined Dr. Shine's group at Texas Tech University, Lubbock, TX, as Senior Research Associate. He started his industrial career at Roche Carolina in 2001 as a process chemist. His research interests are focused on organic synthesis, reaction mechanism, and development of chemical processes for large-scale production of pharmaceutical intermediates and APIs. He has developed a Mechanism-guided Process Development (MPD) Strategy and applied it toward his process research and development.

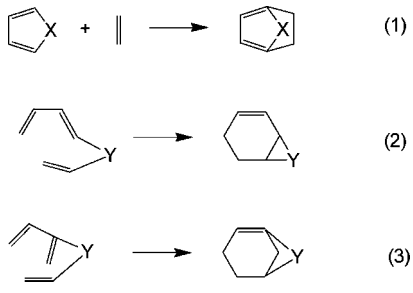
containing organic compounds. The polarized unsaturated bond(s) is allowed to create a 1,3-dipolar reaction center in the ring-closure step. 1,3-Dipolar [3 + 2] cycloadditions can be catalyzed by metal cations. Nitrones as 1,3-dipoles in [3 + 2] cycloaddition reactions are capable of reacting with a great variety of dipolarophiles giving rise to a vast array of products. Besides [3 + 2] cycloadditions, [5 + 2], [8 + 2], [4 + 3], [6 + 3], and [6 + 4] cycloadditions are also widely employed to construct bridge-containing organic compounds.

Molecular rearrangement plays an important role in the formation of bridged compounds. Intramolecular ring-opening/closure process and ring fragmentation are commonly used approaches to synthesize bridged cyclic organic compounds. Utilizations of intramolecular Schmidt reaction, Polonovski and Prins-type cyclization, and Pinacol rearrangement are proved to be versatile synthetic tools in the preparation of bridge-containing organic molecules. Another powerful method is the combination of Claisen rearrangement with Diels−Alder reaction.

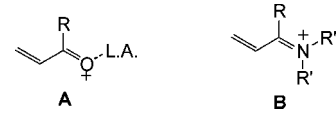
Free-radical reactions as one of the synthetic tools have been frequently applied toward the total synthesis of natural products containing bridge segments.

Transition-metal-catalyzed[4] annulation reaction is of increasing importance in synthetic organic chemistry for the construction of complex organic compounds including bridged-ring systems. Compared to the traditional organic transformations, most of the transition-metal-catalyzed transformations go through sequential processes involving more than one reactive species. This makes it difficult in both elucidation of the reaction mechanisms and design of new reactions.

Scheme 1



Scheme 2



This review will address the applications of the most recently developed asymmetric D−A reactions (section 2), [*n* + *m*] cycloaddition reactions (section 3), molecular rearrangements (section 4), free-radical reactions (section 5), and transition-metal-catalyzed cyclization reactions (section 6) toward the syntheses of APIs and natural products with bridge-containing ring systems. Furthermore, this review will also cover other newly developed methods such as halogen-promoted cyclizations, nucleophilic additions and substitutions, condensation reactions, etc. (section 7). The literature from 2000 to 2009 will be included in this review.

2. [4 + 2] Cycloaddition Reactions

The Diels−Alder cycloaddition reaction is one of the most fundamental synthetic transformations and has been the cornerstone in countless total syntheses.[5] In particular, the asymmetric catalytic DA reaction has recently received unprecedented attention, presumably due to the ability to rapidly provide complex enantiopure carbocycles from simple substrates.[6] The bridged bicyclic compounds can be prepared via either intermolecular or intramolecular DA reactions. In the intermolecular cycloaddition, cyclic diene is required to build a bridged bicyclic product wherein the endo cycloadduct usually predominates. When a molecule contains both diene and dienophile functionalities, an intramolecular Diels−Alder reaction can take place given that the tethered chain is in the right length to afford bridge-containing organic compounds.

2.1. Intermolecular [4 + 2] Cycloadditions

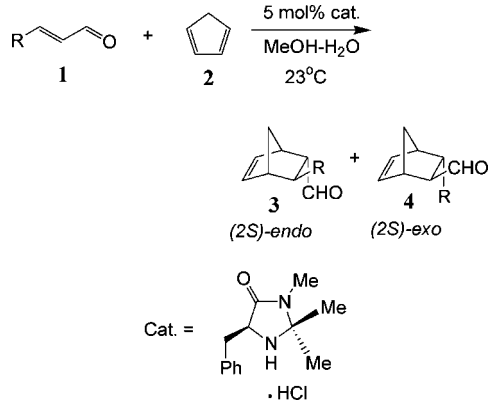
2.1.1. Catalyst-Promoted Asymmetric Diels−Alder Reactions

Lewis-acid-catalyzed asymmetric DA reactions have attracted great attention due to their ability to construct complex carbocyclic frameworks in an enantiomerically enriched form.[7] Studies on the unsaturated aldehydes,[8] bidentate alkenoyl-oxazolidinones,[9] and α,β-unsaturated amide bearing chiral auxiliaries[10] as dienophiles have been reported. Corey's research group has pioneered enantioselective DA reactions catalyzed by chiral Lewis acids and demonstrated their applications to the synthesis of complex molecules. A great review written by Corey addressed these Lewis-acid-catalyzed asymmetric [4 + 2] cycloaddition reactions.[11]

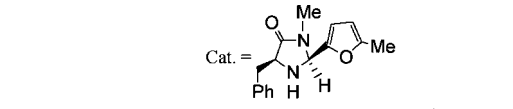
Activation of α,β-unsaturated ketone (**A**) by Lewis acid or by forming iminium ion (**B**) is illustrated in Scheme 2. Due to the fact that the equilibrium dynamics and π-orbital electronics of iminium (**B**) are inherent to the complex of ketone−Lewis acid (**A**), MacMillan revealed an attractive prospect that chiral amines might function as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.

As a result, an enantioselective DA reaction of α,β-unsaturated aldehydes with cyclopenta-1,3-diene was devel-

Scheme 3



Scheme 4



entry	R^1	R^2	*endo:exo*	Yield, %	% ee
1	Me	Me	14:1	85	61
2	Me	Et	25:1	89	90
3	Me	*n*-Bu	22:1	83	92
4	Me	*i*-Am	20:1	86	92
5	Me	*i*-Pr	8:1	24	0
6	*n*-Pr	Et	15:1	84	92
7	*i*-Pr	Et	6:1	78	90

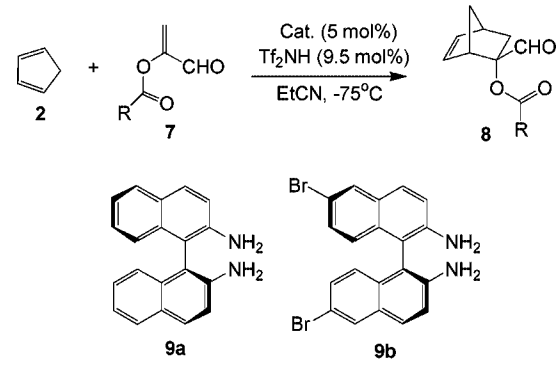
oped.[12] The use of 5 mol % of chiral imidazolidin-4-one hydrochloride salt afforded an exo/endo mixture (1:1) of bicyclo[2.2.1]hept-5-ene-2-carbaldehyde derivatives **3** and **4** with good enantioselectivity (exo > 84% ee, endo > 90% ee) in high yields (75−99%) (Scheme 3).[12] The R group can vary from alkyl, such as methyl, propyl, and isopropyl, to aryl, such as phenyl and furyl.

This methodology was further extended to α,β-unsaturated ketones **5**, and the first efficient asymmetric Diels−Alder reaction using chiral amine catalyst was reported by MacMillan (Scheme 4).[13] All ketones except isopropyl-substituted ketone (Scheme 4, entry 5) led to high yields with good enantioselectivity.

Analogous to chiral imidazolin-4-one derivatives as DA cycloaddition catalyst, Ishihara demonstrated that chiral primary amines **9** could activate α,β-unsaturated aldehydes **7** for highly enantioselective DA reactions (Scheme 5).[14] In contrast to the results reported by MacMillan,[13] the asymmetric DA cycloaddition catalyzed by **9a** or **9b** afforded *exo*-bicyclo[2.2.1] adducts **8** as major products. Moreover, when the reaction was conducted in the presence of 10 mol % of water, both the yield and the enantioselectivity were increased. Water might promote the hydrolysis of the aldimine intermediate to increase the catalytic turnover rate.

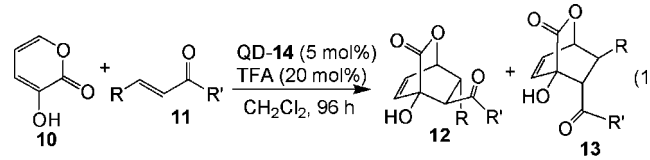
Following the work done by MacMillan[13] and Ishihara,[14] Deng[15] and co-workers developed an enantioselective DA reaction by applying cinchona alkaloid-derived chiral catalysts toward the [4 + 2] cycloaddition. By screening various cinchona alkaloids, Deng's group uncovered that among six cinchona alkaloids 9-amino QD-**14** gave the best results for the DA reaction of 2-pyrone **10** with α,β-unsaturated ketones

Scheme 5

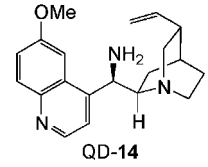


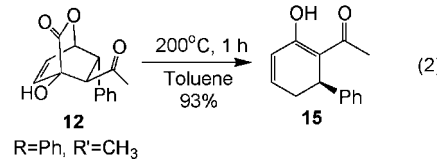
R= *p*-MeOC$_6$H$_4$, Cat= **9a**, 48% (*exo*/*endo* 93:7, 94% ee)
R= *p*-MeOC$_6$H$_4$, Cat=**9b**, 99% (*exo*/*endo* 87:13, 87% ee)
R=*c*-C$_6$H$_{11}$, Cat=**9a**, 80% (*exo*/*endo* 94:6, 86% ee)
R=*c*-C$_6$H$_{11}$, Cat=**9b**, 78% (*exo*/*endo* 86:14, 83% ee)
R=*c*-C$_5$H$_9$, Cat=**9a**, 95% (*exo*/*endo* 92:8, 88% ee)

Scheme 6



R	R'	Yield % (**12**+**13**)	dr (**12**:**13**)	ee % of **12**
H-	CH_3	87	80:20	98
F-	CH_3	92	81:19	98
Cl-	CH_3	89	79:21	98
Br-	CH_3	96	81:19	97
MeO-	CH_3	68	84:16	97
CH_3	CH_3	92	84:16	99
$CH_3(CH_2)_4$	CH_3	95	75:25	99
CH_2=CH	C_2H_5	99	97:3	99
CH_2=CH	$CH_3(CH_2)_4$	98	93:7	96

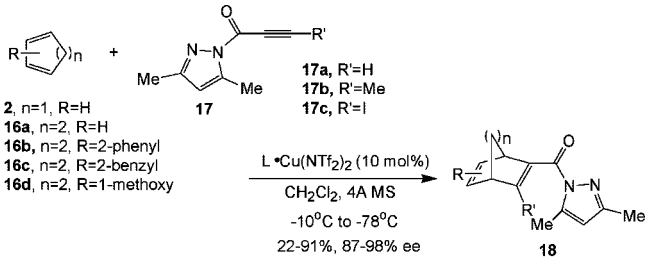




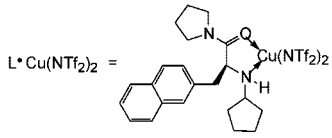
11 (Scheme 6, eq 1). Cleavage of the lactone bridge **12** provides a useful asymmetric route to a wide range of cyclic chiral building block, such as chiral ketone **15** (Scheme 6, eq 2), amenable for further synthetic elaborations.

A catalytic enantioselective [4 + 2] cycloaddition of cyclic electron-rich dienes **2** or **16** with electron-deficient propiolamide derivatives **17** was achieved by Ishihara (Scheme 7).[16] As expected, a temperature effect was noticed for a reaction of cyclopentadiene **2** with **17a** and a bridged cycloadduct **18** was obtained with 93% ee in 50% yield at −78 °C and with 88% ee in 91% yield at −40 °C, respectively.

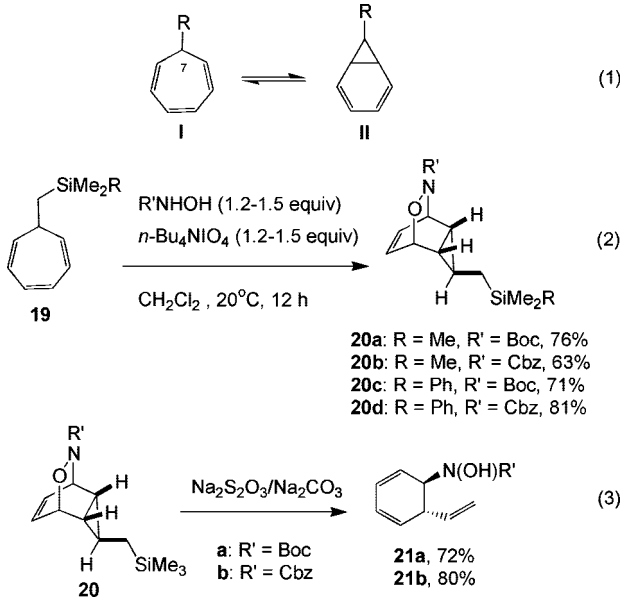
Scheme 7



diene	R'	Temp (°C)	Yield (%)	ee (%)
2	H	-78	50	93
2	H	-40	91	88
2	Me	-20	22	89
2	I	-78 to -40	82	89
16a	H	-20	48	93
16a	I	-10	70	96
16b	H	-78 to -20	50	87
16b	I	-20	83	95
16c	H	-78 to -20	69	89
16c	I	-40 to -20	83	96
16d	I	-40	84	96



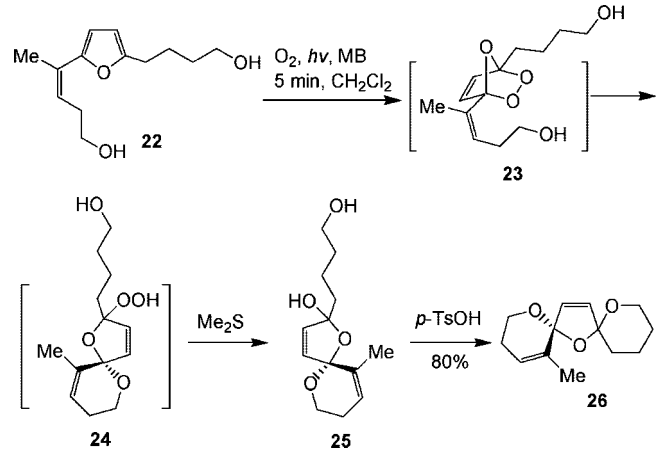
Scheme 8



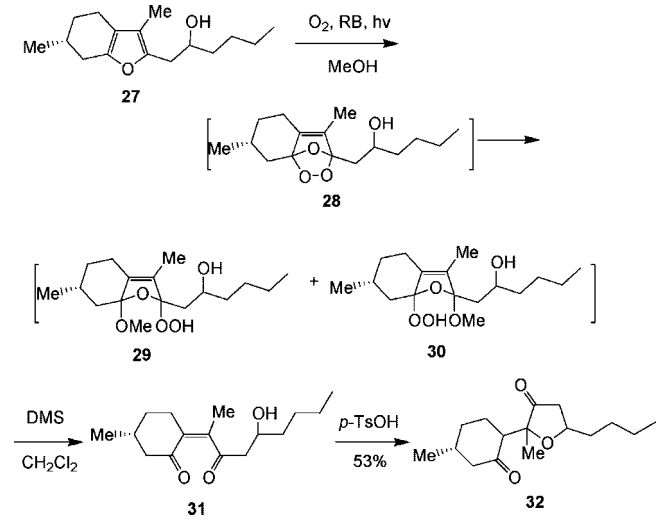
2.1.2. Hetero [4 + 2] Cycloadditions

The equilibrium of valence isomerism between cycloheptatriene **I** and norcaradiene **II** is influenced by the substituents (R) at C7. An electron-withdrawing R group tends to shift the equilibrium toward the norcaradiene **II**, whereas a π-electron-donating group favors cycloheptatriene (Scheme 8, eq 1). Although the equilibrium has been studied on cycloheptatrienes having various electronically differentiated substituents,[17] very little is known about the effect of silyl-substituted cycloheptatrienes (**I**, R = SiR_3) and their silylmethyl homologues (**I**, R = CH_2SiR_3).[18] Nevertheless, a [4 + 2] cycloaddition of norcaradiene **II** in the equilibrium of **19** with nitroso dienophiles generated in situ by oxidation[19] of hydroxylamine with tetrabutylammonium periodate (n-Bu_4NIO_4) led to bridged products **20** in good yields (Scheme 8, eq 2).[20] The resulting bridged compounds **20** could be converted into valuable synthetic intermediates **21** in good yields (Scheme 8, eq 3). Formation of the vinyl group probably occurs through the ring opening of the cyclopropane moiety of **20a**,**b**, with concomitant desilylation.

Scheme 9



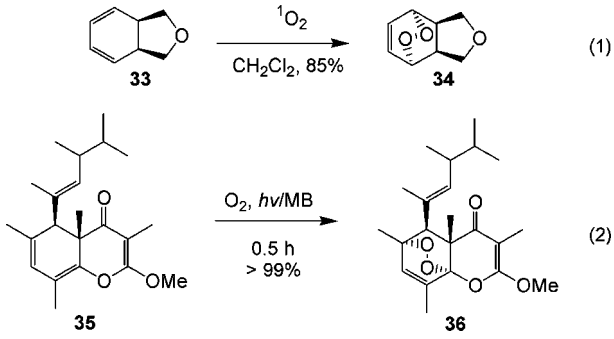
Scheme 10



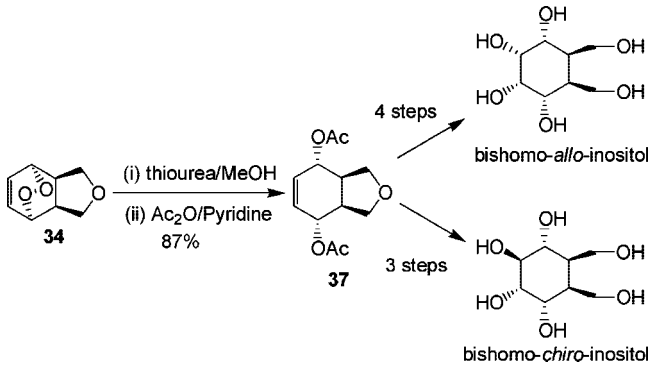
The structure-inherent instability of the heterobicyclo [2.2.n] ring systems (n = 1 or 2) is utilized by Vassilikogiannakis's group[21] to cultivate a versatile and general method for the synthesis of bis-spiroketal. Bis-spiroketal functionality exists in a wide range of interesting natural products, such as spirolides,[22] pinnatoxins,[23] pteriatoxins,[24] and the azaspiracids.[148,25] As depicted in Scheme 9, a tandem sequence began with a [4 + 2] cycloaddition reaction, leading to a transient bridged intermediate **23**.[26] The subsequent reactions including S_N2-type ring opening, peroxide **24** reduction, and cyclization afforded the desired bis-spiroketal **26**.

Further utilization of the attractive singlet-oxygen-mediated tandem process to synthesize tetrahydrofuran-3-one **32** was demonstrated by the same group in Scheme 10.[27] Obviously, an intramolecular nucleophilic ring opening of cycloadduct ozonide **28** is unlikely because of an unfavorable 4-*exo*-cyclization compared to the 6-*exo*-cyclization of **23** (Scheme 9). However, an intermolecular nucleophilic ring opening was effected when the reaction was conducted in methanol, resulting in a mixture of products **29** and **30**. Without

Scheme 11



Scheme 12



isolation, exposure of the mixture of **29** and **30** to dimethyl sulfide (DMS) followed by treatment with a catalytic amount of *p*-TsOH furnished **32** in 53% yield.

In the absence of nucleophiles, a bicyclo[2.2.2] ring system, such as **34** (Scheme 11, eq 1),[28] could be isolated in 85% yield as colorless crystals. Surprisingly, the resulting bridged bicyclic endoperoxide **34** is fairly stable with a melting point of 123−126 °C. When a [4 + 2] reaction of tridachiahydropyrone **35** was carried out in the presence of 0.2 equiv of methylene blue, complete conversion into the desired product, oxytridichiahydro-pyrone **36** (Scheme 11, eq 2),[29] was realized in quantitative yield.

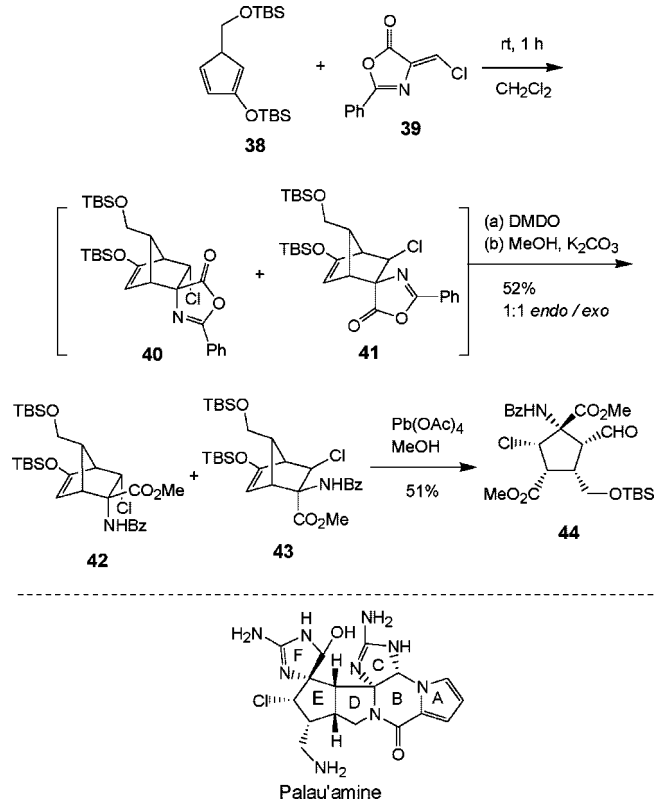
The isolated endoperoxide **34** (Scheme 11, eq 1) was in turn selectively reduced with thiourea under very mild conditions followed by acetylation in pyridine, affording the diacetate **37** in 87% yield (Scheme 12).[28] In the event, stereoselective synthesis of bishomo-*allo*-inositol and bishomo-*chiro*-inositol was realized in four and three additional steps, respectively.

2.1.3. Other [4 + 2] Cycloaddition Reactions

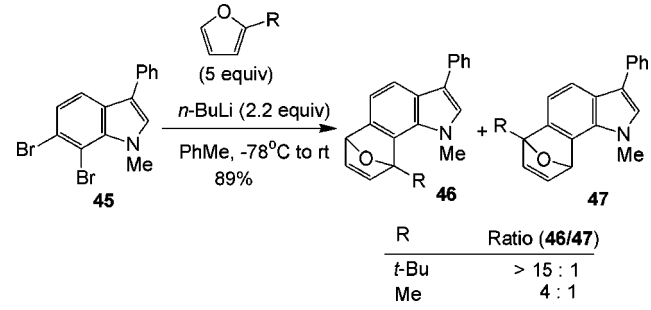
2,5-Disubstituted cyclopentadiene **38** is highly competent in Diels−Alder cycloadditions with a wide variety of dienophiles under very mild reaction conditions. Gleanson and co-workers employed a room-temperature Diels−Alder cycloaddition of the substituted cyclopentadiene **38** toward the synthesis of the bridged [4 + 2] cycloadduct **42**, a potential intermediate for construction of the E ring in palau'amine-marine alkaloid (Scheme 13).[30]

A recent report by Buszek and co-workers describes a useful intermolecular DA cycloaddition of indole arynes. It was found that while 4,5- and 5,6-indolynes show virtually no regioselectivity in Diels−Alder cycloadditions, the 6,7-indolyne by contrast is highly regioselective, presumably due to the polarization influence of the pyrrole ring. This regioselective DA cycloaddition of 6,7-indolyne, being

Scheme 13



Scheme 14



formed in situ from dibromide **45** in the presence of *n*-butyllithium, furnished a mixture of ether-bridged compounds **46** and **47** (Scheme 14).[31]

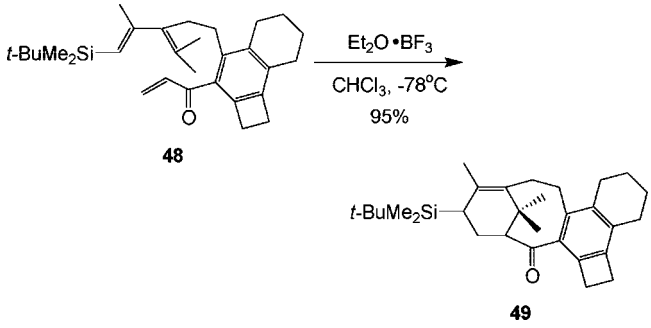
2.2. Intramolecular [4 + 2] Cycloadditions

2.2.1. Lewis-Acid-Catalyzed Diels−Alder Reactions

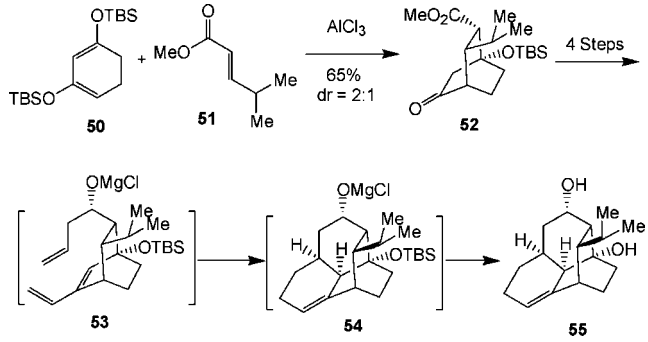
Lewis-acid-catalyzed intramolecular Diels−Alder (IMDA) reactions usually proceed under mild conditions with high reaction rates, resulting in good selectivity owing to the reduction in the degrees of freedom of the transition. Type 2-IMDA of **48** wherein the diene and dienophile are separated by a cyclohexene moiety occurred to afford taxane skeleton **49** (Scheme 15).[32]

A combination of intramolecular Diels−Alder cycloaddition with intermolecular Diels−Alder cycloaddition, developed by Baran's group,[33] constitutes a powerful tool to access a key tricyclic carbon skeleton **56** (Scheme 17) in the total synthesis of vinigrol.[34] A Lewis-acid-catalyzed intermolecular Diels−Alder cycloaddition of cyclohexadiene **50** with α,β-unsaturated ester **51** afforded bicyclic ketone **52**. Without isolation, a DA reaction of alkoxide **53** at 105

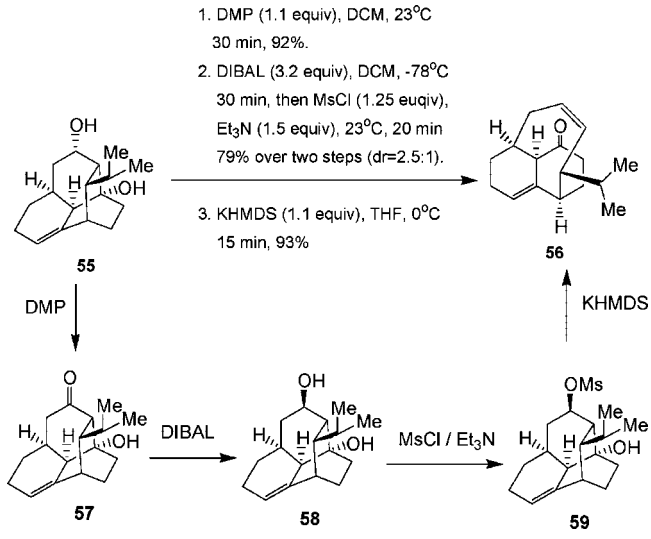
Scheme 15



Scheme 16



Scheme 17



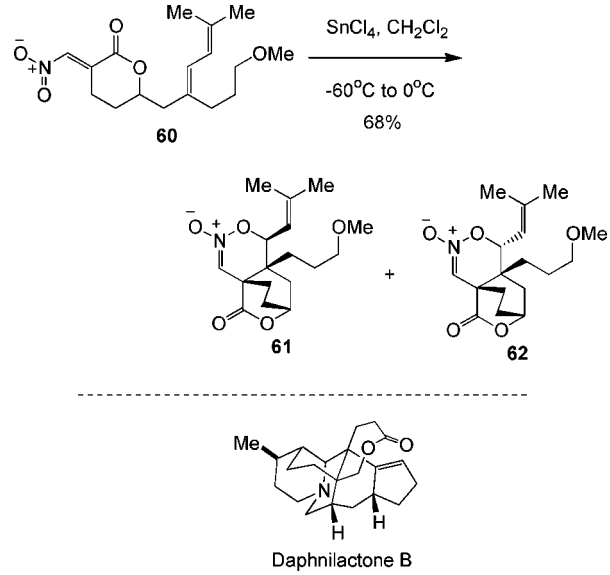
°C gave **54**, whose reaction with TBAF furnished the tetracycle **55** in 75% overall yield (Scheme 16).

Grob fragmentations are generally performed under nucleophilic or basic conditions, albeit some Grob fragmentations are conducted under certain acid conditions.[35] The fragmentation process may proceed through a concerted or stepwise pathway, depending on stereochemical and stereoelectronic factors.[36] Notably, tetracyclic intermediate **55** is unreactive toward Grob fragmentation, presumably due to the lack of correct antiperiplanar atomic arrangement. Eventually, a Grob fragmentation of its diastereoisomer **58**, being inverted from **55**, was realized to furnish the desired bridged **56**, Scheme 17.

2.2.2. Hetero [4 + 2] Cycloadditions

The Diels−Alder reaction is a powerful method for creation of complex polycyclic structures containing a

Scheme 18



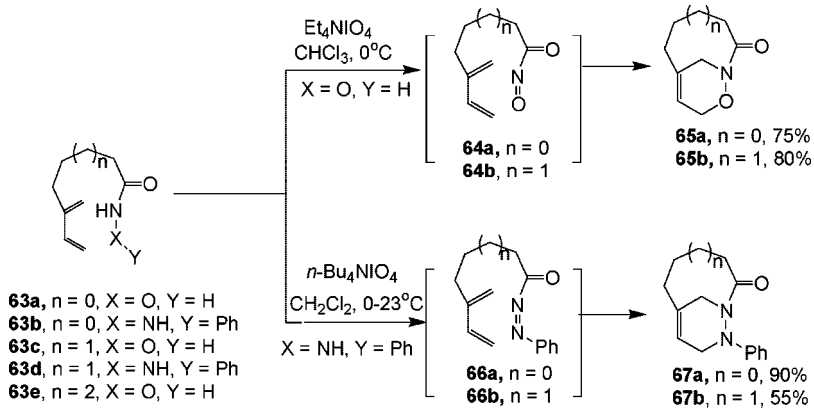
number of stereogenic centers in a single step.[5c] The bridged adduct **61** (or **62**) features vicinal quaternary stereocenters representing the correct relationship for the vicinal quaternary stereogenic centers in the core of daphnilactone B (Scheme 18). A nitro-substituted olefin **60** with a pendant diene functional group underwent heterointramolecular [4 + 2] cycloaddition reactions in the presence of Lewis acid $SnCl_4$, leading to cycloadducts **61** and **62** (Scheme 18).[37]

The type-2 IMDA cycloaddition of heteroatom variants provides a general route toward heterocycles with alkene bridgeheads.[1f,2,38] Under oxidative conditions, hydroxylamines or hydrazides **63** were converted in situ into dienophiles, *N*-acylnitroso-**64** and *N*-acylazo-**66**, whose intramolecular DA cycloadditions provide an efficient method for the preparation of bridged bicyclic heterocycles (Scheme 19).[39] A condition of using tetraalkylammonium (meta)periodate (Et_4NIO_4 or n-Bu_4NIO_4) as oxidant was adopted as a general method to convert hydroxylamines or hydrazides **63** into the corresponding *N*-acylnitroso-**64** or *N*-acylazo-**66** dienophiles (Scheme 19).

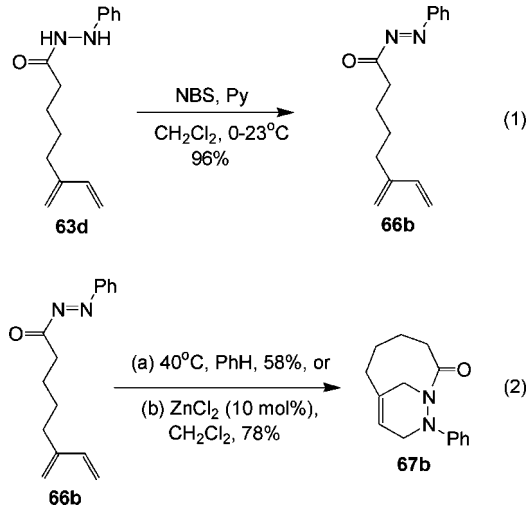
Employing a protocol described by Evans and co-workers,[40] *N*-acylazo **66b** was isolated in 96% yield (Scheme 20, eq 1), which was used to examine the subsequent IMDA under both thermal and Lewis-acid-catalyzed conditions. *N*-Acylazo dienophile **66b** was found to be unstable at temperatures >40 °C in benzene, and cycloadduct **67b** was not observed. The best results were obtained at 40 °C, producing cycloadduct **67b** in only 58% yield. Lewis-acid catalyst allows a DA reaction to occur at mild conditions, which circumvents the decomposition of labile organic compounds. Thus, in the presence of 10 mol % of $ZnCl_2$, a DA cycloaddition of **66b** led to cycloadduct **67b** in 78% yield (Scheme 20, eq 2).[39b]

A complex mixture was obtained when application of the oxidative cycloaddition condition (Et_4NIO_4, $CHCl_3$, 0 °C) to **63e** due to other competing processes. This obstacle was overcome by a thermal generation of the *N*-acylnitroso species from a 9,10-dimethylanthracene adduct **69**. In the event, 1,3-adduct **70** along with its isomeric 1,4-adduct **71** was obtained in 60% and in a 1:1 ratio (Scheme 21, eq 1).[39a] α-Substituted hydroxylamines **72** underwent regioselective IMDA reaction, and 1,3-adducts **73a** and **73b** were obtained

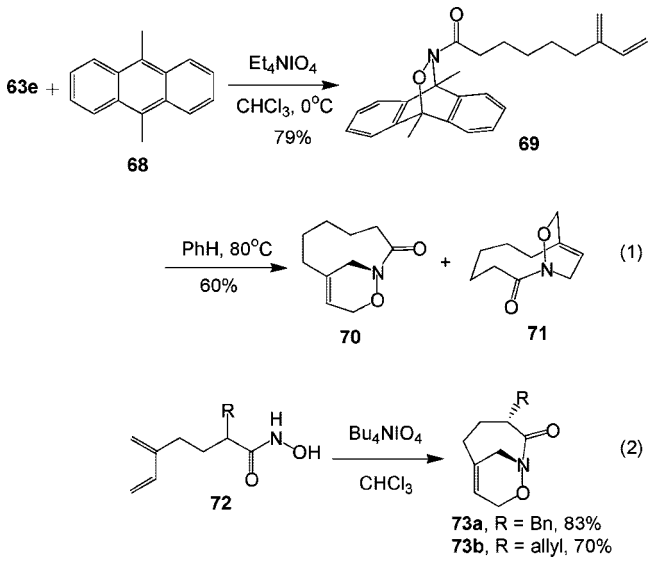
Scheme 19



Scheme 20



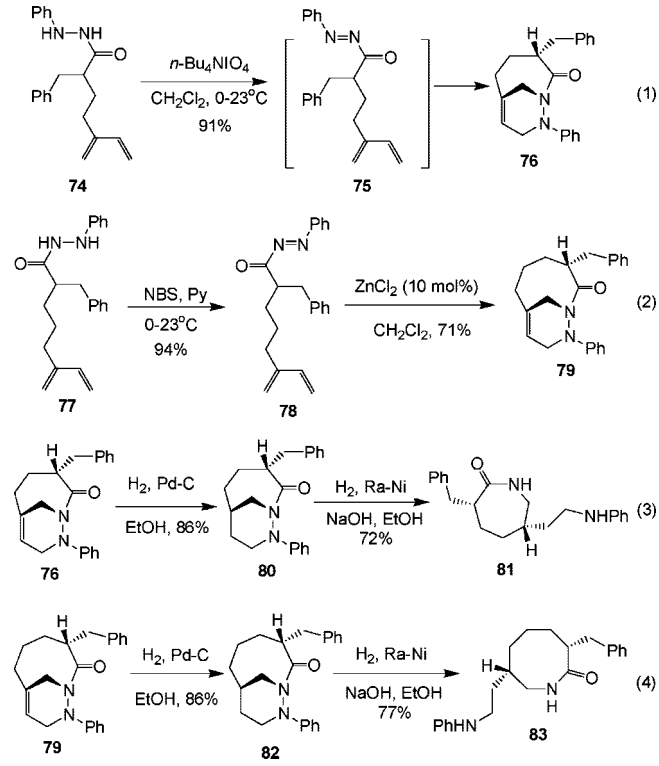
Scheme 21



as single diastereomers in 83% and 70% yields, respectively (Scheme 21, eq 2).[39a]

Furthermore, stereoselective IMDA reactions were observed for α-substituted *N*-acylazo dienophiles **74** and **77** under either thermal (for **75**) or Lewis-acid-catalyzed (for **78**) conditions, affording a single diastereomer **76** or **79**, in yields of 91% and 71%, respectively (Scheme 22, eqs 1 and 2).[39b] Hydrogenation and successive reductive N−N bond

Scheme 22



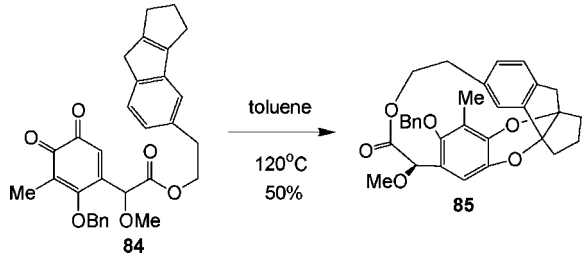
cleavage of the two bridged cycloadducts **76** and **79** afforded *cis*-3,6-disubstituted caprolactam **81** and *cis*-3,7-disubstituted enantholactam **83**, respectively (Scheme 22, eqs 3 and 4).[39b] This sequence of transformations offers a convenient route for the diastereoselective synthesis of medium-ring nitrogen heterocycles.

Recently, Nicolaou's group revealed an intramolecular [4 + 2] cycloaddition reaction in the synthesis of the sporolide ring framework **85** (Scheme 23).[41] This IMDA reaction of *o*-quinone **84** occurred in toluene at 120 °C, affording the desired cycloadduct **85** in 50% yield.

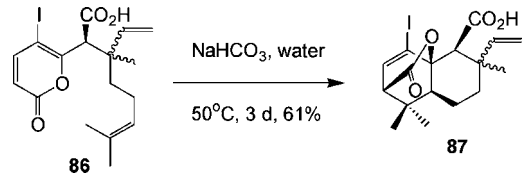
2.2.3. Other [4 + 2] Cycloaddition Reactions

A report from Johansson's group uncovered a construction of a transtaganolide carbon skeleton through an intramolecular DA cycloaddition under very mild condition (Scheme 24).[42] It was found that under aqueous basic conditions at 50 °C a bridged lactone **87** was obtained in 61% yield with a dr ratio of 2:1, while heating the carboxylic acid **86** in

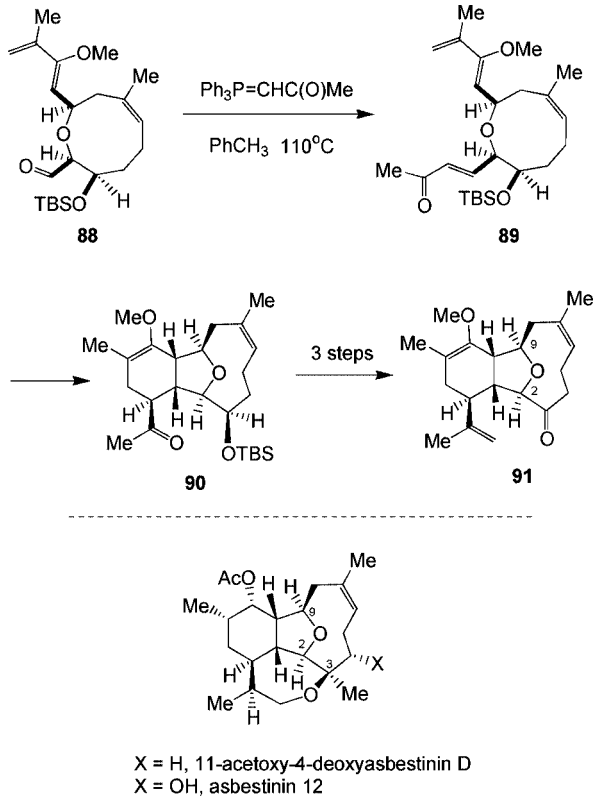
Scheme 23



Scheme 24



Scheme 25

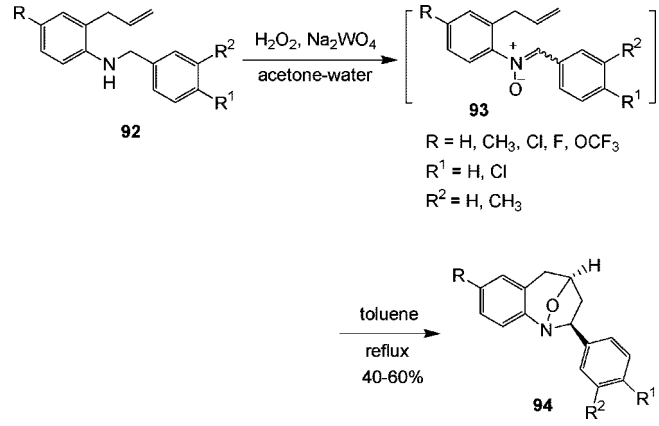


X = H, 11-acetoxy-4-deoxyasbestinin D
X = OH, asbestinin 12

toluene at 120 °C or in benzene at 80 °C resulted in decarboxylation.

11-Acetoxy-4-deoxyasbestinin D[43] and asbestinin-12[44] have attracted much attention by synthetic chemists due to their intriguing biological properties and unique chemical structures. Both molecules have a fully substituted tetrahydrofuran moiety with 9 contiguous stereocenters in 11-acetoxy-4-deoxyasbestinin D and 10 in asbestinin-12, respectively. The enantioselective total synthesis of 11-acetoxy-4-deoxyasbestinin D and asbestinin-12 involves a common ketone intermediate **91** wherein the C2 and C9 are linked together by an oxygen bridge. The synthesis of the ketone intermediate **91** is outlined in Scheme 25. Wittig reaction of aldehyde **88** led to **89**, which triggered a rapid in-situ IMDA cycloaddition, furnishing tricyclic compound **90**. The conversion of **90** to the desired ketone **91** was effected in three steps (Scheme 25).[45]

Scheme 26



3. [n + m] Cycloaddition Reactions

3.1. [3 + 2] Dipolar Cycloadditions

The applications of dipolar cycloaddition reactions have been found in many useful organic syntheses, particularly with respect to the preparation of complex molecules including natural products with chiral centers.

3.1.1. 1,3-Dipolar Cycloaddition of Nitrones

Nitrones have proved to be very useful intermediates in the construction of structurally complex molecules.[46] Nitrones as 1,3-dipoles in cycloaddition reactions are capable of reacting with a great variety of dipolarophiles, giving rise to a vast array of products. Owing to their high reactivity, nitrones are usually generated in situ.

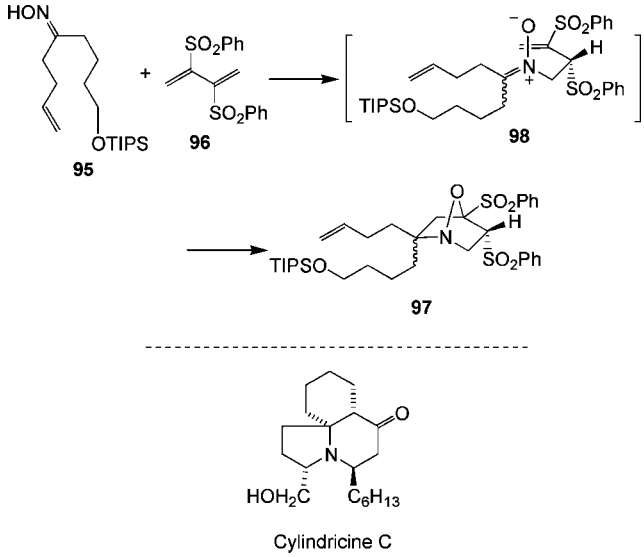
1,3-Dipolar cycloaddition of nitrone to olefin has been used in the synthesis of five- and six-membered nitrogen-containing heterocycles.[47] Palma and et al.[48] described an intramolecular 1,3-dipolar cycloaddition reaction of nitrones **93** to access bridged compounds **94** (Scheme 26). Nitrones **93** were generated in situ from oxidation of *ortho*-allyl-*N*-benzylanilines **92** according to a methodology described by Murahashi.[49]

Despite the oxidative method, nitrone **98** was generated from intermolecular nucleophilic addition of oxime **95** and used in situ toward intramolecular [3 + 2] dipolar cycloaddition to access an oxygen-bridged cycloadduct **97**, a key intermediate in the total synthesis of cylindricine C (Scheme 27).[50]

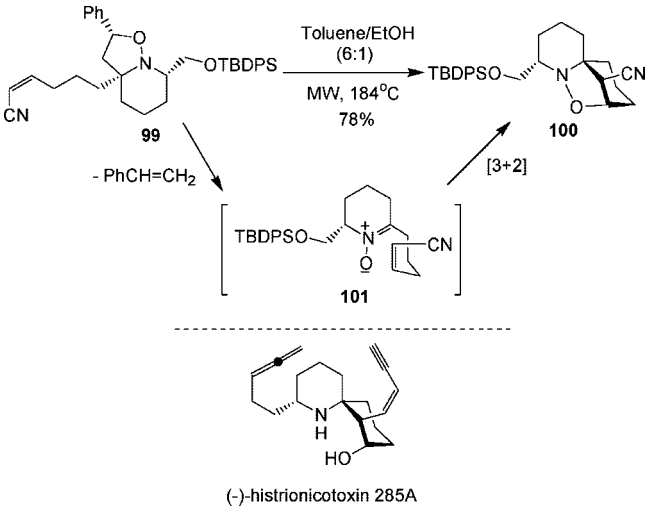
Nitrones can also be generated thermally and used in situ as dipoles. Scheme 28[51] demonstrates a [3 + 2] cycloaddition of nitrone intermediate **101** in the synthesis of a bridged tricyclic nitrile **100**, an intermediate in the total synthesis of (−)-HTX 285A. The nitrone **101** was generated by a microwave (MW) thermally induced 1,3-dipolar cycloreversion of **99** with accompanying extrusion of styrene (Scheme 28).[52]

1,3-Dipolar cycloaddition of azomethine ylides with alkenes or alkynes is a very effective method for the construction of *N*-containing heterocycles.[53] Due to their high reactivity, azomethine ylides are usually generated in situ. Recently reported by Pandey and co-workers, azomethine ylide was employed in the [3 + 2] cycloaddition reaction to access challenging vicinal quaternary and tertiary stereocenters of the 5,10b-ethanophenanthridine skeleton **103** of maritidine. This nonstabilized azomethine ylide **104** was generated in situ by removing a TMS group (Scheme 29).[54]

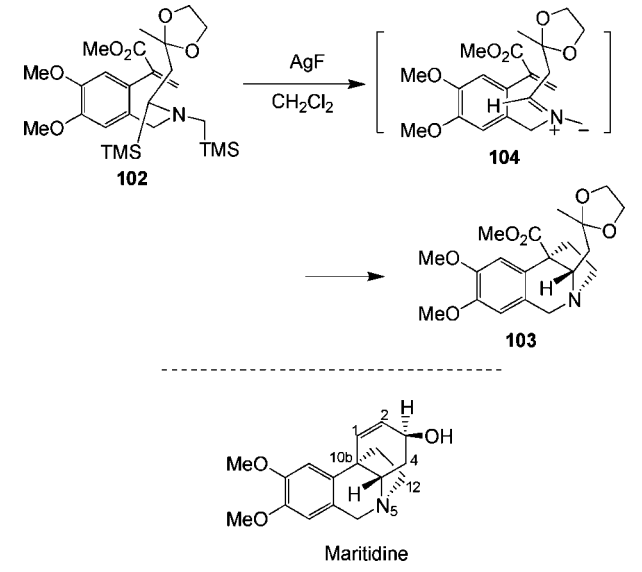
Scheme 27



Scheme 28



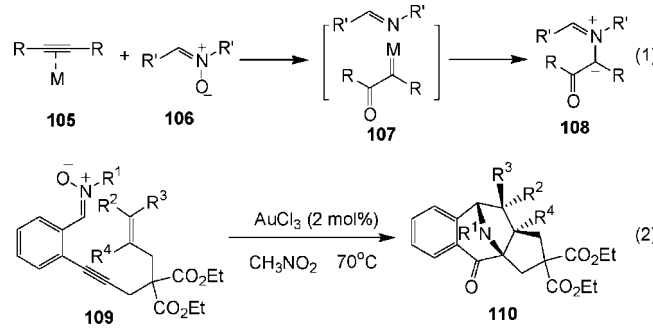
Scheme 29



3.1.2. Metal-Catalyzed [3 + 2] Cycloadditions

An approach for generation of α-carbonyl carbenoid **107** and subsequent formation of azomethine ylide equivalent **108** was reported by Shin et al. (Scheme 30, eq 1).[55] Azabicyclo [3.2.1]octanes **110** were synthesized by a gold(III)-catalyzed cycloaddition of *N*-alkylnitrones **109** followed by [3 + 2] dipolar cycloaddition (Scheme 30, eq 2).[55] Various substituents on the enyne skeleton were well tolerated.

Scheme 30



R^1	R^2	R^3	R^4	yield, %
Bn	H	H	H	82
Bn	H	H	Me	59
Bn	Me(H) (E/Z = 3 : 1)	H(Me)	H	80
Bn	Me	Me	H	67
Bn	CO_2Me	CO_2Me	H	83
Me	H	H	H	75

This gold(III)-catalyzed reaction is proposed to involve a gold−carbenoid intermediate **112**,[56] generated by Au(III)-promoted 6-*exo-dig* cycloaddition of **109** (R^1 = Bn, R^2 = R^3 = R^4 = H) followed by retro-electrocyclization to cleave the N−O bond (Scheme 31). An intramolecular addition of imine to this carbenoid leads to **113** (or **114**). Ultimately, a dipolar cycloaddition leads to the observed bicyclo[3.2.1]octane product **110**.

Analogously, Pt-mediated [3 + 2] cycloaddition of enynal **115** (or **117**) was developed to access ether-bridged multiring system **116** (or **118**) (Scheme 32, eqs 1 and 2).[57]

A possible reaction mechanism was proposed and is illustrated in Scheme 33.[57] A Huisgen-type [3 + 2] cycloaddition of Pt(II)-activated enynal **115** (or **117**) occurs to yield a tetracyclic platinum−carbene complex **120** via platinum−pyrylium intermediates **119**. The platinum−carbene **120** is trapped by benzylic C−H bond insertion[58] to furnish the product **116** (or **118**).

In addition to intramolecular [3 + 2] cycloaddition, application of intermolecular [3 + 2] cycloaddition toward a regioselective pyrrole synthesis was developed by Park and co-workers (Scheme 34).[59]

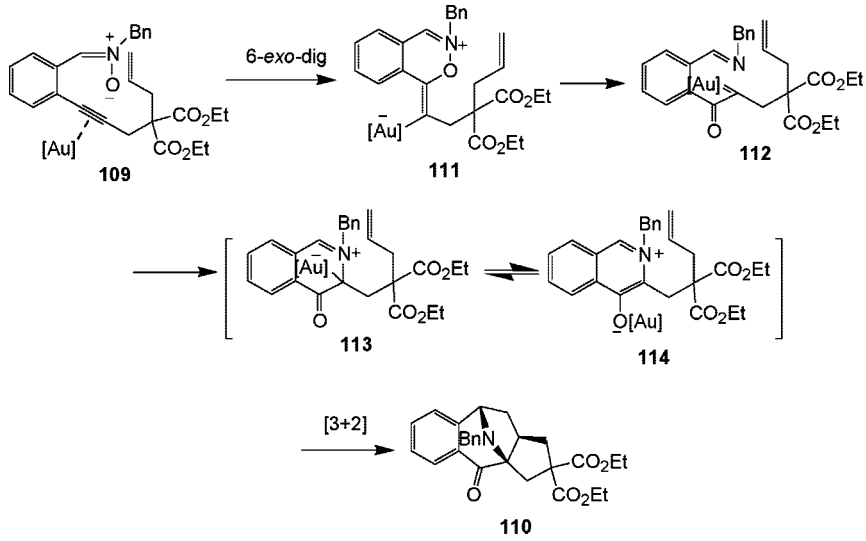
Scheme 35 outlines the proposed reaction pathway which involves a heterocyclic bridged intermediate **127**, formed via [3 + 2] cycloaddition, whose spontaneous decarboxylation furnishes the product **124**.

3.2. [5 + 2] Cycloadditions

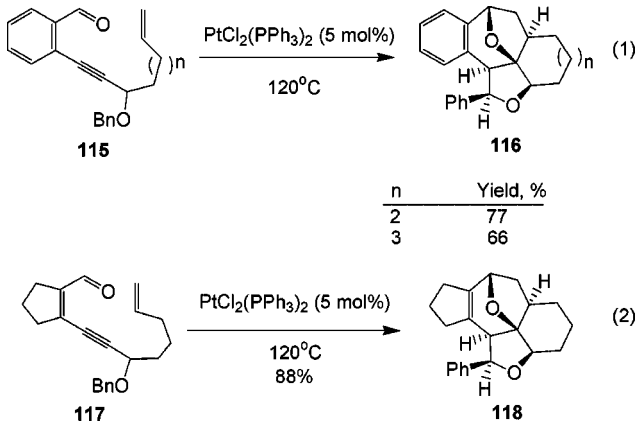
Wender and et al. developed an intramolecular [5 + 2] cycloaddition approach to synthesize a BC ring system of 1α-alkyldaphnanes **131** (Scheme 36).[60]

Harrowven designed a total synthesis of colombiasin **A** and elisapterosin **B** which involves a common intermediate **132** (Scheme 37).[61] Colombiasin **A** was obtained by intramolecular DA cycloaddition followed by deprotection with 2 equivalents of diethyl ether−trifluoroborane. In contrast, direct treatment of **132** with 2 equivalents of $BF_3 \cdot OEt_2$ afforded the [5 + 2] cycloaddition product, elisapterosin **B**.

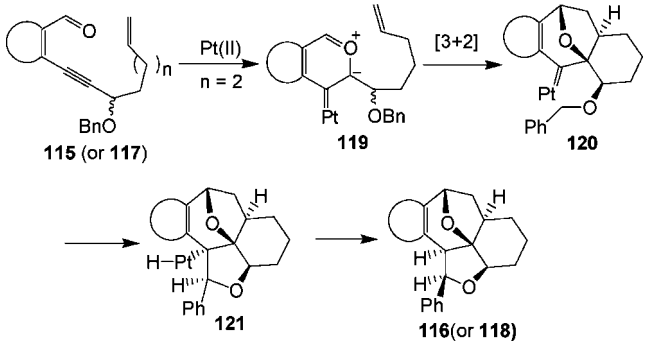
Scheme 31



Scheme 32



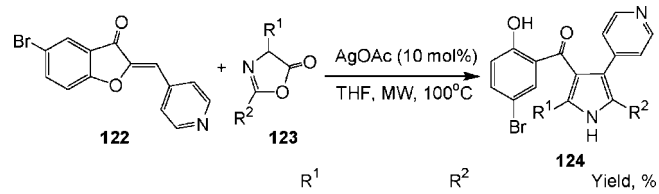
Scheme 33



3.3. [8 + 2] Cycloadditions

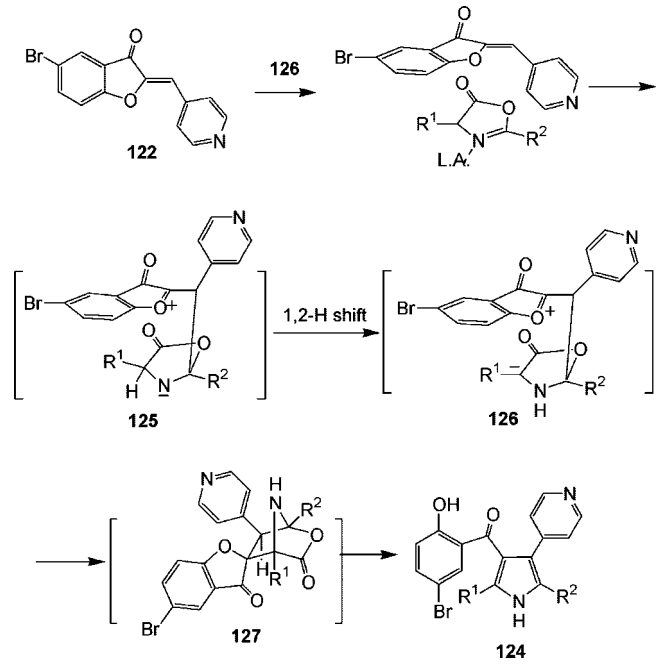
The [8 + 2]-cycloaddition reaction is a potentially powerful method for the preparation of 10-membered ring systems, although it is limited to geometrically constrained tetraenes wherein the terminal atoms at positions 1 and 8 are rigidly held in close proximity. Yu and et al. proposed two reaction pathways for formation of the bridged 10-membered ring systems:[62] a stepwise pathway via formation of either a diradical or a zwitterionic intermediate followed by ring closure and a pathway which starts from a concerted, asynchronous [4 + 2] reaction and a diradical [1,5]-vinyl shift. Thus, these two pathways can compete with one another to furnish both [8 + 2] and [4 + 2] cycloadducts.

Scheme 34



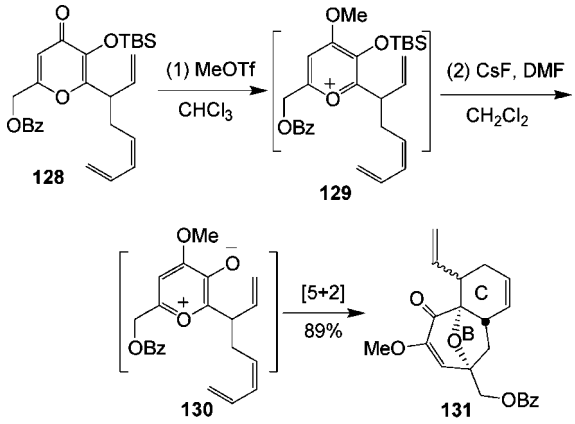
R^1	R^2	Yield, %
benzyl	methyl	90
methyl	benzyl	75
phenyl	methyl	93
isobutyl	methyl	79
phenyl	cyclohexyl	97
phenyl	phenyl	94
phenyl	benzyl	91
phenyl	*n*-butyl	95

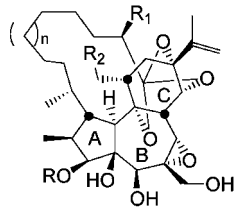
Scheme 35



Notably, the selectivity for the [8 + 2] cycloadduct **136** (except entry 4) is attributed to the planar orientation in **134** between the enol ether and isobenzofuran (Scheme 38).[63] The steric effect of TMS-substituted enol ether **134** (entry 4), in contrast, features an orthogonal orientation between

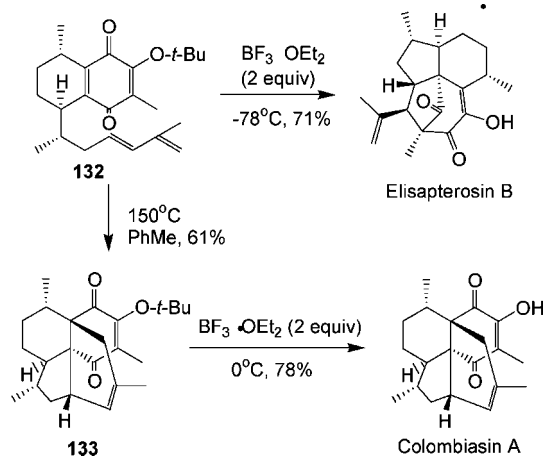
Scheme 36





1α-Alkyldaphnane

Scheme 37



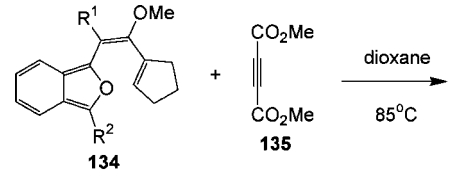
the enol ether and isobenzofuran which would prevent [8 + 2] cycloaddition.

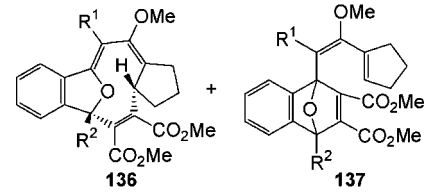
3.4. [4 + 3] Cycloadditions

The intramolecular [4 + 3] cycloaddition of allyl cations with cyclic dienes such as furan and cyclopentadiene provides stereochemically defined oxabicyclic and carbobicyclic scaffolds where subsequent stereocontrolled ring-opening reactions afford useful intermediates for the syntheses of natural products. The use of epoxy enol triethylsilanes as oxyallyl cation precursors in the [4 + 3] cycloaddition was developed by Chiu and co-workers[64] to produce hydroxylated cycloheptanoids. Scheme 39 demonstrates the application of this intramolecular [4 + 3] cycloaddition reaction toward the synthesis of a bridged tricyclic ring system with high diastereoselectivity (entries 1−6). Only in the case of the hindered substrate (entry 7) was the reaction high yielding but unselective.

Furthermore, intermolecular [4 + 3] cycloaddition of the epoxy enol silanes **141** with furan **142** performed equally well, leading to an ether-bridged seven-membered ring system **143** (Scheme 40, eq 1).[64] The sterically demanding 2,5-dimethylfuran **144** was reluctant toward undergoing cycloaddition, giving diminished yields of **143** (R = H) (Scheme 40, eq 2).[64]

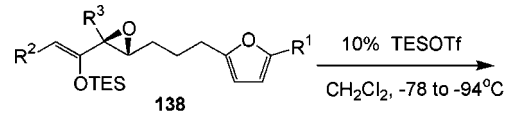
Scheme 38

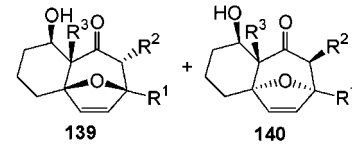




entry	R^1	R^2	136	137
1	Bu	Ph	76%	3%
2	Me	Ph	61%	0%
3	H	Ph	72%	9%
4	TMS	Ph	5%	62%

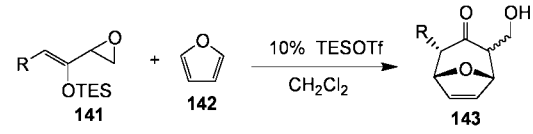
Scheme 39





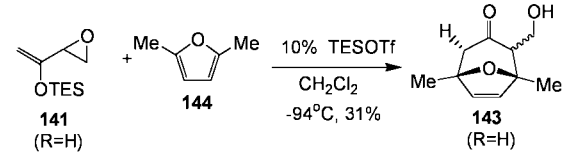
				yeild, %	
entry	R^1	R^2	R^3	139	140
1	H	H	H	83	
2	CH_3	H	H	76	
3	$CH_2OTBDPS$	H	H	83	
4	$CH_2(CH_2)_3OTBS$	H	H	81	
5	H	CH_3	H	70	
6	H	H	CH_3	52	7
7	CH_3	CH_3	H	40	57

Scheme 40



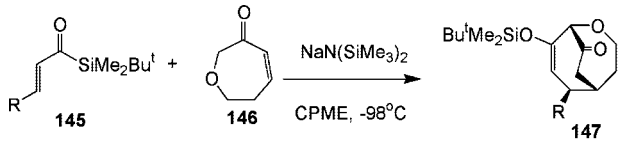
(1)

R	T (°C)	Yield, %
H	-94	75
Ph	-50	61



(2)

Scheme 41



R	Yield, %
$SiMe_3$	83
$SiMe_2Ph$	73
$SiMe_2Bu^t$	77
i-Pr	79
t-Bu	77

Takeda and co-workers reported that a stereoselective construction of 2-oxabicyclo[3.3.2]decenone derivatives **147** was effected by Brook rearrangement-mediated [4 + 3] cycloaddition (Scheme 41).[65] As the enolate of cycloheptenone **146** is unstable at −80 °C, replacement of THF with cyclopentyl methyl ether (CPME, mp < −140 °C) was able to perform this cycloaddition at −98 °C. As a result, the yields of cycloadducts **147** were improved.

Recently, a diastereoselective Brook rearrangement-mediated [4 + 3] annulation was developed by the same group. Applications of this [4 + 3] annulation toward a formal synthesis of (+)-laurallene are illustrated in eqs 1−3 of Scheme 42. A bridged ketone **150** was prepared by using [4 + 3] annulation of enantiomerically enriched (−)-*trans*-**149** (90% ee) with potassium enolate **148** of 2-cycloheptenone (Scheme 42, eq 1).[66] [4 + 3] annulation of lithium enolate of **151**, being formed in situ, with acryloylsilane **152** gave bridged ketone **153** in 76% yield as a single isomer (Scheme 42, eq 2).[67] When Davis' oxaziridine **155** was added to a THF solution of sodium enolate of **154** with an extra amount of NaHMDS and 18-crown-6, α-hydroxy ketone **156** was obtained in 64% yield (Scheme 42, eq 3).[67]

Harmata and co-workers employed intramolecular [4 + 3] cycloaddition to access a bridged cycloadduct **158** bearing a bromo substituent at a bridgehead (Scheme 43).[68]

A [4 + 3] cycloaddition/quasi-Favorskii rearrangement approach was introduced in the synthesis of (±)-sterpurene by the same group in which a mixture of trifluoroethanol (TFE) and benzene was used as reaction solvents (Scheme 44).[69] A tricyclic bridged ketone **161** was obtained via an intermolecular [4 + 3] cycloaddition. A subsequent quasi-Favorskii rearrangement followed by reduction with LAH afforded tricyclic alcohol **162**.

Furthermore, Harmata's [4 + 3] cycloaddition/quasi-Favorskii rearrangement approach was applied toward the syntheses of the spatane ring system **167** (Scheme 45)[70] and spatol ring system **172** (Scheme 46).[71]

3.5. [6 + 3] Cycloadditions

A phosphine-catalyzed [6 + 3] annulation is a simple and expedient method for constructing bridged carbocycles (Scheme 47).[72]

The reaction mechanism is rationalized in Scheme 48.[72] The formation of [6 + 3] cycloaddition product **179** is presumably through two intermediates **177** and **178** being generated via 1,6-conjugate additions of ylide **176** onto **174**. With the *tert*-butyl carbonate derivative **173** (X = OBoc), the reaction can be carried out in the absence of base because of the in-situ-generated *tert*-butoxide anion.

An enantioselective palladium-catalyzed [6 + 3] cycloaddition reaction of trimethylenemethane (Pd−TMM) with cycloheptatrienone (tropones) was developed by Trost and co-workers, which allowed direct access to asymmetric substituted bicyclo[4.3.1] decadienes **182** (Scheme 49).[73]

3.6. [6 + 4] Cycloadditions

Ingenol offers several synthetic challenges including a bicyclo[4.4.1]undecanone unit with the BC ring substructure as well as a highly strained inside, outside intrabridgehead stereochemical relationship at the BC ring juncture. A facile entry into the ingenane core **184** using a Lewis-acid-catalyzed intramolecular [6 + 4] cycloaddition of **183** has been developed (Scheme 50, eq 1).[74] The out,out cycloadduct **184** was obtained in 80% yield in low enantioselectivity (40% ee). Furthermore, an expeditious construction of a highly functionalized ABC core of ingenol via an intramolecular, metal-free [6 + 4] cycloaddition of cycloheptatrienone and furan was reported by the same group (Scheme 50, eq 2).[75]

Isomerization of the out,out stereoisomer **187** into the highly strained inside−outside stereoisomer **189** was effected by Pd-promoted rearrangement of an allylic epoxide followed by 1,5-H migration (Scheme 51).[76]

Despite the popular intramolecular [6 + 4] cycloadditions, an intermolecular [6 + 4] cycloaddition was observed when heating a mixture of 8,8-dicyanoheptafulvene **190** with electron-rich dienes **191**, leading to **192** in high yields (Scheme 52).[77]

4. Molecular Rearrangements

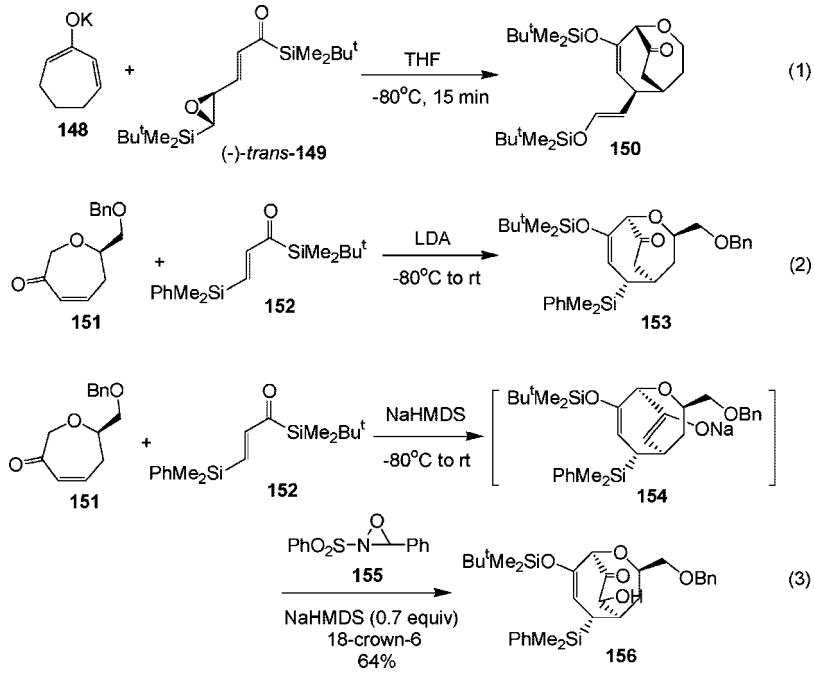
4.1. Ring Rearrangements

Development of a methodology for the synthesis of the bicyclo[5.3.1]undecane ring system, a structurally important feature of the taxane, is an attractive area for organic chemists.[78] The ring strain of a fused small-sized (3- and 4-membered) ring system can, under certain conditions, cause ring fragmentation, resulting in a bridged bicyclic ring system. The intramolecular photocycloaddition/fragmentation reaction has been applied to the synthesis of inside−outside *trans*-bicyclo[*n*.3.1]alkanones,[79] perhydrohistronicotoxin,[80] and saudin.[81] Acid-catalyzed fragmentation of [2 + 2] photoadduct **194** led to a *trans*-bicyclo[5.3.1]undecan-11-one **195** in 80% overall yield (Scheme 53, eq 1).[82] The inside−outside stereoisomer structure is unambiguously proven by X-ray. In addition, the use of base in this photo [2 + 2] cycloaddition/4-membered-ring fragmentation afforded a bridged tricyclic ketone **198a**, an intermediate for the total synthesis of (±)-ingenol (Scheme 53, eq 2).[83]

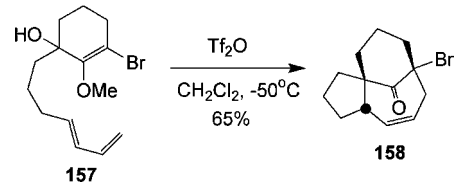
A 4-membered ring in tricyclic compound **199** could be cleaved by Wagner−Meerwein rearrangement (Scheme 54, eq 1).[84] In addition, fragmentation of cyclopropane derivative **201** was effected by samarium(II) catalyst (Scheme 54, eq 2).[85]

The intramolecular ring-opening/closure process is a commonly used approach to synthesize bridged cyclic organic compounds. In order to ensure the ring-opening/closure tandem process can be easily achieved, a reaction design typically involves a small-sized ring, such as cyclopropane and epoxide. Owing to the dipolar nature of the cyclopropane moiety in **204**, a cascade process involving dioxasilinane ring cleavage/intramolecular nucleophilic cyclopropane opening and simultaneously 1,3-dioxolane forma-

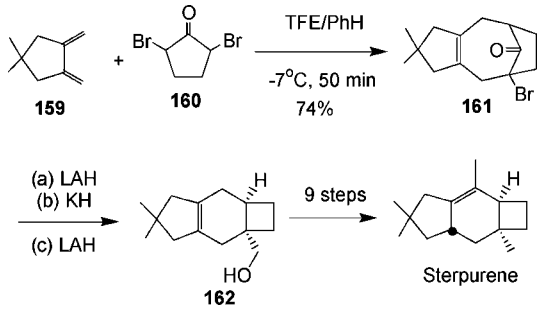
Scheme 42



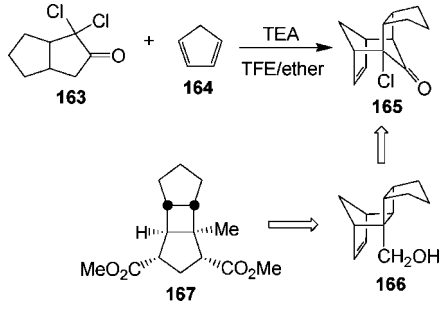
Scheme 43



Scheme 44



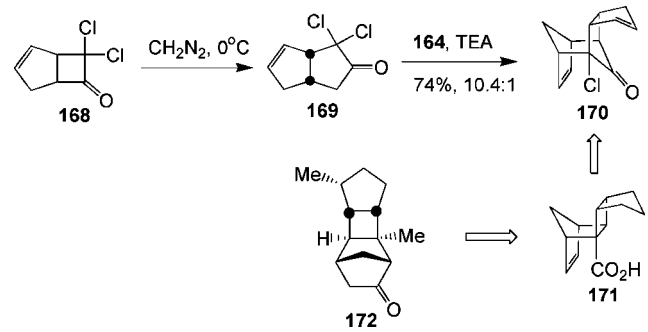
Scheme 45



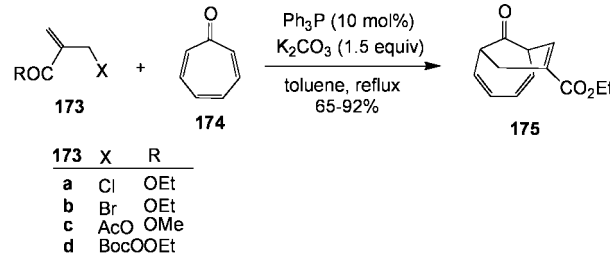
tion led to an ether-bridged tricyclic anhydrosugar **205** in 80% yield (Scheme 55).[86]

A Dieckmann cyclization and epoxide ring-opening sequence was employed by the Maier group in the synthesis of oxabicyclooctane ring system **208**, a fully functionalized core structure of abyssomicin C (Scheme 56, eq 1).[87]

Scheme 46



Scheme 47

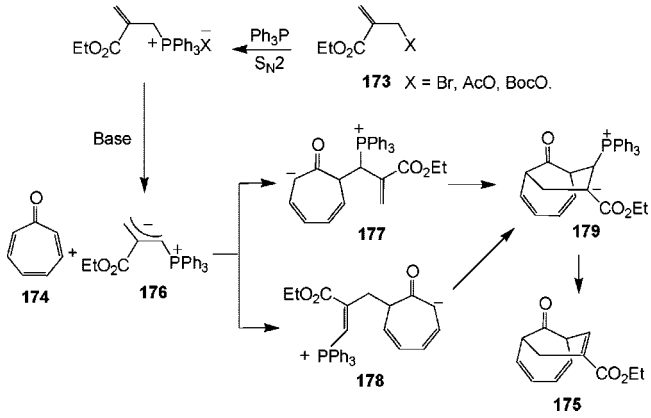


173	X	R
a	Cl	OEt
b	Br	OEt
c	AcO	OMe
d	BocOO	Et

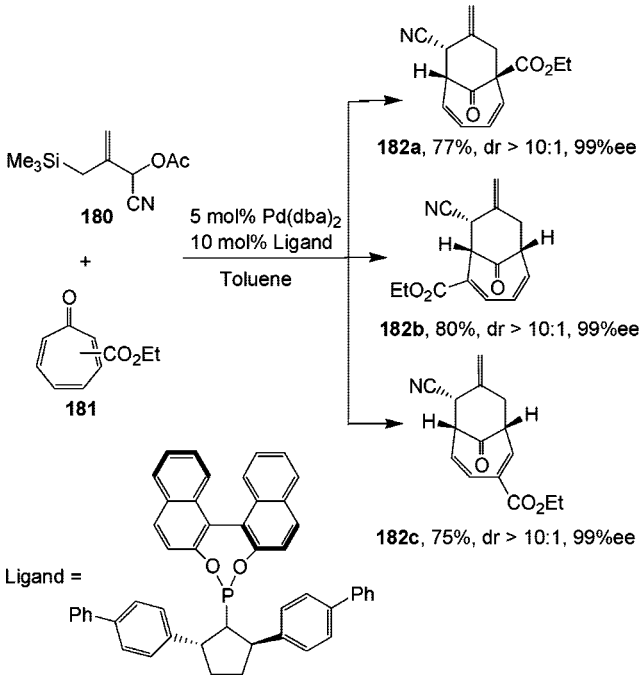
Analogously, Nicolaou and co-workers used this strategy to synthesize oxabicyclic intermediate **210** (Scheme 56, eq 2).[88] A similar approach was applied to prepare bridged 6-oxabicyclo[3.2.1]-octane derivative **212** by opening the epoxide ring in **211** (Scheme 56, eq 3).[89]

A natural product, (+)-pinnatoxin A, is comprised of a 27-membered carbocycle incorporating a unique A,G-spiroimine and E,F-6,8-dioxa-bicyclo[3.2.1]octane segment. This E/F ring system is bridged by an ether bond and assembled by a cascade process (Scheme 57).[90] The cascade process involves deprotection, epoxide ring formation, and simultaneous cleavage of the 1,3-dioxane ring with extrusion of benzaldehyde to furnish alkoxide **215**. An intramolecular nucleophilic attack on the carbonyl group furnishes 7-membered oxepane **216** whose nucleophilic epoxide ring opening affords the oxygen-bridged E/F ring system **214**.

Scheme 48



Scheme 49

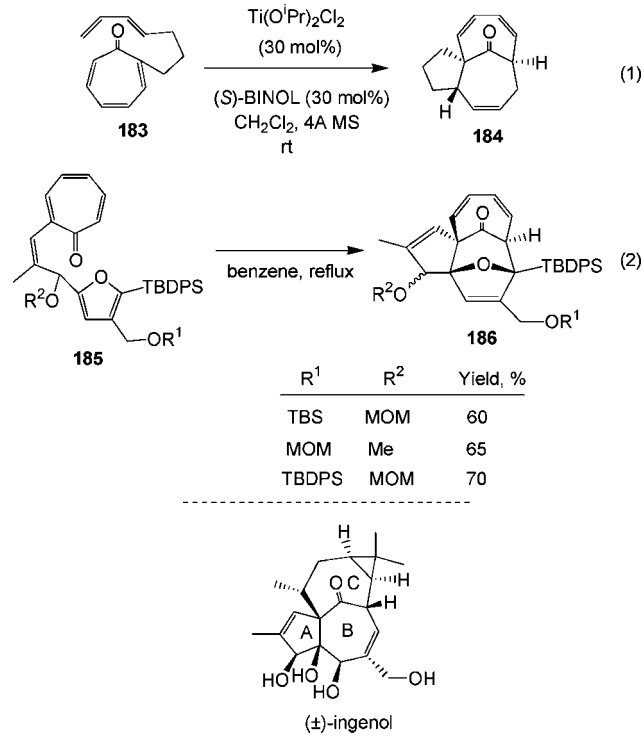


A cascade reaction was designed by Nicolaou and coworkers to construct the "left domain" of haplophytine (Scheme 58).[91] Upon epoxidation of tetrasubstituted olefin **217**, the epoxide intermediate **218** underwent regioselective epoxide ring opening, followed by skeleton rearrangement, furnishing a desired bridged cyclization product **220**.

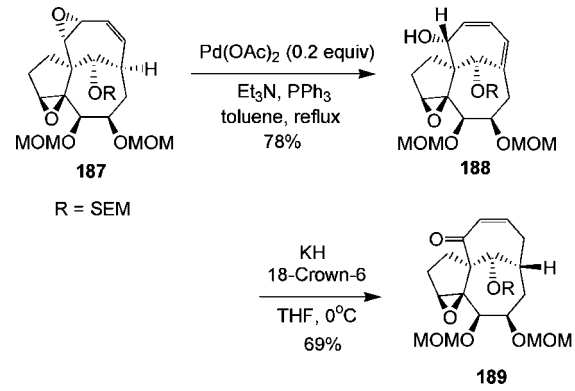
4.2. Schmidt Reactions

Synthesis of the bridged bicyclic lactams with the nitrogen at a bridgehead position is challenging because the "twisted amide" tends to undergo rapid hydrolysis. Utilization of intramolecular Schmidt reaction allows accessing bridged bicyclic lactams. A Lewis-acid-catalyzed Schmidt reaction of ketones **221** led to two lactams, bridged bicyclic **222** and fused bicyclic **223** (Scheme 59).[92] The nature of the substituent groups in the keto azide **221** affects the distribution of the two products, which is largely controlled by the steric effect and 1,3-cation$-\pi$ interaction (R^2 = Ar).[92] This Lewis-acid-catalyzed Schmidt reaction may go through any of the intermediates (**224**, **225**, or **226**). In the event, reaction of **221c** or **221d** with R^2 = aromatic groups (especially with an electron-releasing group) proceeds for the most part through intermediate **226**, leading predominantly to bridged

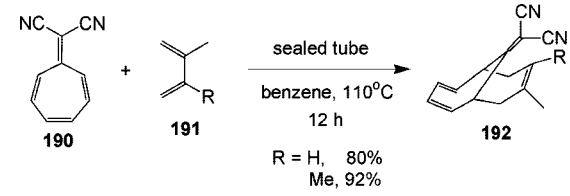
Scheme 50



Scheme 51



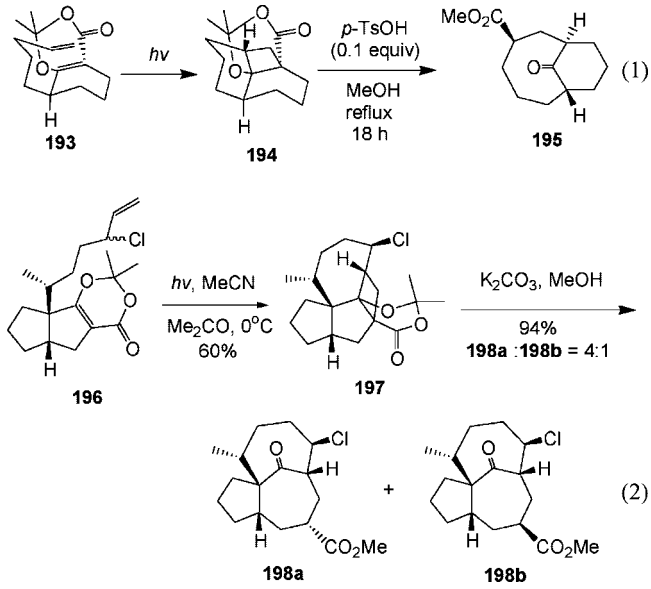
Scheme 52



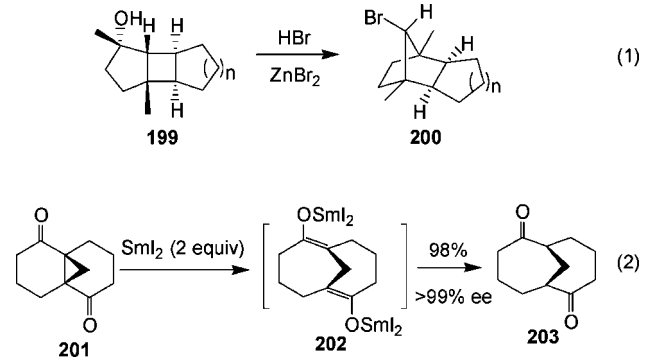
lactam **222c** or **222d** by cleaving the C(a)−C(c) bond. In contrast, reaction of **221a** occurrs through intermediate **224**, providing **223a** as the only product in 96% yield.

The intramolecular Schmidt reaction of **227** led to tricyclic diketone **228** in 82% (Scheme 60, eq 1).[93] The tricyclic diketone **228** is the key intermediate in the total synthesis of (+)-aspidospermidine.[94] Surprisingly, reaction of the monoprotected ketone **229** occurred through a process involving presumably two intermediates, **231** (formed via ring opening of ketal) and **232** (via carbon migration), affording only **230** (Scheme 60, eq 2).[93]

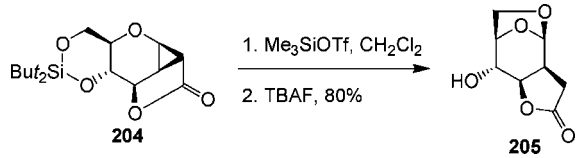
Scheme 53



Scheme 54



Scheme 55



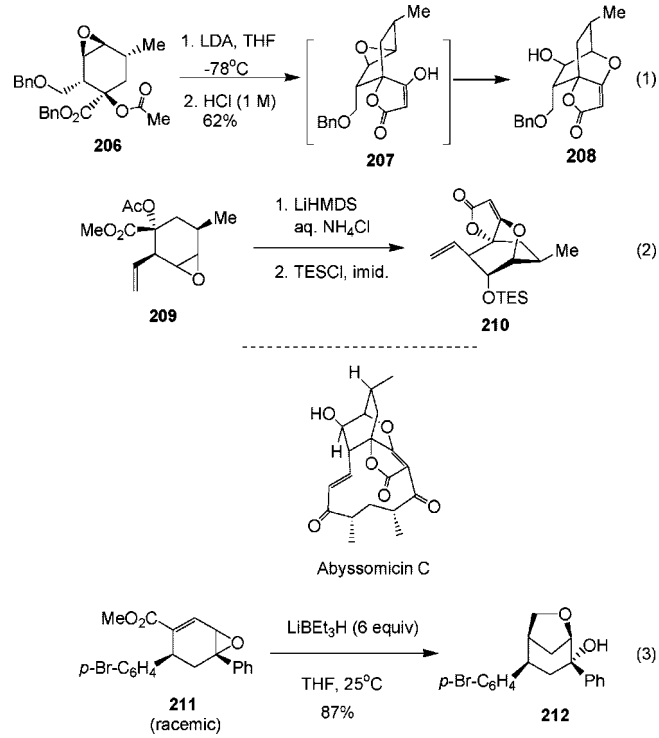
4.3. Pinacol Rearrangements

Many natural products bearing the β-araneosene ring system[95,96] are biologically active.[97] Pinacol rearrangement allows 1,2-diol in the presence of acid to generate ketone by migrating the alkyl group. It was found, by Corey's group[98] during the total synthesis of β-araneosene, that the conformational rigidity of *trans*-12-membered ring **233** resulted in undesired Pinacol rearrangement product **234** via cleavage of the C(a)−C(b) bond (Scheme 61, eq 1). This importance of conformation is also evidenced by a very facile rearrangement of hydroxy ketone **235** to **236** by exposure to silica gel at 23 °C (Scheme 61, eq 2). Under identical conditions as of eq 1, however, the *cis*-diol isomer **237** provided the desired bicyclo-ketone **238** through cleavage of C(a)−C(c) bond with migration of tertiary carbon (Scheme 61, eq 3).

4.4. Claisen/Diels−Alder Cascade Process

A chemical transformation of xanthone derivative **239** into **242** and **243** was developed by Nicolaou and co-workers

Scheme 56



(Scheme 62).[99] It was observed that this Claisen/Diels−Alder cascade sequence was accelerated by water. The concurrent acceleration of the Diels−Alder component is due to the hydrophobic effect[100] and the unique internal pressure of water.[101]

4.5. Polonovski Rearrangements

Application of a modified Polonovski reaction for serratinine **244** resulted in generation of serratezomine A **245** (Scheme 63).[102]

The bridged lactone **245** could be converted into lactone **246** by treatment with *p*-TsOH or conducting the reaction at 20 °C. This modified Polonovski reaction showed a strong solvent effect, and THF or toluene as solvent shut down the reaction completely (Table 1).[102]

A possible mechanism of this one-pot reaction was proposed and is outlined in Scheme 64.[102] Obviously, the trifluoroacetylation of the *N*-oxide **247** serves as the driving force for formation of hemiketal **249** and iminium **250**.

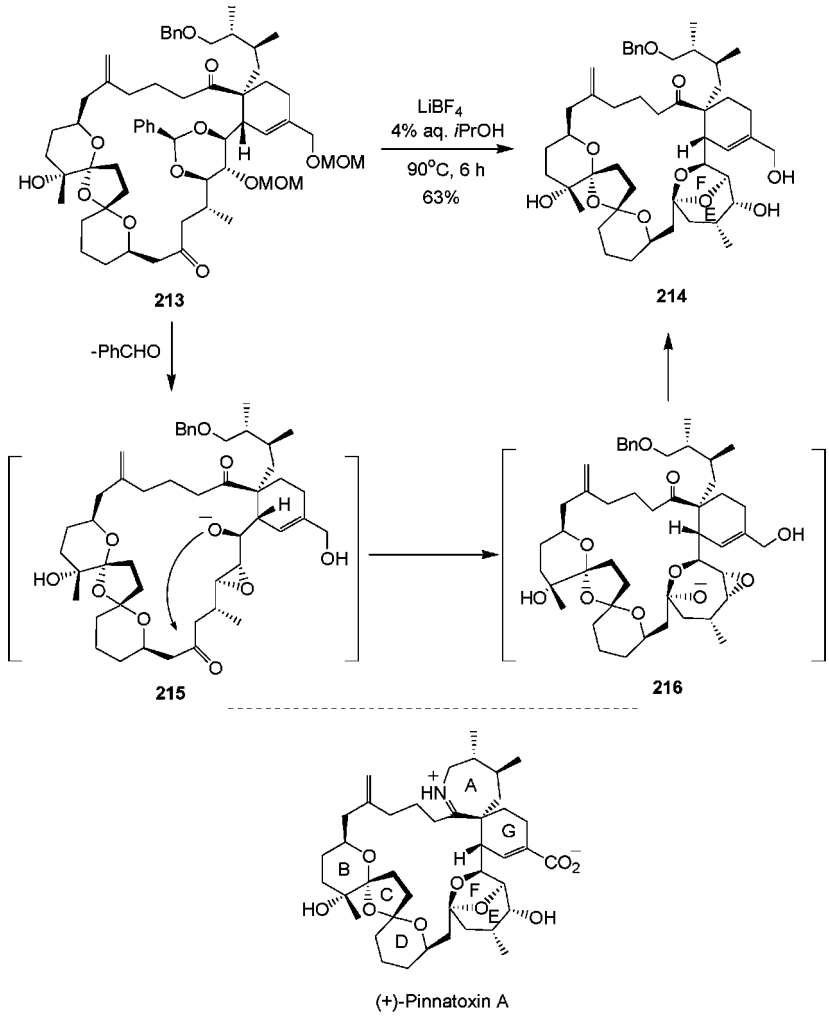
4.6. Prins-Type Reactions

Reiβig and co-workers developed a synthetic approach by utilization of Lewis-acid-catalyzed Prins-type cyclization reactions to access bridged bicyclic compounds,[103] which presents an efficient and stereodivergent synthesis of C2-branched 4-amino sugars.

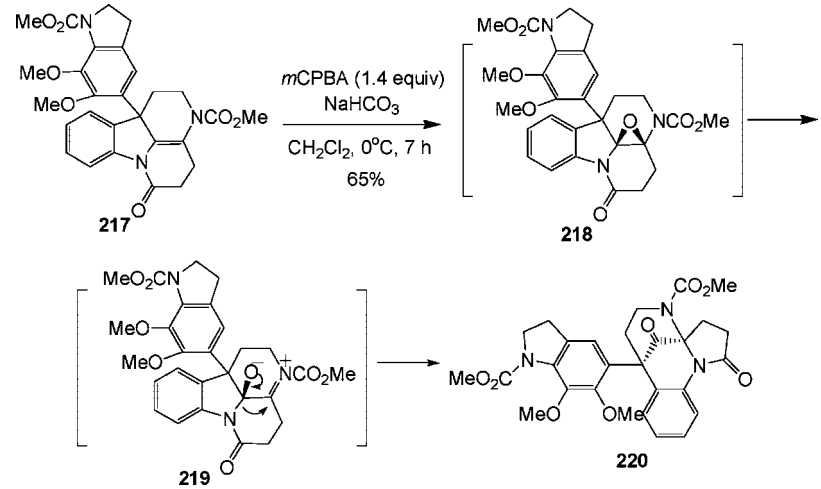
Coordination of the Lewis acid to the more easily accessible oxygen of the acetonide in **252** leads to ring-opening intermediate **253** (Scheme 65). This electrophilic species attacks the enol ether moiety similar to Prins-type reaction to form intermediate **254**. With the R^1 group being either 2-(trimethylsilyl)ethyl (TMSE) or 4-(*p*-methoxybenzyl) (PMB), a bridged bicyclic ketone **255** is produced through cleavage of the R^1 group.

Table 2 demonstrates the scope of the Prins-type cyclization reactions. Although the rearrangement could be ac-

Scheme 57



Scheme 58

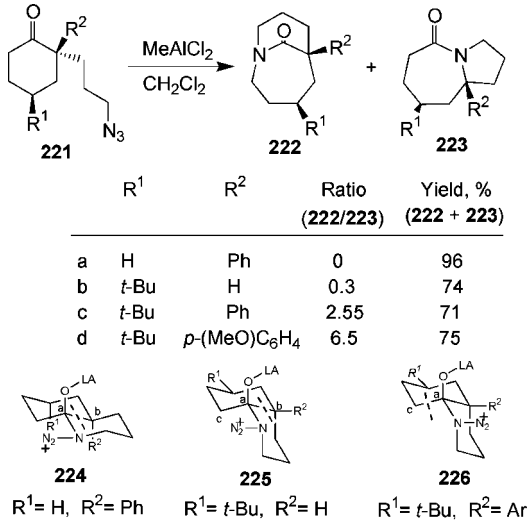


complished with different Lewis acids, dibutylboron triflate, trimethylsilyl triflate, and tin tetrachloride proved to be the best promoters. To introduce the more stable *tert*-butyldimethylsilyl (TBS) protecting group, *syn*-**252** was treated with *t*BuMe$_2$SiOTf (3 equiv) and then with triethylamine to generate bicyclic products **255** (entries 3−5).

In a similar manner, rearrangement of diastereomeric 1,2-oxazine *anti*-**252** led to protected bicyclic 1,2-oxazine **256** (Scheme 66).[103c]

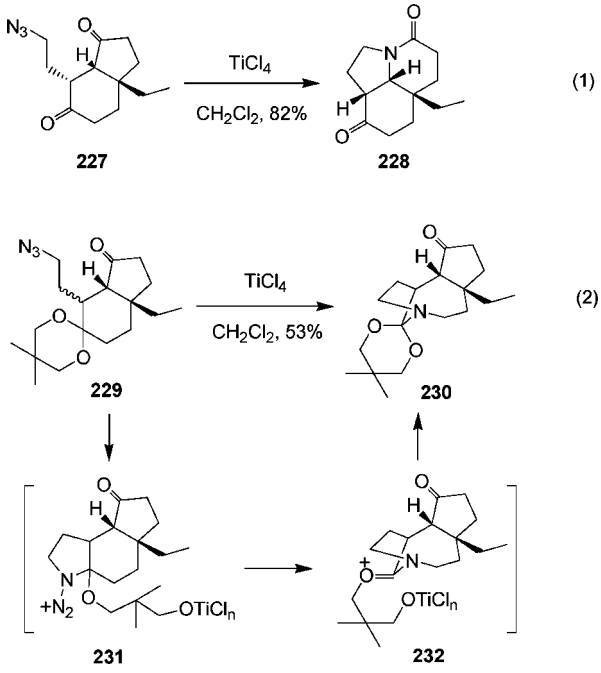
Mascareñas and co-workers developed a Lewis-acid-promoted *Prins*-type cyclization to assemble oxabicyclo[*n*.3.1] ring systems **258** (Scheme 67, eq 1).[104,105] 10-Oxabicyclo[4.3.1]decane **258a** was obtained in 82% yield as a mixture of isomers (8:2) at the tertiary center from acetals **257a** with a tethered terminal alkene group ($n = 1$) (Scheme 67, eq 2).[104] Remarkably, the same reaction with trimethylsilylalkene **257b** produced only one stereoisomer **258b** in 86% yield. The use of Prins-like cyclization allowed

Scheme 59



	R^1	R^2	Ratio (222/223)	Yield, % (222 + 223)
a	H	Ph	0	96
b	*t*-Bu	H	0.3	74
c	*t*-Bu	Ph	2.55	71
d	*t*-Bu	*p*-(MeO)C_6H_4	6.5	75

Scheme 60



access to the oxabicyclo[3.3.1] ring system **258c** (Scheme 67, eq 3).[105]

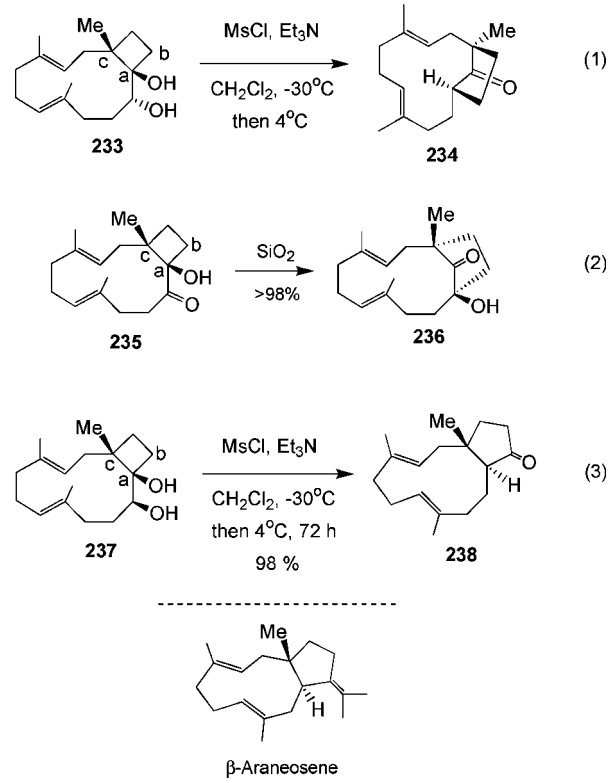
5. Free-Radical Reactions

5.1. Intramolecular Radical Cycloadditions

Free-radical reaction as a synthetic tools has been frequently applied to the total synthesis of natural products. Myers' group presented an excellent application of free-radical reaction toward the synthesis of amide-bridged tetracyclic compound **260**, a key intermediate in the total synthesis of alkaloid stephacidin B (Scheme 68).[106] This challenging transformation involves formation of an aminoacyl radical intermediate[107] whose attack on the more substituted carbon of the enamide C−C double bond and expulsion of thiophenyl radical leads to the desired product **260**.

Pattenden's group[108] utilized a radical domino reaction to construct the taxane skeleton. Exposure of iodo compound

Scheme 61



262 to radical reaction conditions (Bu_3SnH/AIBN) led to tricyclic bridged diketone **263** as a mixture of two diastereomers (3:1) albeit in only 25% yield (Scheme 69).

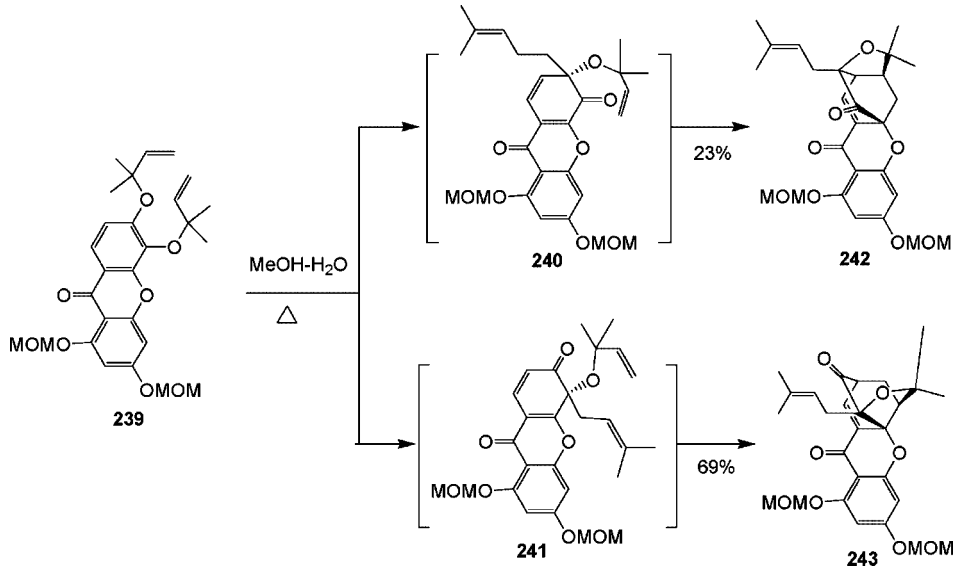
A radical cycloaddition of bromide **264** occurred at elevated temperature, affording a tricyclic core of alkaloid (−)-aphanorphine analogs **265** (Scheme 70).[109]

A radical process was developed to extend the one-carbon bridge into a two-carbon bridge (Scheme 71).[110] Two products were obtained with the desired rearranged product **267** in 77% yield along with about 15% of **268**. The bicyclo[2.2.2] diene **267** is a key intermediate in the synthesis of platencin. Two competitive radical additions are described in Scheme 71: addition of radical **269** onto the exo double bond to lead to the desired product **267** via radical intermediate **270** and addition onto the tethered double bond to produce the tricyclic **268**.

Taking advantage of labile diazo compound **272**, a radical reaction was employed to build a methylene bridge **274** via a biradical intermediate **273** (Scheme 72).[111]

It was found that a thermally more stable radical initiator **276** allows for cleaner, continuous generation of radicals required for the radical cycloaddition of alkoxycarbonyl selenide **275** during the total synthesis of (−)-pseudolaric acid B (Scheme 73).[112] In the event, two radical cycloaddition products **277** and **278** were obtained from secondary alkoxycarbonyl selenide **275**. A double-bond isomer **278** was converted cleanly to a desired bridged lactone **277** by addition of DBU to the reaction mixture after completion of the cycloaddition. A unique feature of this radical cycloaddition is that the radical generation is controlled by the low rate of decomposition of radical initiator **276**; consequently, an operationally simple procedure could be adopted by mixing all of the reagents together at the beginning.

Scheme 62



Scheme 63

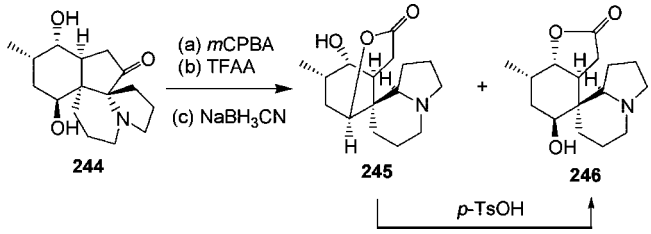
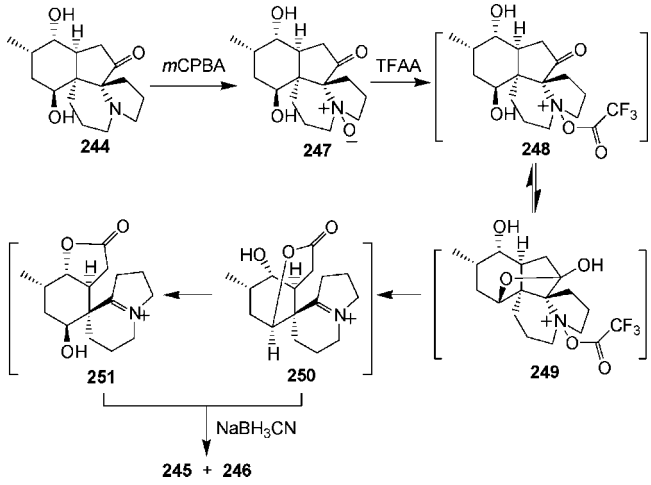


Table 1. Solvent and Temperature Effect[102]

		yield, %		
solvent	T (°C)	**244** (recovered)	**245**	**246**
CH_2Cl_2	−50		30	6
CH_2Cl_2	−20		48	27
CH_2Cl_2	0		17	38
CH_2Cl_2	20			65
$CHCl_3$	−20		27	13
CH_3CN	−20		17	6
THF	−20	66	0	0
toluene	−20	54	0	0

Scheme 64



5.2. Other Radical Reactions

Recent findings in Baran's laboratory[113] demonstrate that C−C bond formation can occur through a metal-mediated oxidative coupling.[114] Mechanistically, it is believed that conversion of indole derivative **279** into its corresponding bridged compound **280** by forming a key C_6-C_{22} bond in the enantioselective total synthesis of stephacidin A involves radical species (Scheme 74).

In addition to radical initiator, radical species can be generated by means of an electron-transfer process as well. Formation of bridged lactones **283** was hypothesized to involve a radical process initiated by an electron-transfer reaction between dihydropyridine **285**[115] and triflic anhydride (Schemes 75 and 76).[116] A radical combination of trifluoromethyl radical ($\cdot CF_3$), generated by dissociation of SO_2 from unstable trifluoro-methanesulfonyl radical ($CF_3SO_2\cdot$),[117] with dihydropyridine cation radical provides **287**. The final trifluoro-methanesulfonic acid anion-promoted intramolecular cycloaddition gives the desired product **283**.

Notably, a tandem alkoxy radical fragmentation−etherification sequence was designed to access a tricyclic compound **289**, a key intermediate in the synthesis of the AB subunit of angelmicin B (Scheme 77).[118] Formation of ether-bridged **289** is presumably via β-iodine intermediate **291**.

The use of an intramolecular hydrogen abstraction reaction of alkoxy radicals was applied toward the synthesis of the 2,7-dioxabicyclo[2.2.1]heptane ring system by Suárez and co-workers (Scheme 78).[119] The resulting C radical is oxidized to give an oxycarbenium ion that is then internally trapped by the nucleophilic alcohol to furnish 2,7-dioxabicyclo[2.2.1]heptanes **289**.

Scheme 65

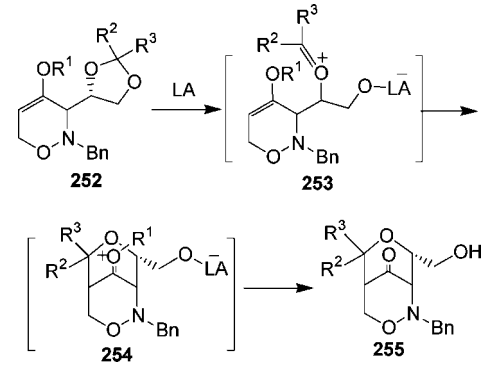
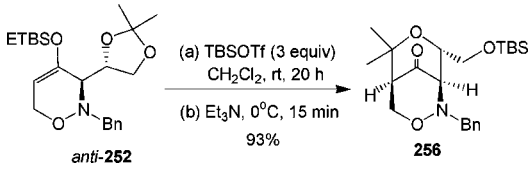


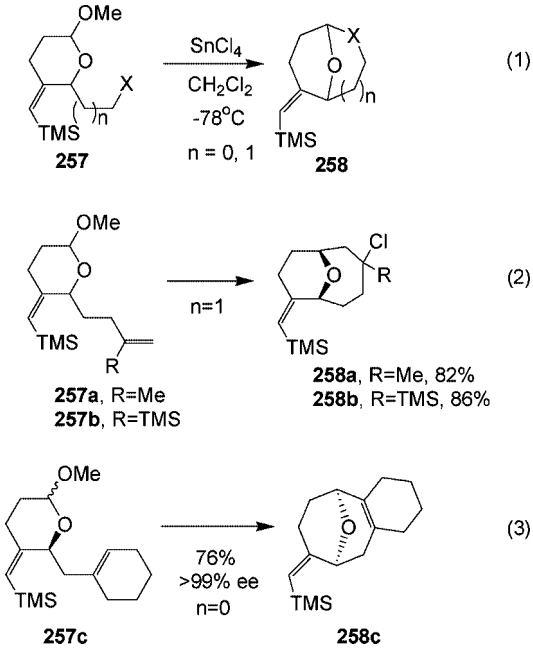
Table 2. Reaction Conditions for the Conversion of *syn*-252 to 255

entry	R^1	R^2	R^3	LA	solvent	T (°C)	R^4	yield, %	refs
1	TMSE	CH_3	CH_3	$SnCl_4$ (3 equiv)	CH_3CN	−30	H	quant.	103c
2	TMSE	CH_3	CH_3	Me_3SiOTf (0.05 equiv)	CH_2Cl_2	−30	TMS	79	103c
3	TMSE	CH_3	CH_3	$tBuMe_2SiOTf$ (3 equiv)	CH_2Cl_2	0	TBS	quant.	103c
4	TMSE	$-(CH_2)_5-$		$tBuMe_2SiOTf$ (3 equiv)	CH_2Cl_2	0	TBS	quant.	103c
5	TMSE	Ph	H	$tBuMe_2SiOTf$ (3 equiv)	CH_2Cl_2	0	TBS	quant.	103c
6	PMB	CH_3	CH_3	$SnCl_4$	CH_3CN	−30	H	58	103b
7	TMSE	CH_3	CH_3	BF_3 OEt_2	CH_2Cl_2	rt	H	63	103b
8	TMSE	H	SPh	Me_3SiOTf (2 equiv)	CH_2Cl_2	−30	H	75	103a

Scheme 66



Scheme 67



6. Transition-Metal-Catalyzed Cyclization Reactions

6.1. Gold-Catalyzed Reactions

Electrophilic transition-metal salts and complexes are uniquely selective Lewis acids that have a high affinity for π bonds. Owing to the electron configuration ($[Xe]4f^{14}5d^{10}6s^1$), gold catalysts mainly exist in the +1 and +3 oxidation states. As a soft Lewis acid, gold catalysts can activate unsaturated functionalities such as alkynes, alkenes, and allenes to create carbon−carbon and carbon−heteroatom bonds under extremely mild conditions.[120] Furthermore, gold catalysts can catalyze the formation of carbon−carbon and carbon−heteroatom (oxygen and nitrogen) bonds by activating the sp, sp^2, and sp^3 carbon−hydrogen bonds.[120] Most Au(I)-catalyzed reactions are well tolerated by oxygen, water, and alcohols, which is in sharp contrast to most air- and moisture-sensitive Lewis-acid- or transition-metal-catalyzed reactions.

A diastereoselective synthesis of eight-membered carbocycles **295** involves gold- or platinum-catalyzed 6-*exo*-cycloisomerization followed by a Prins-type cyclization tandem process (Scheme 79, eq 1).[121] The reaction tolerates different substituents on the substrate alkynes **294**, and in addition, a number of alcohols proved to be effective nucleophiles. A highly efficient cycloisomerization of bis-homopropargylic diols **296** catalyzed by Au(I) or Au(III) under very mild conditions furnished functionalized strained bicyclic ketals **297** (Scheme 79, eq 2).[122]

Mechanistically, these reactions involve additions of hydroxyl group onto the metal-activated triple bond, leading to vinyl gold intermediates **298** or **300**. The resulting intermediates may then be protonolyzed, providing enol ethers **299**, which then undergo another intramolecular addition[123] of the remaining hydroxyl group, leading to the cyclic ketals **297** (Scheme 80, eq 1). In the absence of internal hydroxyl group, the enol ethers **301** may go through a Prins-type cyclization, affording the ether-bridged **295** (Scheme 80, eq 2).

A new and highly convenient Ag-catalyzed intramolecular oxycyclization of alkynes proved to be expedient in the synthesis of epoxy-bridged tetrahydropyran skeletons, which are present in a wide range of natural products, including (+)-*exo*-brevicomin, (−)-frontalin, (+)-dedemniserinolipid B, (+)-xanthane epoxide, and phyllaemblic acid.[124] Oxycyclization of bis-homopropargylic diols **302** in the presence of 5 mol % of AgOTf led to bridged tetrahydropyrans **303** in good yields (Scheme 81, eq 1).[125] Extension of this Ag-catalyzed cyclization to other diols is demonstrated in eqs 2 and 3 of Scheme 81. Interestingly, cyclization of carboxylic acid **308** was also successful by heating, giving bridged lactone **309** in 70% yield (Scheme 81, eq 4).[125]

6.2. Cu(II)-Catalyzed Cyclizations

Diazo compounds are used as precursors to carbenes, which are generated by light and heat or in the presence of transition-metal catalyst. These carbenes in turn can undergo intramolecular cyclizations to form bridged carbocycles. The use of Cu(II) catalyzed intramolecular cyclization of alkynes bearing a diazo functionality allowed access to ether-bridged ketones **311** (Scheme 82).[126]

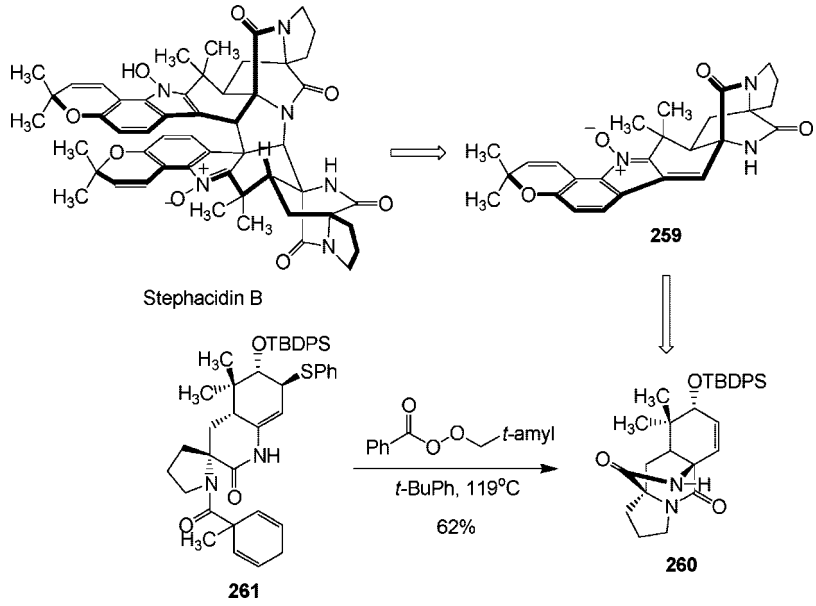
In another case, this Cu(II)-catalyzed cyclization was brilliantly combined with ring expansion of oxonium ylide **314**, affording ether-bridged macrocyclic ketone (*Z*)-**315** in excellent yield (Scheme 83).[127]

6.3. Rhodium-Catalyzed Reactions

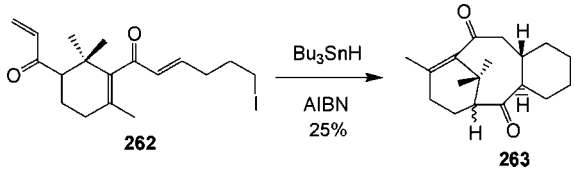
6.3.1. Rh(II)-Catalyzed Reactions

The transition-metal-catalyzed carbenoid insertion reaction of α-diazocarbonyl compounds is an important tool in synthetic organic chemistry.[128] Rh(II) has important applications in the catalytic generation of carbenoid intermediates[129] from diazo compounds. Intramolecular 1,3-dipolar cycloaddition of **317**, being generated from Rh(II)−carbenoid,

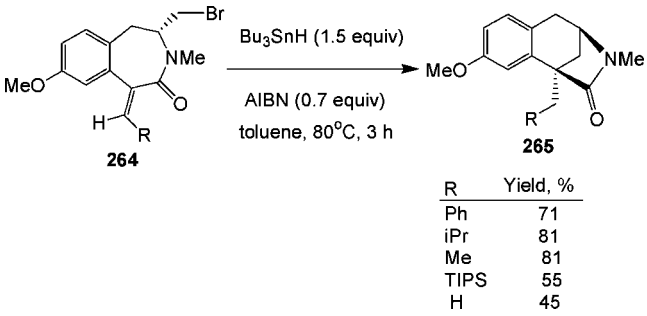
Scheme 68



Scheme 69



Scheme 70



R	Yield, %
Ph	71
iPr	81
Me	81
TIPS	55
H	45

furnished ether-bridged polycyclic system **318** in 90% yield (Scheme 84).[130]

Similarly, an ether-bridged cycloadduct **321**[131] was formed from dipole intermediates **320**, generated via trapping the rhodium carbenoid intermediates by the adjacent amido carbonyl group (Scheme 85).[132] This cycloaddition process was applied toward the generation of a pentacyclic skeleton in the synthesis of indole alkaloids,[133] such as (±)-3*H*-epivincamine and (±)-tacamonine.[132]

6.3.2. Rh(I)-Catalyzed Reactions

Analogous to Rh(II), Rh(I) reveals great diversity in C−H bond activation, which results in an alkenylation/electrocyclization process (Scheme 86).[134] A 9-membered ring **326** with an exocyclic double bond is presumably formed via intermediate **324** and 10-membered Rh complex **325**. Electrocyclization of the resulting azatriene **326** gives the bicyclic enamine **323** with bridgehead unsaturation (Scheme 86).[134]

6.4. Palladium-Catalyzed Reactions

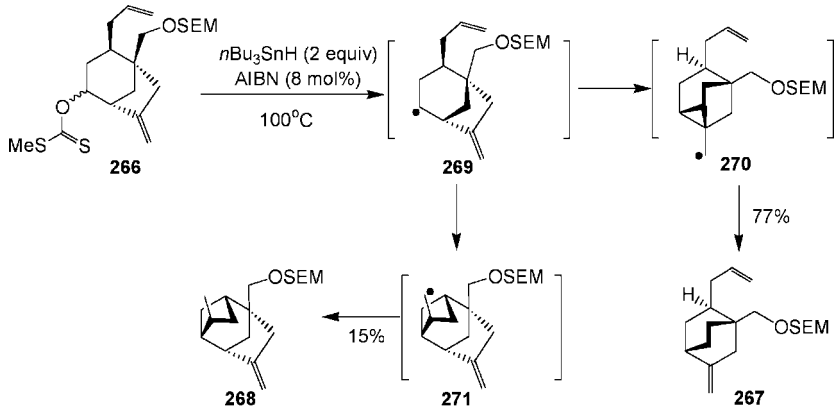
Murrayazoline, isolated from the genus Murraya,[135] displays potent antiplatelet aggregation activity.[136] During the synthesis of murrayazoline, a Pd-based intramolecular Buchwald−Hartwig C−O coupling reaction[137] was utilized to assembly a [3.3.1] heterocyclic ring system by Chida's group in Japan. Construction of the methylene bridge in this hexa-heterocyclic structure is the final step of the total synthesis of murrayazoline. This Pd-mediated C−O coupling reaction of **327** furnished the desired murrayazoline in 80% yield (Scheme 87).[138] However, this C−O coupling reaction would need some optimization prior to any practical application due to the prerequisite of stoichiometric amounts of $Pd(OAc)_2$.

Paterson and co-workers[139] presented another application of palladium(II)-catalyzed cyclization toward the preparation of bicyclo[3.2.1] acetal **330** in the total synthesis of the orthinine decarboxylase inhibitors saliniketals **A** and **B**. Saliniketals **A** and **B** were isolated in 2007 by Fenical and co-workers from the marine actinomycete *Salinispora arenicola*.[140] The use of catalytic $PdCl_2$ and $CuCl_2$ in THF under an atmosphere of oxygen at 0 °C was found to give a good yield (88%) of the acetal **330**. The desired [3.2.1]-dioxabicycle **330** likely arises from the expected 5-exo attack of the C13 hydroxyl group in diol **328** onto the palladium-activated terminal double bond followed by β-H elimination to lead to intermediate **329**. The subsequent acid-catalyzed acetal formation furnishes the desired bicyclo[3.2.1]acetal **330** (Scheme 88).[139]

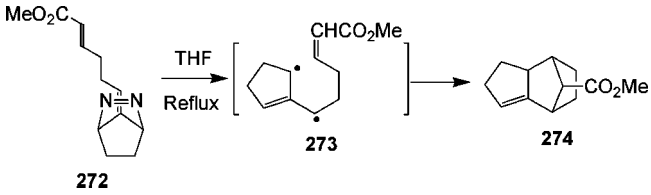
Similar to gold(I) or gold(III), Pd(II)-catalyzed cycloisomerization of alkyne **331** was applied toward constructing the bridged 6,8-dioxabicyclo[3,2,1]octane core **332** in the total synthesis of didemniserinolipid B (Scheme 89).[141]

A novel and efficient palladium-catalyzed intramolecular allylic alkylation was performed by Wipf's research group, affording bridged adducts **334a** and **334b** in excellent yields (Scheme 90).[142]

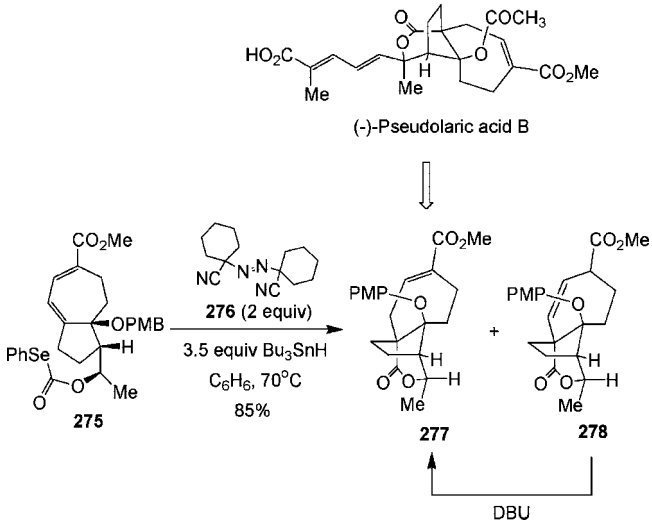
Scheme 71



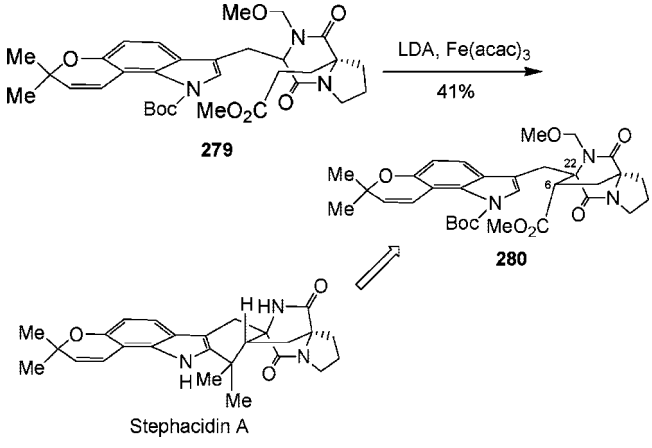
Scheme 72



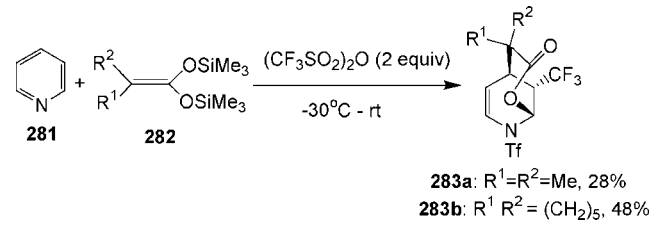
Scheme 73



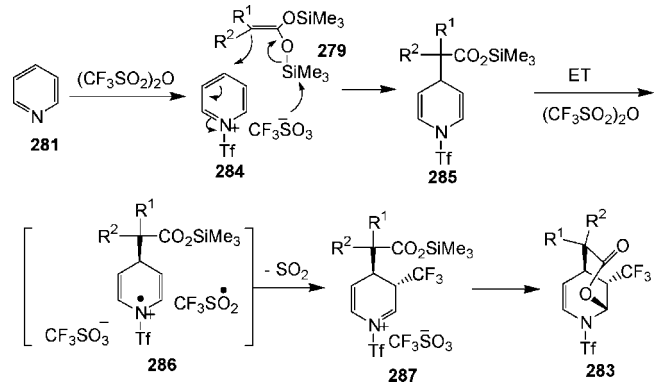
Scheme 74



Scheme 75



Scheme 76



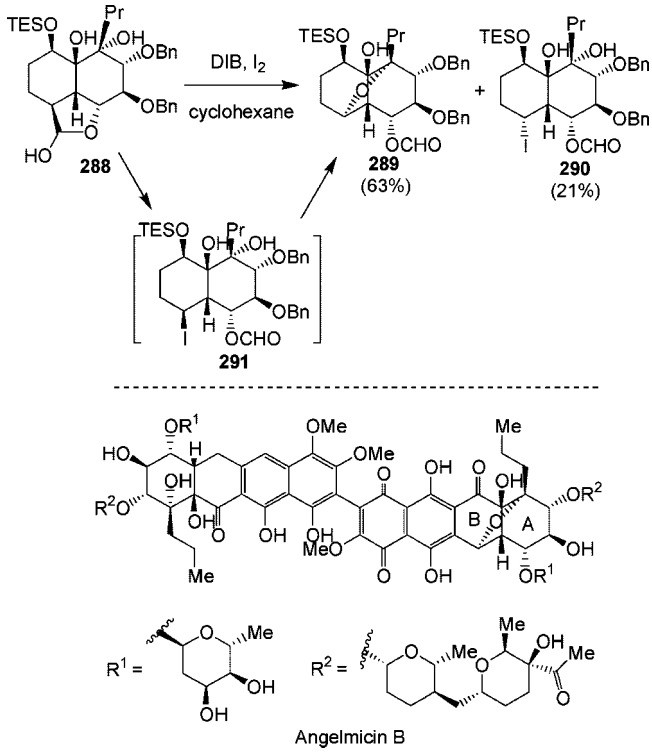
7. Other Reactions

7.1. Iodine-Promoted Cyclizations

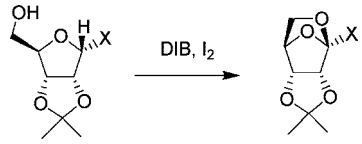
The triterpene garsubellin A, first isolated by Fukuyama and colleagues from the wood of *Garcinia subelliptica*, is a molecule with biological activity and structural complexity. Not surprisingly, the total synthesis of garsubellin has caught the interest of many research groups.[143] Iodine-promoted cyclization allows the formation of C−C or C−heteroatom bonds under basic but mild conditions, which has been used in total synthesis.

Using Nicolaou's condition (I_2, KI, $KHCO_3$, THF−H_2O),[143a,b] Danishefsky and co-workers were able to synthesize diiodide **336**, an intermediate of garsubellin A, in one step (Scheme 91, eq 1)[144] A new and short enantioselective pathway for the synthesis of the anti-influenza neuramidase inhibitor oseltamivir phosphate (Tamiflu) was developed by Corey's group.[145,146] As one of the intermediates, a bridged bicyclic lactam **338** was synthesized by iodolactamization of **337** using the Knapp protocol[147] in 84% yield (Scheme 91, eq 2).

Scheme 77



Scheme 78



X	Yield, %
CO_2Me	75
CH_2OH	66
OH	70
$CH{=}CH_2$	88

Nicolaou's group employed an intramolecular iodoetherification to construct the G ring system during the total synthesis of azaspiracid-1, a neurotoxin isolated from mussels, and iodoether **340** was obtained in 62% yield (Scheme 92).[148]

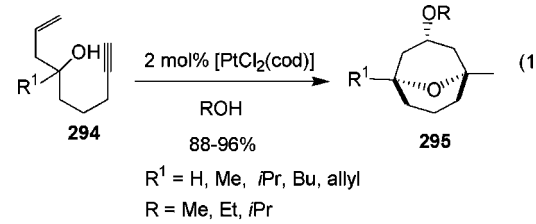
7.2. Pictet−Spengler Cyclizations

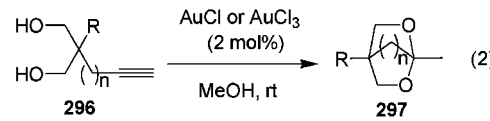
Multicomponent reactions (MCRs) involving domino processes[149] have emerged as powerful tools used in modern organic chemistry. A multicomponent domino reaction involving Pictet−Spengler cyclization was developed to synthesize polyfunctionalized 2,6-diazabicyclo[2.2.2]octane derivative **344** (Scheme 93).[150]

Scheme 94[150] underscores this three-component reaction pathways. Molecular sieves (4 Å) act as both dehydrating agent and heterogeneous catalyst for the initial Michael addition.[151] The key steps of the present one-pot process are the successive formation of three iminium intermediates, **347**, **348**, and **349** via Pictet−Splengler reaction.

Despite the total synthesis of ecteinascidin 743,[152] an extremely potent antitumor agent,[153] which has been achieved by Corey and co-workers[154] and others,[155] investigations into new synthetic approaches are still of great interest for

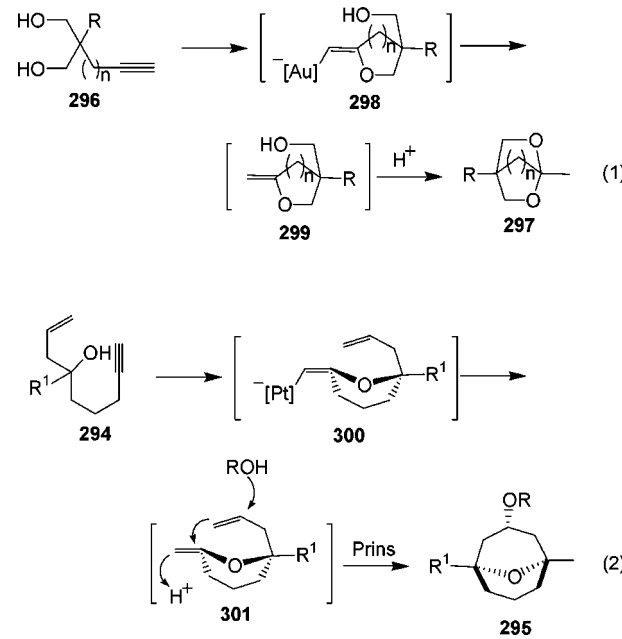
Scheme 79





R	n	Cat	Yield, %
Bn	1	AuCl	99
Ph	1	AuCl	99
n-Bu	1	AuCl	80
cinnamyl	2	AuCl	82
allyl	2	AuCl	91
cinnamyl	1	$AuCl_3$	82
Bn	1	$AuCl_3$	99
Ph	1	$AuCl_3$	99
Allyl	1	$AuCl_3$	74
cyclohex-2-enyl	1	$AuCl_3$	94
3-methylbut-2-enyl	1	$AuCl_3$	77

Scheme 80

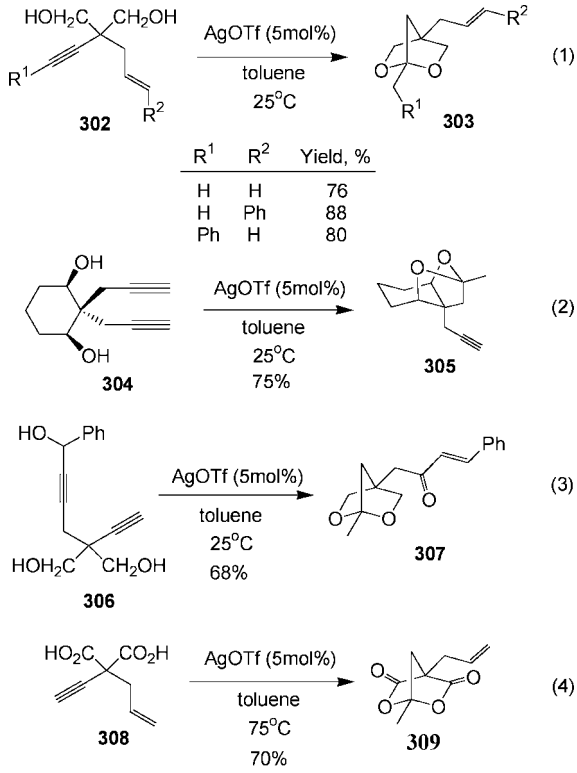


synthetic chemists. A pentacyclic product **351** containing the ABCD ring system[156] was constructed by an intramolecular Pictet−Spengler cyclization of aldehyde **350** triggered by cleavage of the Boc protection group (Scheme 95).[157]

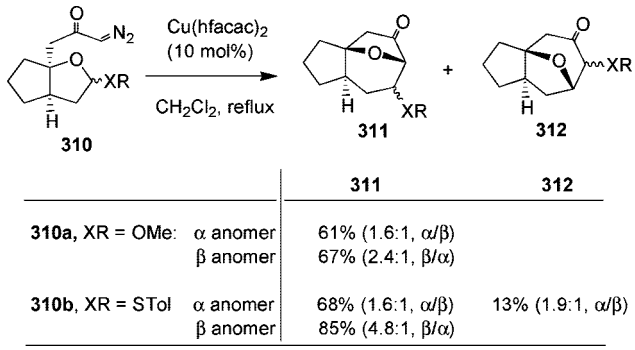
7.3. Nucleophilic Substitutions

A process involving intramolecular conjugate S_N2-type displacement was devised by Clive and co-workers for constructing a broad range of carbocycles.[158] This metal-free process offers different opportunities from palladium-catalyzed cyclization[159] of allylic acetates and should tolerate the presence of palladium-sensitive groups. A bridged bicyclic compound **353** was synthesized by an intramolecular S_N2-type displacement reaction (Scheme 96).[158] In the

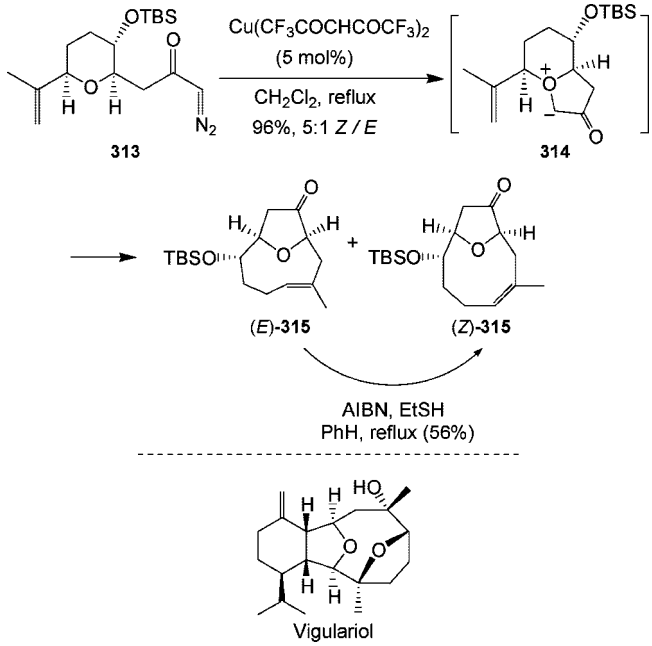
Scheme 81



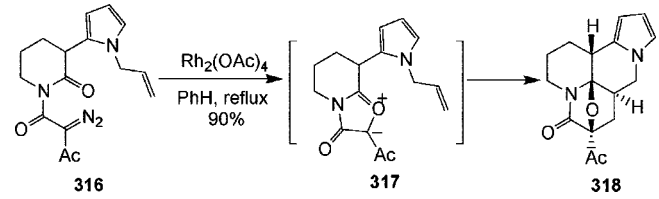
Scheme 82



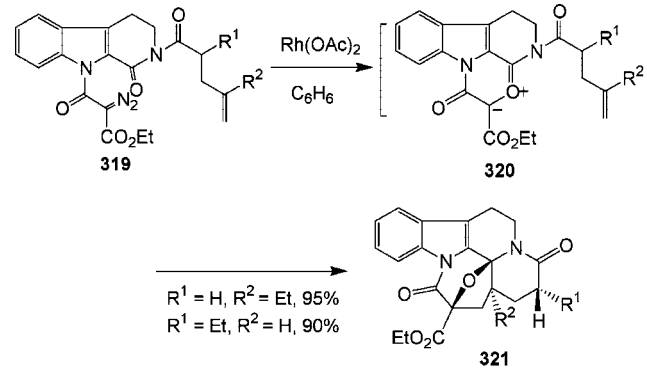
Scheme 83



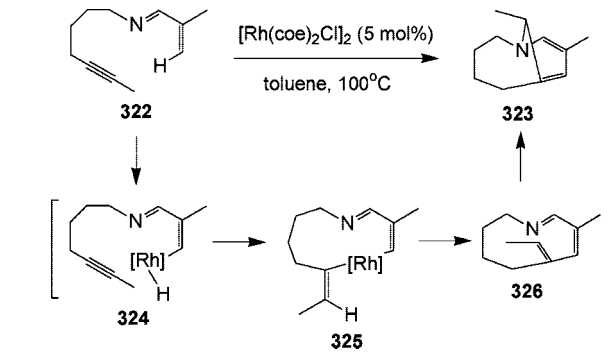
Scheme 84



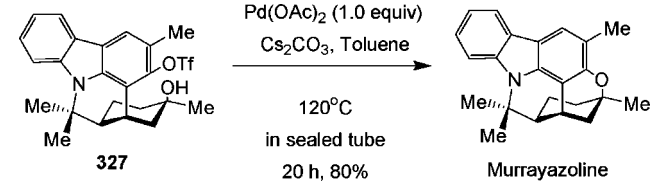
Scheme 85



Scheme 86



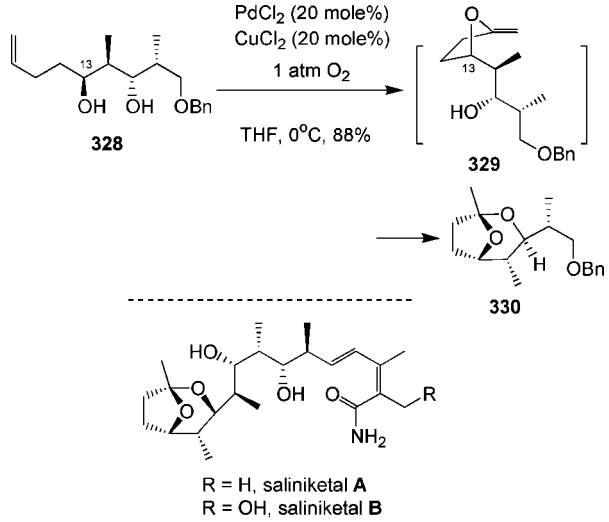
Scheme 87



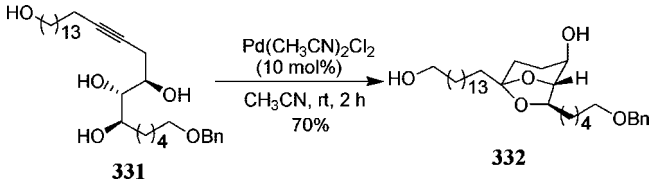
presence of DBU and 50 min of reaction time, a mixture of bicycles **353** and **354** was isolated. However, with the inorganic base (Cs_2CO_3) only bridged bicyclic **353** was obtained in 99% yield. Interestingly, **354** could be converted into **353** by exposure to DBU.

A hypothesis for the formation of **353** and **354** in the presence of DBU is described in Scheme 97.[158] A DBU-facilitated cycloaddition occurred through iminium **355**, leading to bicycle **354**. Formation of **353** from **354** may go through DBU-promoted ring rearrangement with two possible intermediates **356** and **357** or through Claisen rearrangement.

Scheme 88



Scheme 89



S_N2-type cycloaddition/elimination reactions were utilized to form the [2.2.2] bridged bicyclic ring system in asymmetric total syntheses of the fungal metabolites (−)-stephacidin A, (+)-stephacidin B, and (+)-notoamide B. Conversion of allyl chloride **358** to the desired bridged bicycle **359** was completed via a S_N2-type cycloaddition/elimination sequence in 60% yield as a single diastereoisomer (Scheme 98, eq 1).[160] Another example of a S_N2-type displacement was found in the total synthesis of (±)-welwitinone A isonitrile, which gave not the expected dehydration of the C20 alcohol **362** but an undesired bridged product **361** (Scheme 98, eq 2).[161]

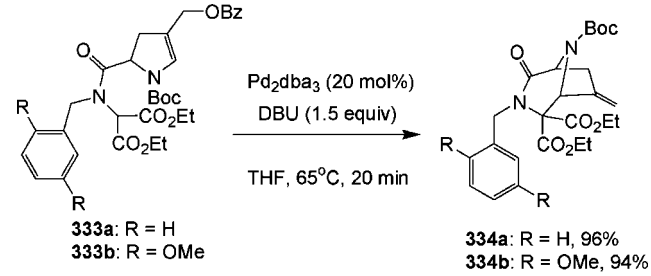
Mesylate is considered an excellent leaving group in nucleophilic substitution reactions. The use of mesylates in the S_N2-type cyclizations was found in the syntheses of cytosine, 11-norcytisine, and (+)-serratezomine A (Scheme 99). The S_N2 displacement of mesylates by nitrogen atoms was demonstrated in the formation of bridged cytisine skeletons **364** and **366** (Scheme 99, eqs 1 and 2).[162] In addition, in-situ-generated carboxylate also participated in an analogous S_N2 displacement in the formation of bridged lactone in (+)-serratezomine A (Scheme 99, eq 3).[163]

An unexpected rearrangement of hemeanthamine-type alkaloids in the presence of halogenating agents has been observed.[164] When hemeanthamine **368** was treated with a large excess of thionyl chloride (20 equiv), **370** was formed in 71% yield via intermediate **369**, which underwent ring rearrangement containing a S_N2-type cyclization/displacement sequence (Scheme 100).[164]

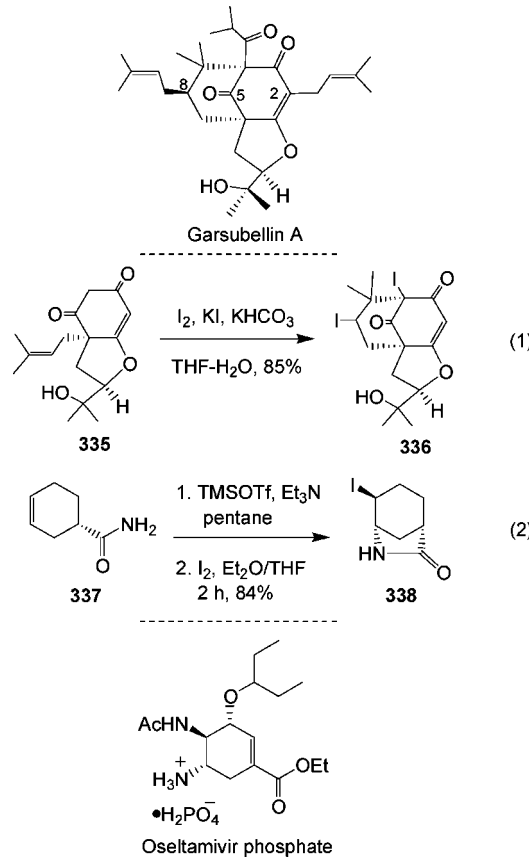
In addition to S_N2-type cyclization, S_N1-type cyclization appears to be equally important in the organic synthesis. An *N*-acyliminium cyclization was promoted with thiophile, $AgBF_4$, giving **372** as a single diastereomer (Scheme 101).[165]

Furthermore, the use of S_NAr ipso substitution in the total of synthesis was described. Bisanthraquinone natural product

Scheme 90



Scheme 91

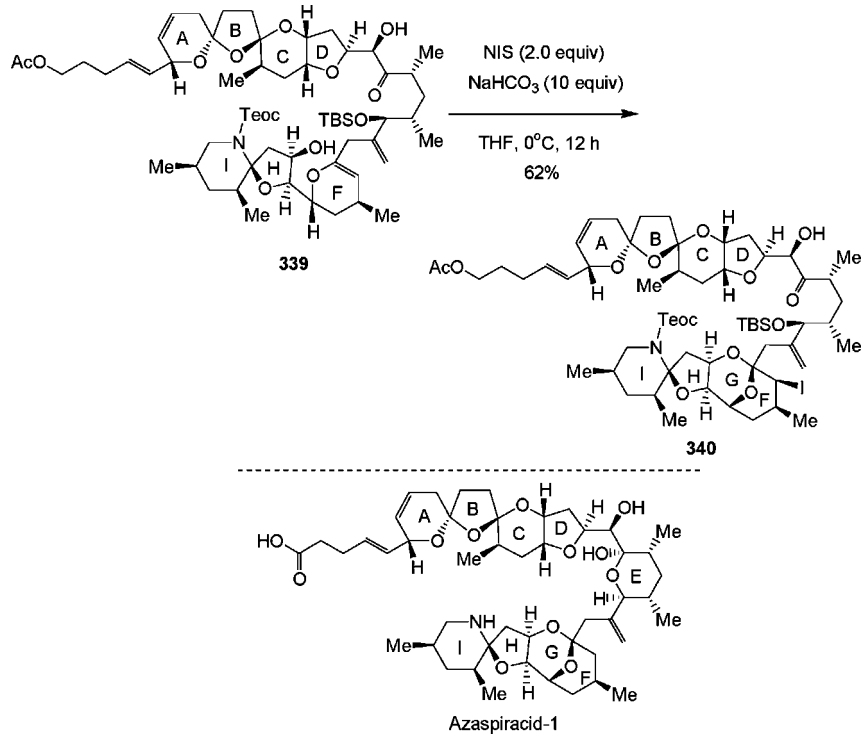


(+)-BE-43472B, an antitumor agent, is composed of two different anthraquinone-type molecules joined together by a sterically hindered carbon−carbon bond and an oxygen bridge in an assembly containing no less than eight rings. Nicolaou and co-workers reported the first total synthesis of this antibiotic. Scheme 102[166] illustrates the synthesis of a key 8-membered ring intermediate **377** through a cascade sequence consisting of Diels−Alder reaction, hemiketal formation, and S_NAr ipso substitution. The DA adduct intermediate **375** undergoes an intramolecular nucleophilic ipso substitution expelling a molecule of MeOH to afford the desired octacycle **377**. This novel cyclization is apparently facilitated by the presence of the adjacent phenolic quinone moiety.

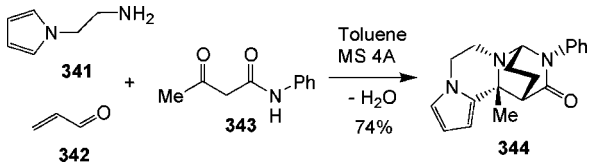
7.4. Nucleophilic Additions

The Michael addition is an important method for diastereo- and enantioselective C−C bond formation. A stereoselective intramolecular Michael addition of ketone **378** in the presence of *t*-BuOK yielded a bridged tricyclic ketone **379** (only the endo isomer) (Scheme 103, eq 1).[167] Hopeahainol

Scheme 92



Scheme 93



A[168] and hopeanol[169] are two recently disclosed molecules, each thought to be biosynthetically derived from two molecules of resveratrol. Nicolaou and co-workers explored the total synthesis of hopeahainol A and hopeanol and found that the transformation of hopeahainol A to hopeanol occurred upon exposure of hopeahainol A to 1 equiv of NaOMe in MeOH at 25 °C, giving hopeanol in 80% yield (Scheme 103, eq 2).[170] It was hypothesized that the base-promoted γ-lactone ring opening allows $C_{1b}-C_{7a}$ bond formation to be effected through an intramolecular conjugate nucleophilic addition of intermediate **380**.

In addition to the base-promoted nucleophilic cycloaddition, an acid-catalyzed reaction was also observed, delivering a bridged bicyclo[3.2.1]octene **382** (Scheme 104, eq 1).[171] Interestingly, no reaction occurred for the diastereomer (β-OMe) under identical conditions, suggesting that rearrangement of **381** may be controlled by the relative configuration of the tetrasubstituted SP^3 carbon. An intermediate **385** containing a 6,9-trioxatricyclo[3.3.2.$0^{3,7}$]decane ring system in a total synthesis of norhalichondrin B was effected involving TBS group removal and an intramolecular hetero-Michael addition (Scheme 104, eq 2).[172] Subjecting the mixture of diastereoisomers **384** to nonaqueous workup conditions ($CaCO_3$, DOWEX 50WX8-400, MeOH) resulted in the desired product **385** in 64% yield.

Utilization of intramolecular nucleophilic addition of α,β-unsaturated ketones **386** toward synthesis of bridged compounds **387** was reported by Goeke and co-workers (Scheme 105).[173] This Lewis-acid-catalyzed cyclization involves a 1,2-H shift followed by 1,2-alkyl group shift cascade process.

The versatility and practicality of this Michael-type intramolecular cycloaddition was nicely demonstrated by Patir's group in the synthesis of a framework of uleine-type alkaloids. A bridged tetracyclic compound **392** was obtained from sequential multistep reactions involving a Michael-type intramolecular cycloaddition of iminium intermediate **390** (Scheme 106).[174]

Furthermore, *N*-tosyl removal provides free indole, which serves as a nucleophile, leading to a bicyclo[3.3.1] ring system **395** (Scheme 107).[175]

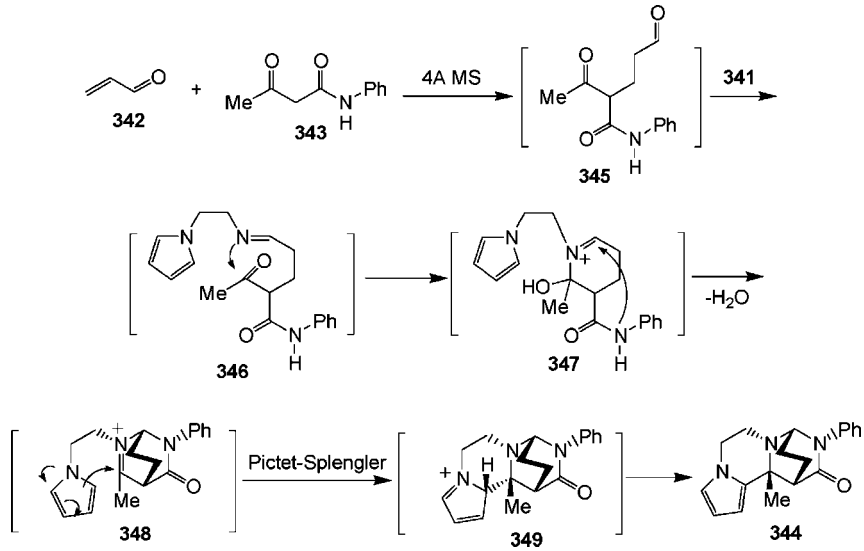
Intramolecular carbolithiation (anionic cyclization) offers a valuable alternative to the related radical cyclization and provides enhanced or complementary stereoselectivity. Tin−lithium exchange and anionic cyclization have been used to construct the azabicyclo[2.2.1]heptane ring system.[176] On treatment of the cis isomer **396** with *n*-butyllithium, the 7-azabicyclo[2.2.1]heptane **397** was formed in good yield and as a single diastereomer (Scheme 108, eq 1).[176] In the presence of electrophiles, 2-substituted 7-azabicyclo-[2.2.1]heptane derivatives **398** were obtained (Scheme 108, eq 2).[176]

Besides the intramolecular nucleophilic addition, a combination of intermolecular nucleophilic addition with intramolecular cycloaddition has been employed in the construction of bridged compounds **401** during the synthesis of tropinones (Scheme 109, eq 1).[177] Formation of 3-oxo-8-aza-bicyclo[3.2.1]octane **401** involves two iminium triflate intermediates **402** and **403** (Scheme 109, eq 2).

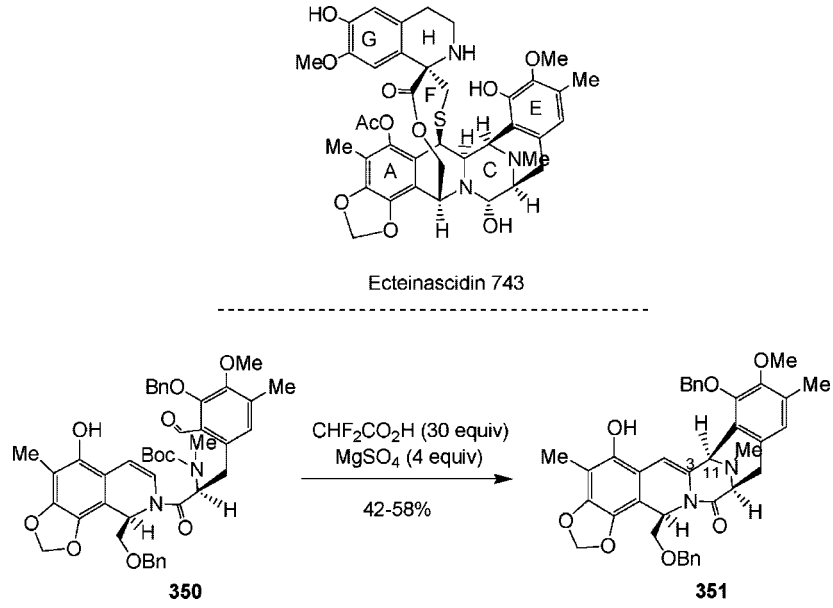
7.5. Aldol-Type Condensation Reactions

Aldol condensation is one of the important organic transformations in organic synthesis. Weinreb and co-workers reported an intramolecular condensation reaction to construct bridged molecules such as tetracyclic lactone **406** via

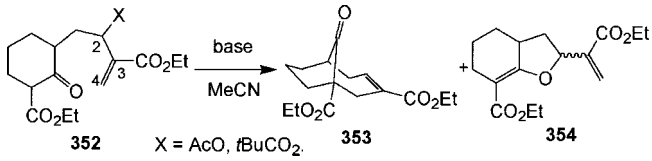
Scheme 94



Scheme 95



Scheme 96



transesterification of intermediate **405** (Scheme 110, eq 1).[178] Reductive lactone ring opening of **407** occurred with DIBAL-H, leading to transitory aldehyde **408** followed by intramolecular aldol cycloaddition to bridged bicyclic alcohol **409** (Scheme 110, eq 2).[179]

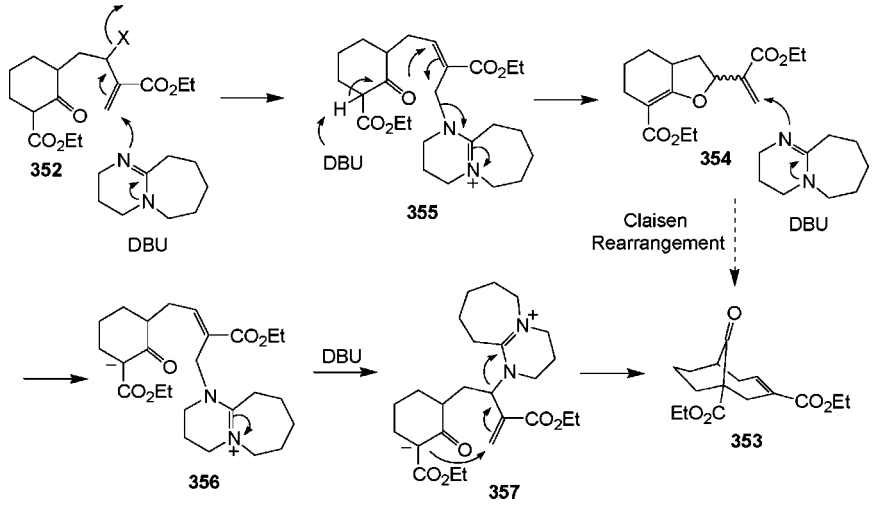
7.6. Friedel−Crafts Cyclizations

An important use of the Friedel−Crafts alkylation reaction is to effect ring closure. The most common method is to heat the aromatic compound with aluminum chloride. Friedel−Crafts alkylation promoted by $SnCl_4$ allowed cyclization of acetals **411** at cryogenic temperature and an optically pure **412**, which were obtained in excellent yields (Scheme 111).[105]

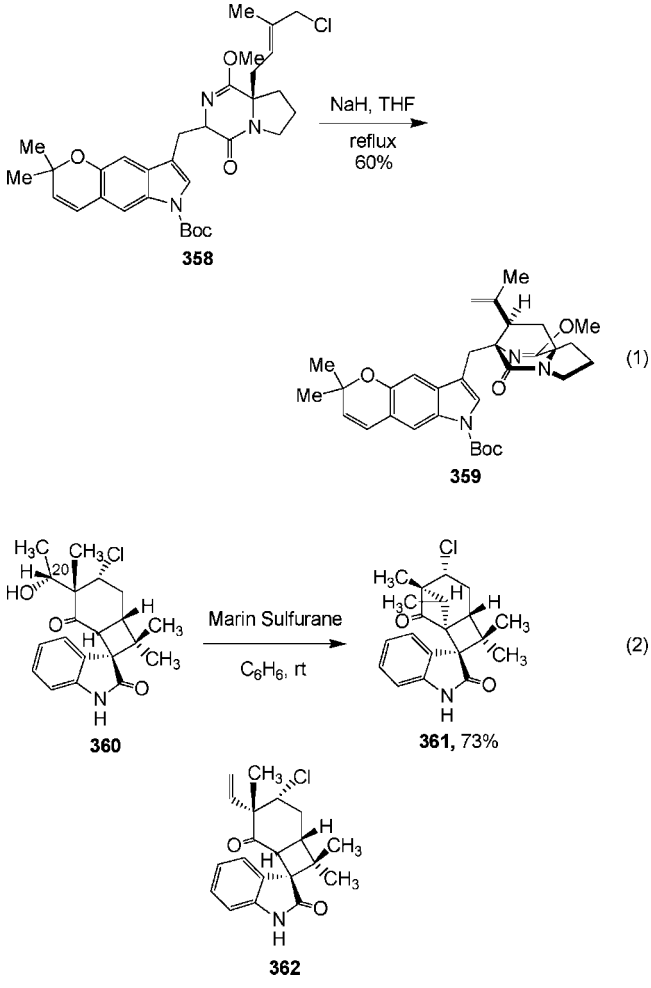
7.7. Ring-Closing Metathesis

Ring-closing metathesis (RCM) is a powerful tool to assemble macrocycles. The RCM method was applied toward the construction of bicyclo[4.2.1]nonan-9-one **414**, a bridged intermediate in the synthesis of cyclooctanoids (Scheme 112, eq 1).[180] Although ring-closing metathesis has been widely used in organic synthesis, its application in constructing medium-sized bridged carbocycles is less common.[181] RCM was utilized to generate the strained tricylic skeleton of platencin. Under reflux in methylene chloride in the presence of Grubbs' second-generation catalyst (7 mol %), triene **415** was converted to **416** in 90% isolated yield (Scheme 112, eq 2).[182] A nice ring-opening metathesis (ROM)−RCM strategy was developed by Ghosh to synthesize the tricycles **418** (Scheme 112, eq 3).[183]

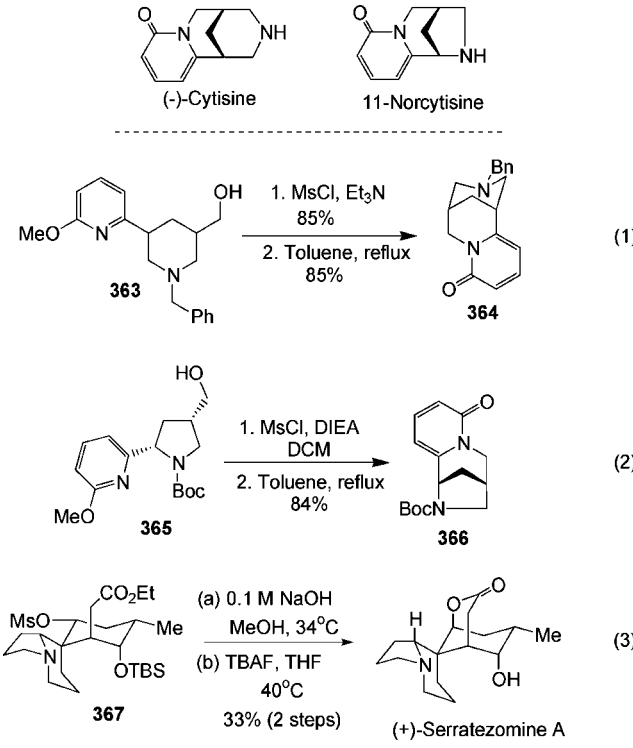
Scheme 97



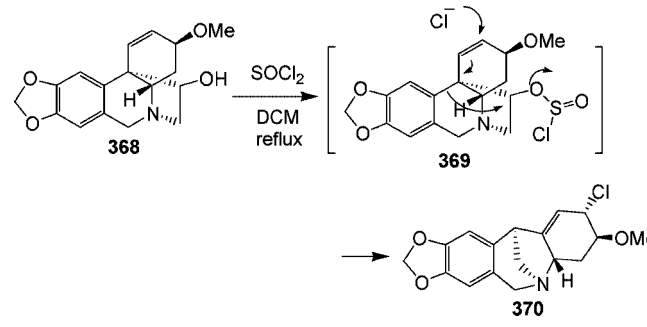
Scheme 98



Scheme 99



Scheme 100

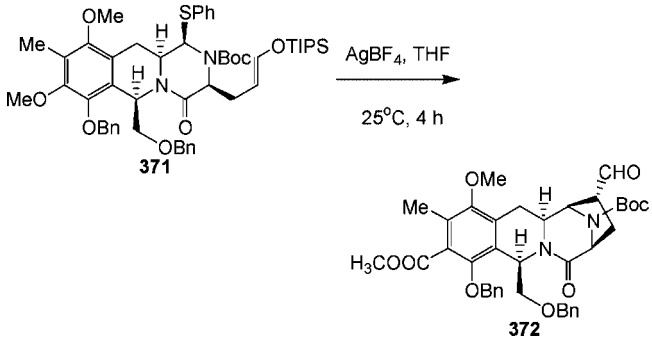


8. Important Classes of Compounds

8.1. Reactions in Synthesis of FR66979 and FR900482

Anticancer agents FR66979 and FR900482 are structurally related to the mitomycins and are believed to act by a similar mechanism but with less toxicity. Both FR900482 and FR66979 possess unique structural features, including hydroxylamine hemiacetal and aziridine functional groups, making it an attractive target for synthetic organic chemists. Although there were a number of reports[184] regarding the synthesis of FR900482 (R = CHO),[185] six individual research groups[186−191] recently revealed new synthetic approaches toward the synthesis of FR900482 and FR66979.

Scheme 101



Williams and co-workers[187] reported a one-pot process for the construction of a bridged bicyclo[3.3.1] intermediate **421** in the synthesis of FR66979 (R = CH_2OH) and FR900482. This one-pot protocol involves cleavage of the *N*-*p*-methoxybenzyl residue and oxidization of the amine to the corresponding hydroxylamine, thus forming the desired hydroxylamine hemiketal. Reactions of **419** furnished **421** as the only isolated product in 30−50% yield, along with recovered starting material (40−50%) (Scheme 113).

An analogous approach was developed by Fukuyama's group[187] toward an enantioselective total synthesis of (+)-FR900482 (Scheme 114). Hydroxymethylation was best effected by treatment of ketone **422** with formalin in the presence of a catalytic amount of LiOH to furnish the desired **423** with high diastereoselectivity (94:6). Subsequent acidification afforded hemiacetal **424**, whose acetonide formation gave the bridged pentacyclic compound **425** in 56% yield from ketone **422**.

Two research groups, Ciufolini[188] and Paleo,[189] demonstrated independently another synthetic method to access the core bridged bicycle **427** (Scheme 115). Exposure of the acetyl-protected hydroxylamine **426** to hydrazine gave directly the transannular cyclization product **427** in quantitative yield.

Oxidative ring expansion can be realized in the presence of oxidant by heterolytic cleavage of the C−N bond of a nitrogen-containing heterocyclic compound. Jimenez and co-workers[190] reported that the oxygen-bridged bicyclo[3.3.1] intermediate **434** was assembled by oxidative ring expansion of bicyclo[3.3.0] **428** and successive intramolecular cyclization (Scheme 116) via intermediates such as iminium salt **430** and ring expansion **433**.

Trost and co-workers modified this oxidative ring expansion with *m*CPBA as the oxidant, which improved the yield of **436** (Scheme 117).[191] This conversion of **435** to **436** went through two intermediates, hydroxylamine **437**[192] and 8-membered ketone **438**.

8.2. Reactions in Synthesis of Platensimycin and Carbaplatensimycin

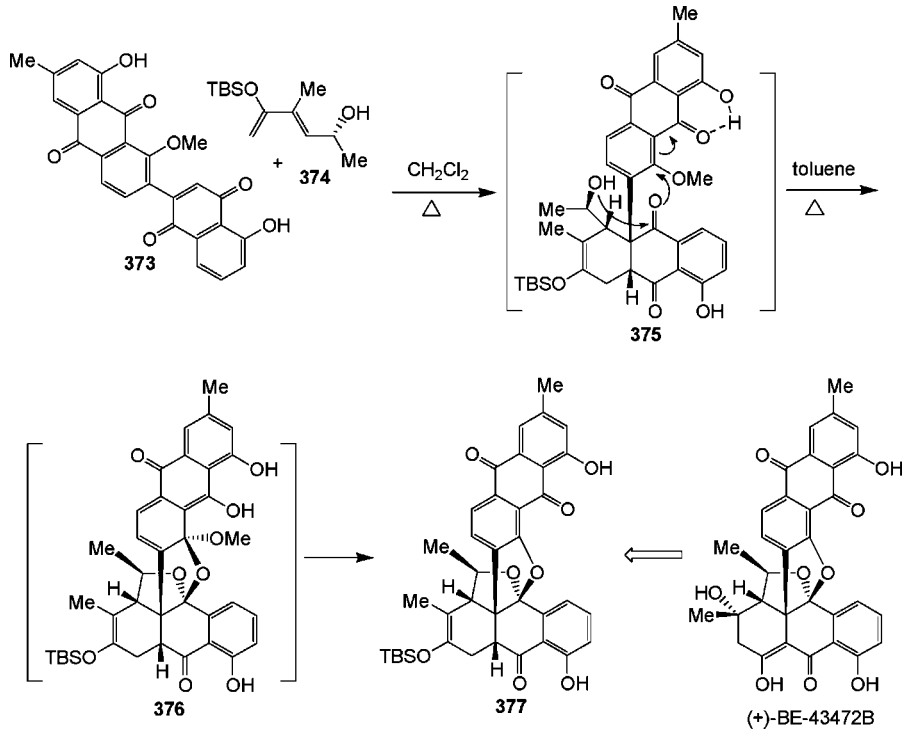
Platensimycin has potent activity against Gram-positive bacteria including multiresistant strains of staphylococci and enterococci. Platensimycin has an intriguing structure (Scheme 118), which features a hydrophilic aromatic unit and a lipophilic tetracyclic unit linked together by an amide bond.

8.2.1. Synthesis of the Cyclohexane Ring System

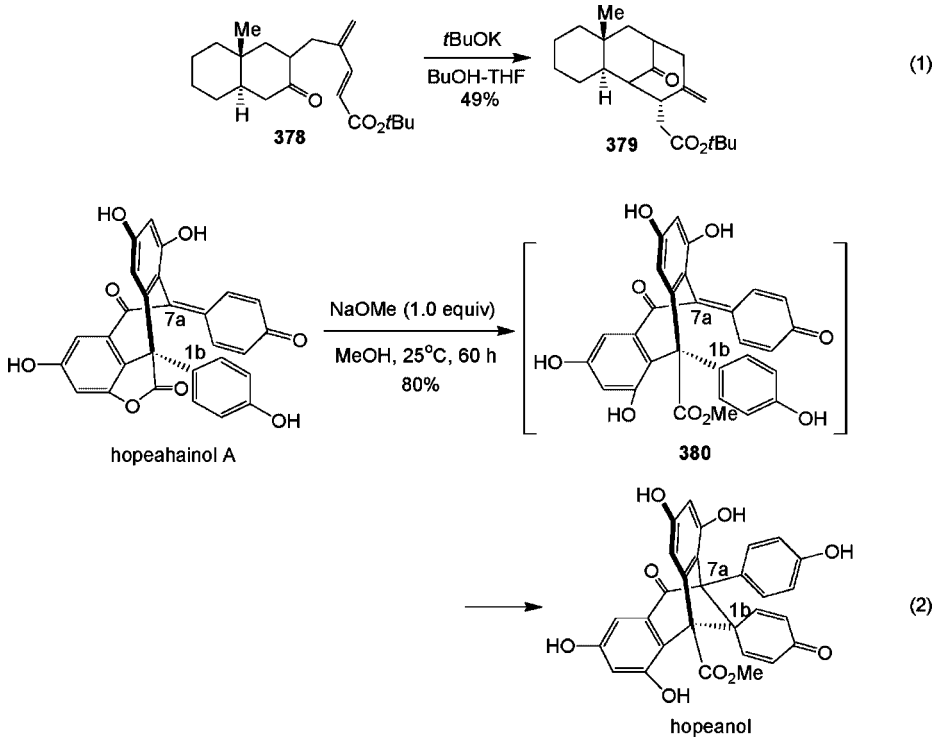
The total synthesis of platensimycin was pioneered by Nicolaou's group, and the first total synthesis of the racemate was reported in 2006.[193] Scheme 119 (eq 1) describes a synthesis of cyclohexane ring through a SmI_2-mediated cyclization reaction, affording **440** and its diastereoisomer in 46% combined yield. Analogously, the same cyclization conditions were applied toward asymmetric total syntheses of platensimycin, and a desired secondary alcohol **442** was obtained in moderate yield (39%) as a single diastereoisomer (Scheme 119, eq 2).[194]

Further development by Nicolaou and co-workers resulted in another approach toward the synthesis of a 6-membered ring system of carbaplatensimycin (Scheme 120).[195] Treat-

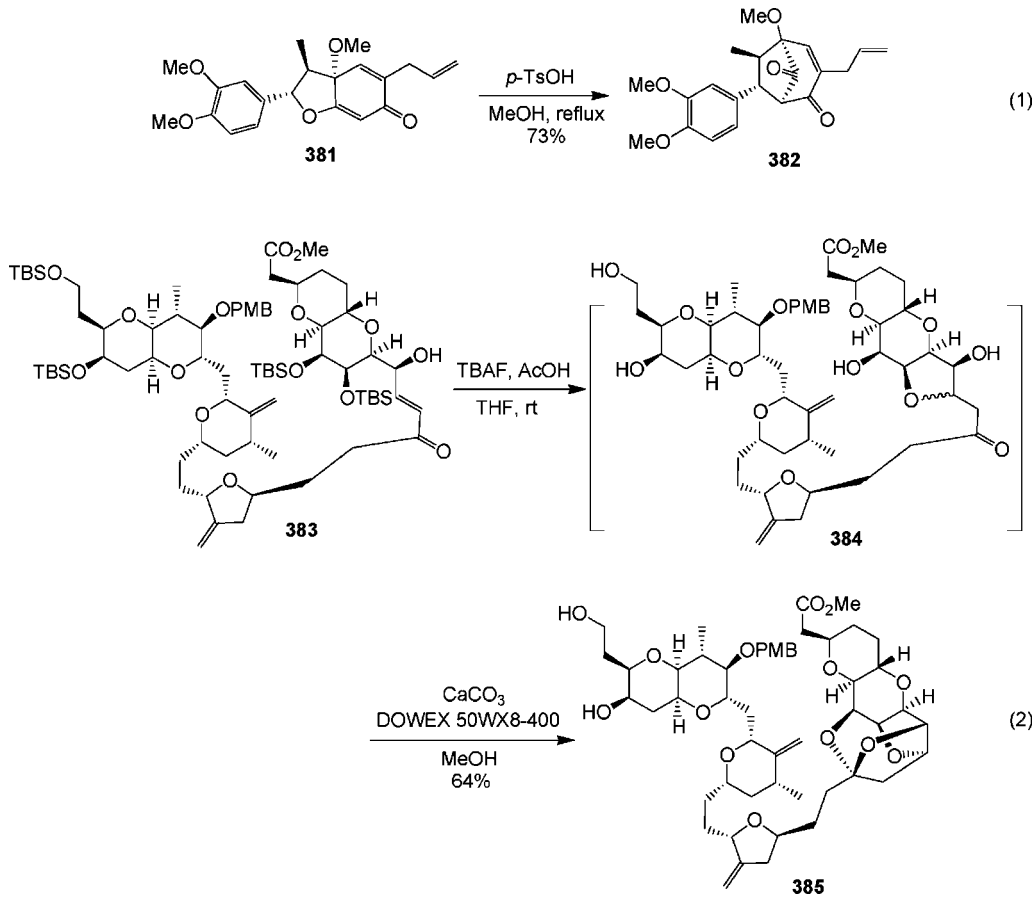
Scheme 102



Scheme 103



Scheme 104

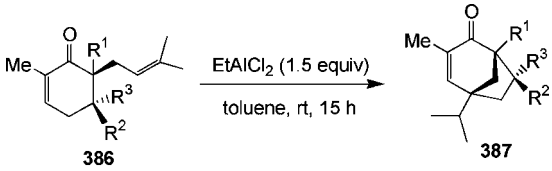


ment of 1-ethoxyethyl (EE) ether **443** with KHMDS induced intramolecular conjugate addition of the transient anion so generated onto the bisenone subunit to afford tricycle **444** in 70% yield as a single epimer at C10.

8.2.2. Synthesis of the Cyclopentane Ring System

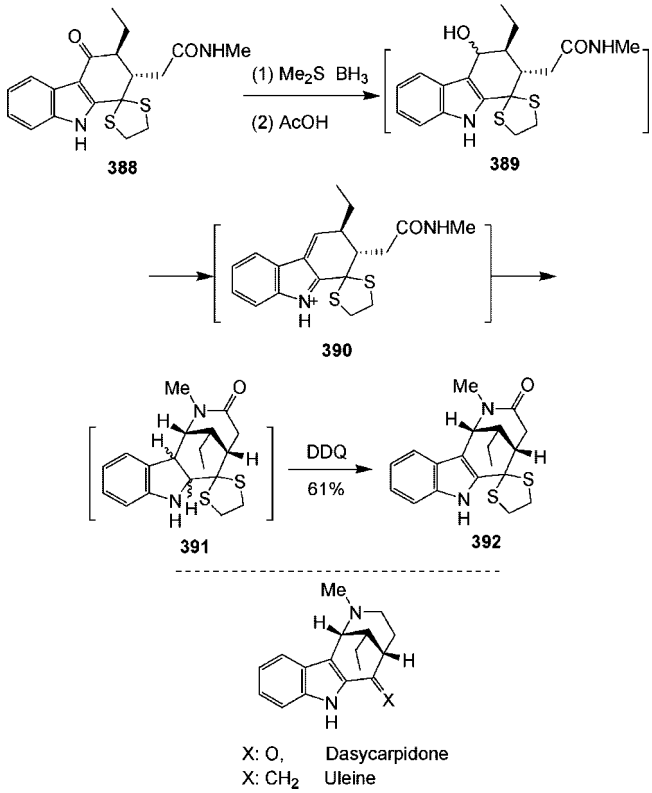
A platensimycin analog **446** was synthesized by exposure of diol **445** to a catalytic amount of $AuCl_3$ (Scheme 121).[196]

Scheme 105

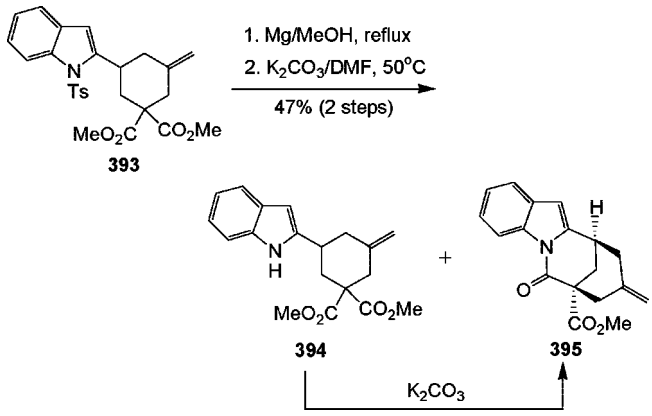


R^1	R^2	R^3	Yield, %
Me	H	H	95
H	H	H	86
H	Me	Me	67
prenyl	H	H	75

Scheme 106

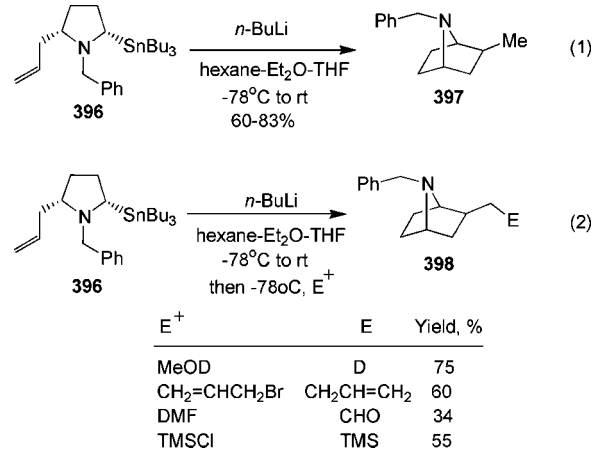


Scheme 107



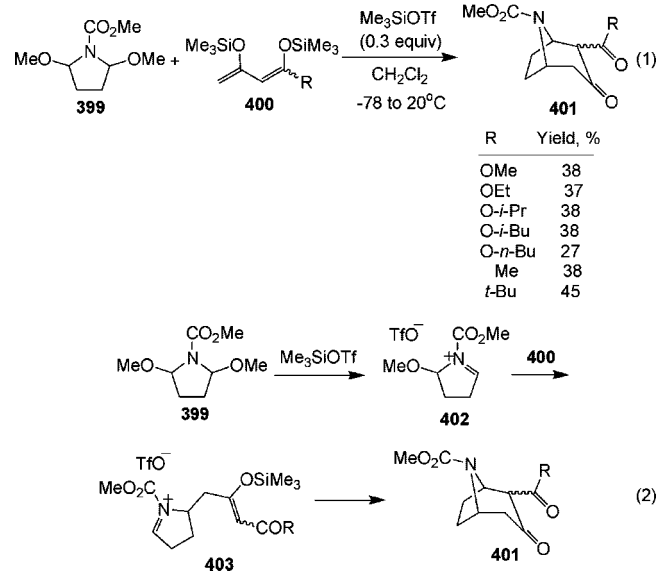
Mechanistically, the reaction involves addition of one hydroxyl group onto the metal-activated triple bond, leading to vinyl gold intermediate **447**. The resulting intermediate may then be protonolyzed, providing enol ethers **448**, which then undergoes another intramolecular addition[123] of the remaining hydroxyl group, leading to the cyclic ketal **446** (Scheme 122).

Scheme 108



E^+	E	Yield, %
MeOD	D	75
CH_2=$CHCH_2Br$	CH_2CH=CH_2	60
DMF	CHO	34
TMSCl	TMS	55

Scheme 109



R	Yield, %
OMe	38
OEt	37
O-*i*-Pr	38
O-*i*-Bu	38
O-*n*-Bu	27
Me	38
t-Bu	45

Analogously, a Au(I)-catalyzed cyclization of acetylenic diene **449** in toluene−methanol (10:1) at 25 °C, reported by Nicolaou's group, afforded a bicyclo[3.2.1] ketone **450** in 94% yield (Scheme 123).[110]

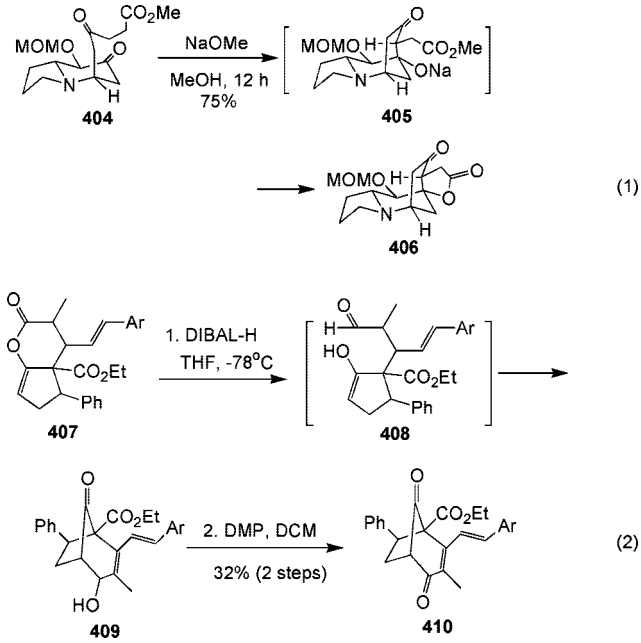
Although a radical approach toward the target molecule was nicely documented in a recent review,[193b] conjugate radical cycloaddition of bromoalcohol **451** was performed by Ghosh and co-workers[197] to access bicyclo[3.2.1] alcohols **452** and **453**, whose subsequent reactions gave bicyclic lactone **454** (Scheme 124).[198]

Another conjugate radical cycloaddition of **455** yielded the tricyclic caged framework **456** (Scheme 125).[199] This radical-mediated cyclization was proved to depend critically on the reaction temperature. An initial attempt at 100 °C gave **456** as a mixture of epimers in a 2.5:1 ratio with 75% yield, while lowering the reaction temperature to ∼65 °C improved both the yield and selectivity (81%, 4.5:1).

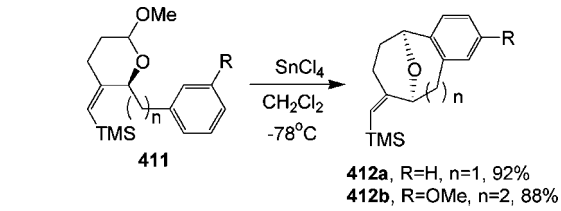
Addition to the radical cyclization, Corey and co-worker released a one-step desilylation of **457** and subsequent S_N2-type cyclization to produce **458** (Scheme 126).[200]

Analogous bicyclo[3.2.1] ring systems **460** and **461** were synthesized by Nicolaou's group via a radical cyclization process shown in Scheme 127.[201] This radical cycloaddition

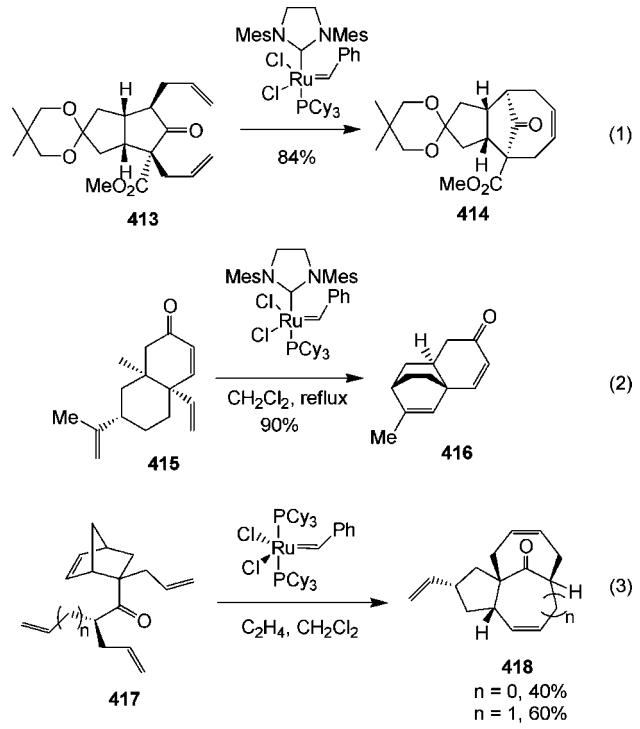
Scheme 110



Scheme 111

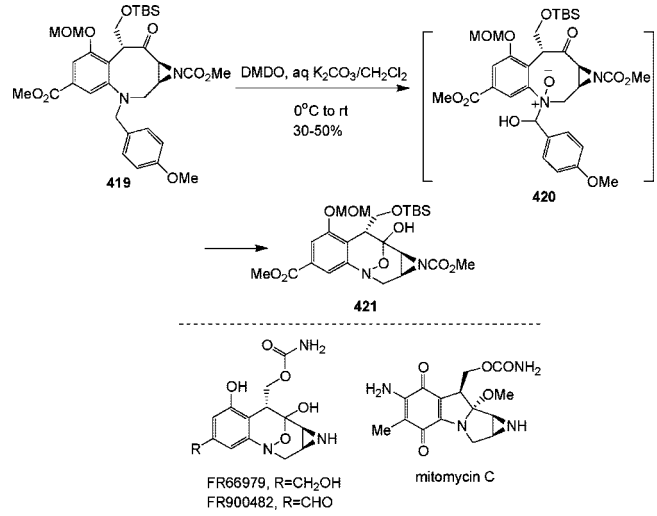


Scheme 112

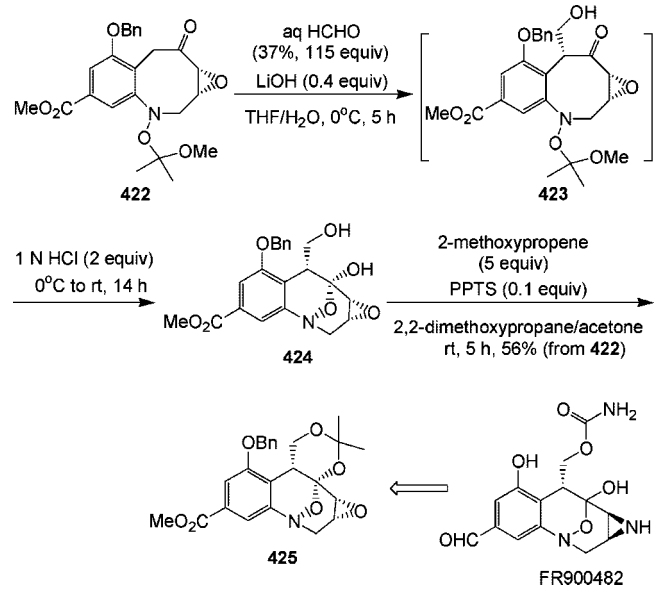


of **459** occurred by application of the sequential oxymercuration/reductive alkylation methodology pioneered by Giese.[202]

Scheme 113



Scheme 114



8.2.3. Synthesis of Tetrahydrofuran and Tetrahydropyran Ring Systems

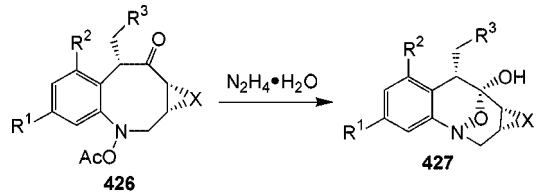
Treatment of an inseparable diastereoisomer mixture of secondary alcohol **440** with TFA led to smooth etherification, affording a cage-like structure **462** in 87% yield (Scheme 128, eq 1).[193] Analogously, the tetrahydrofuran/tetrahydropyran ring system **462** was realized from cyclization of endocyclic olefin **442** under identical conditions in the same yield (Scheme 128, eq 2).[194]

On application of Nicolaou's ether linkage condition,[193] an inseparable 1:1 mixture of diol **463** was treated with TFA in CH_2Cl_2 to effect formation of the desired ring system **464** (Scheme 129).[203] This two-step sequence afforded intermediate **464** with axial alcohol in 39% yield and the equatorial alcohol in 42% yield.

Furthermore, Nicolaou and co-workers developed another novel approach toward the tetrahydrofuran system (Scheme 130).[201] Stereoselective reduction and cycloaddition of ketone **465** resulted, upon acidic workup (1 N aq HCl), in formation of the desired cage hydroxy compound **466** in 80% yield.

Corey's group employed a bromine-promoted cyclization reaction toward the synthesis of a tetrahydrofuran ring system

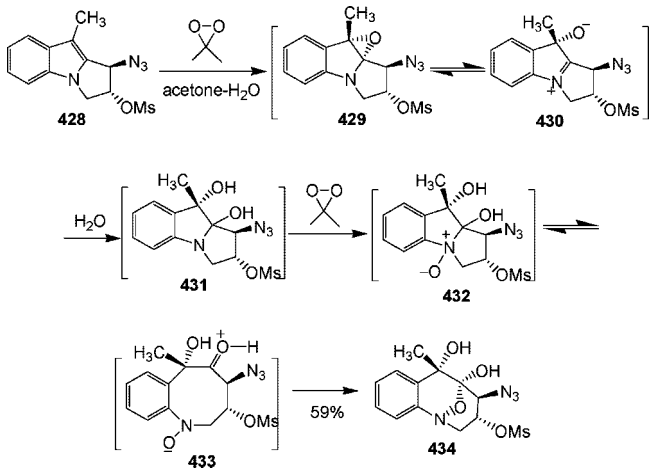
Scheme 115



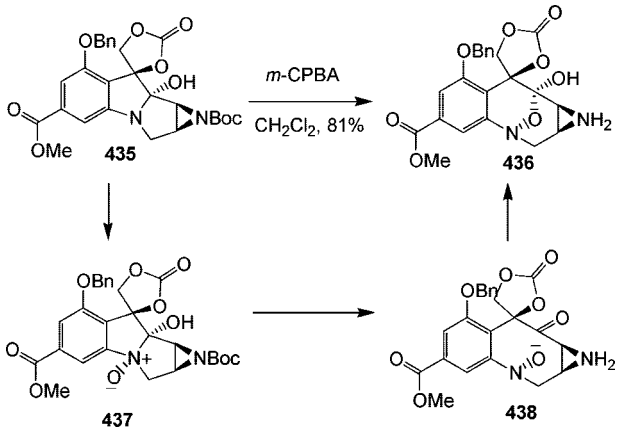
R^1	R^2	R^3	X	Yield, %
CH_2OBn	OBn	OBn	O	100
$CH(OEt)_2$	OMOM	$OCONH_2$	NPf	97

Nf = 9-phenylfluoren-9-yl

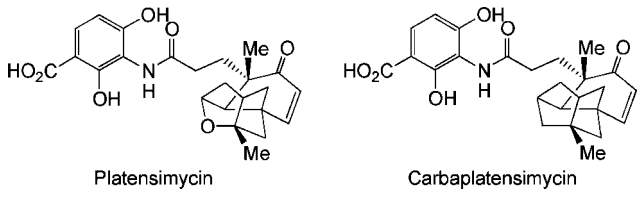
Scheme 116



Scheme 117



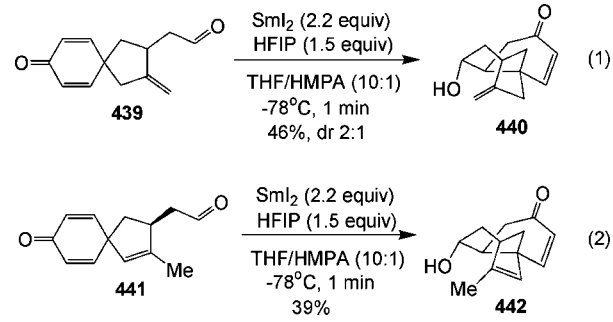
Scheme 118



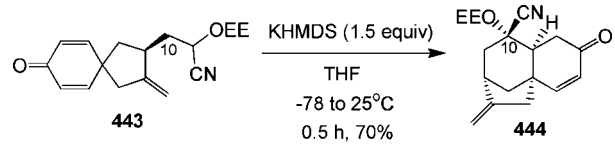
of Platensimycin (Scheme 131).[200] Conversion of phenol **467** to bromoether **468** was effected in two steps with high diastereoselectivity (>10:1 ratio) in 84% overall yield.

A radical cyclization was adopted to construct the cyclopentane ring system in carbaplatensimycin (Scheme 132).[195]

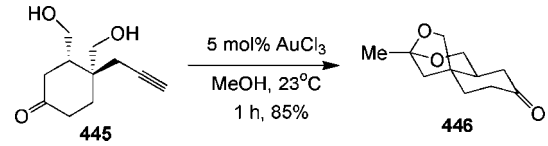
Scheme 119



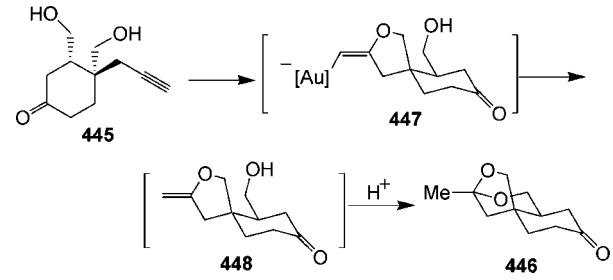
Scheme 120



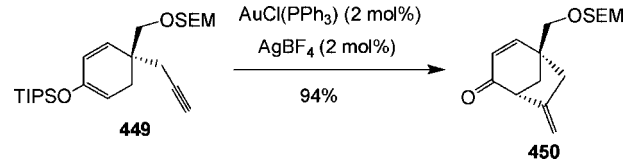
Scheme 121



Scheme 122



Scheme 123

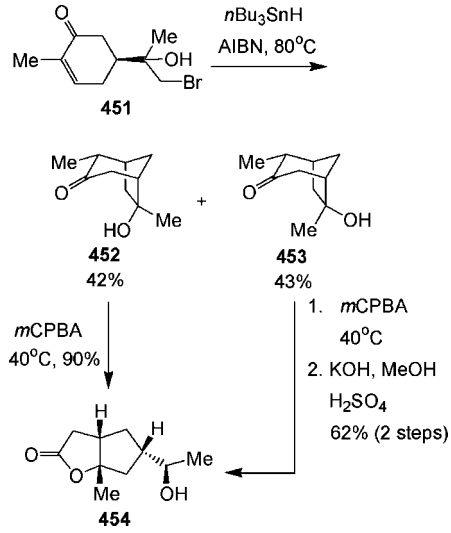


Xanthate **469** undertook a Barton−McCombie deoxygenation[204] furnishing hydrocarbon **470** in 65% yield.

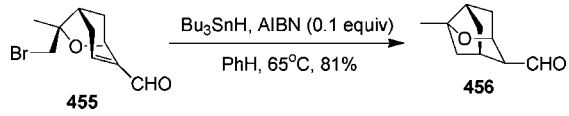
An enantioselective route to the oxatetracyclic core of (−)-platensimycin has been investigated by using an intramolecular Diels−Alder (IMDA) reaction as the key step.[205] An initial attempt with enol ether **471**, in the presence of a catalytic amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical inhibitor, provided the expected oxatetracyclic core **472** in 39% yield (Scheme 133, eq 1). Incorporating the desired methyl group on the dienophile in **473**, the desired DA cycloadduct **474** was obtained in 44% yield at 270 °C (Scheme 133, eq 2). The low yield could be due to side reactions at elevated temperature.

The use of rhodium(II)-catalyzed carbonyl ylide from diazoketone **475** was able to construct the desired ketone **477** via ylide **476** and its subsequent [3 + 2] cycloaddition reaction (Scheme 134).[206]

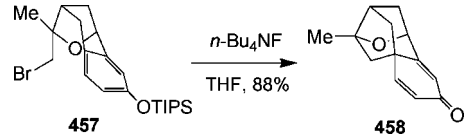
Scheme 124



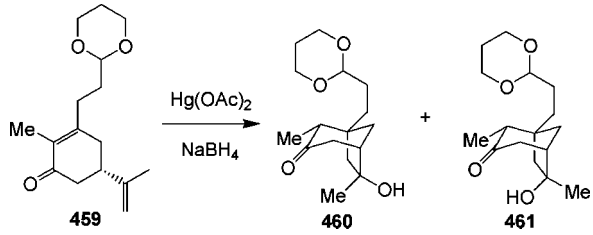
Scheme 125



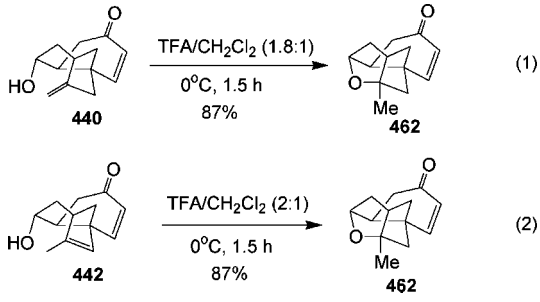
Scheme 126



Scheme 127

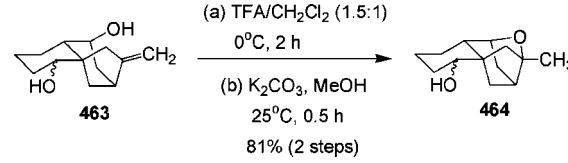


Scheme 128

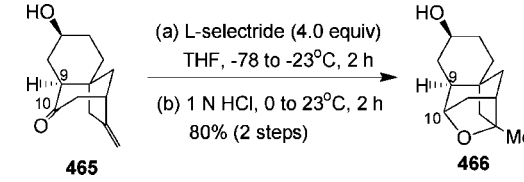


Robinson annulation was accomplished in one pot using L-proline as a chiral control element to mediate an initial intramolecular Michael addition followed by sodium hydroxide treatment to finish the aldol dehydration. The tetracyclic core structure **462** was obtained along with its C-9 epimer in a dr ratio of 5:1 (Scheme 135).[207]

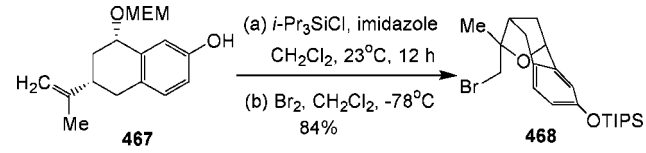
Scheme 129



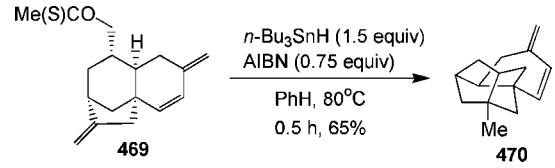
Scheme 130



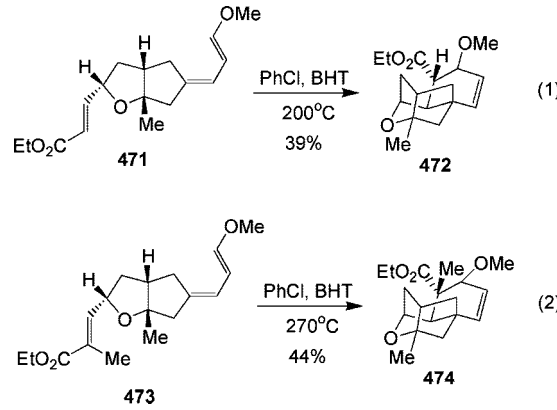
Scheme 131



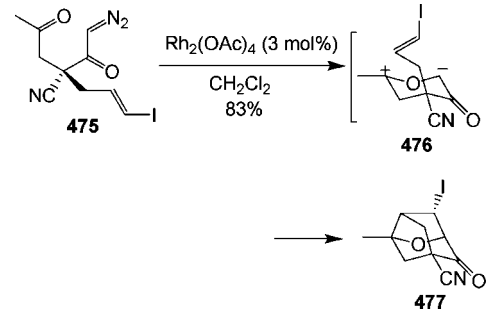
Scheme 132



Scheme 133



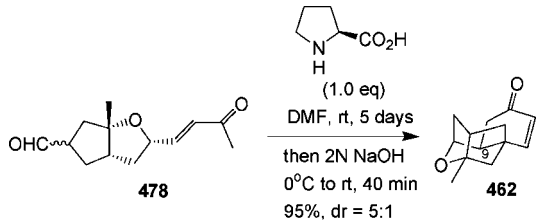
Scheme 134



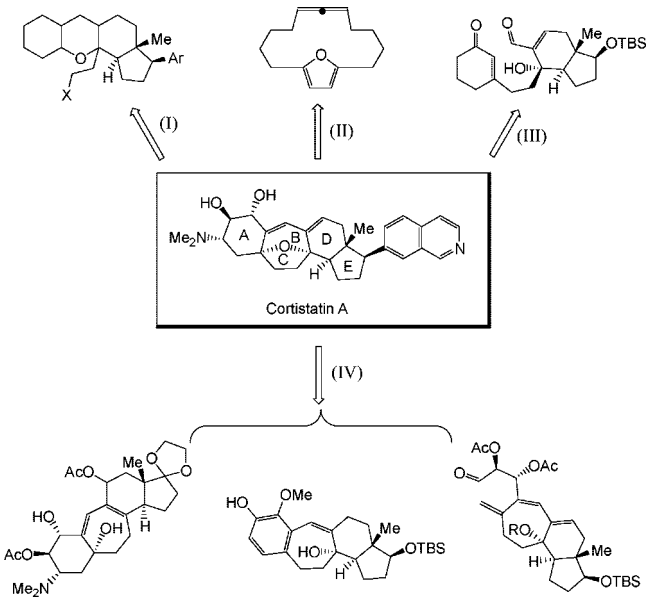
8.3. Reactions in Synthesis of Cortistatin A

Cortistatin A has received a great deal of attention from the synthetic community due to its promising biological

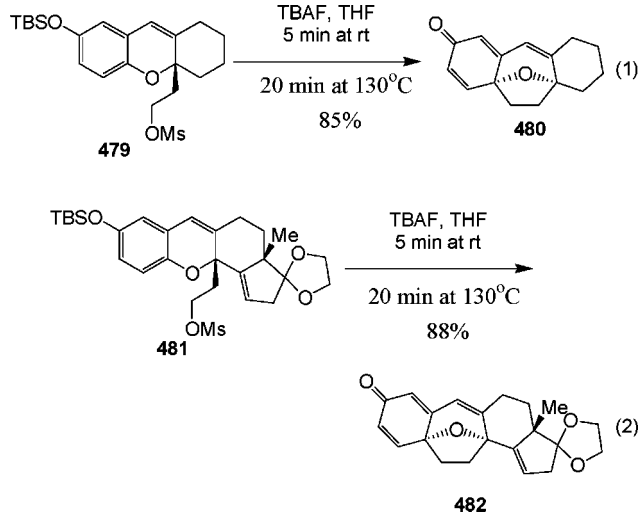
Scheme 135



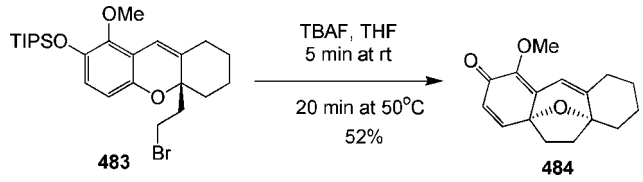
Scheme 136



Scheme 137

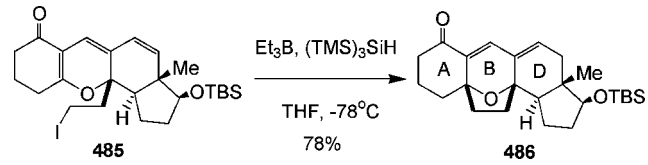


Scheme 138

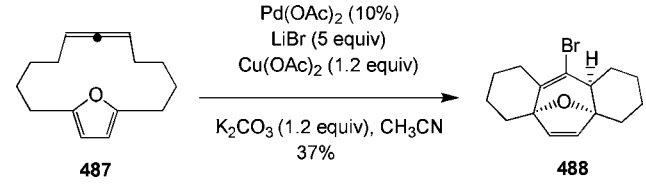


activity and unusual structural features. Since its isolation as a trace component from a marine sponge, *Corticulum simplex*, by Kobayashi in 2006,[208] numerous research groups have embarked on the synthesis of cortistatin A.[212,209] The

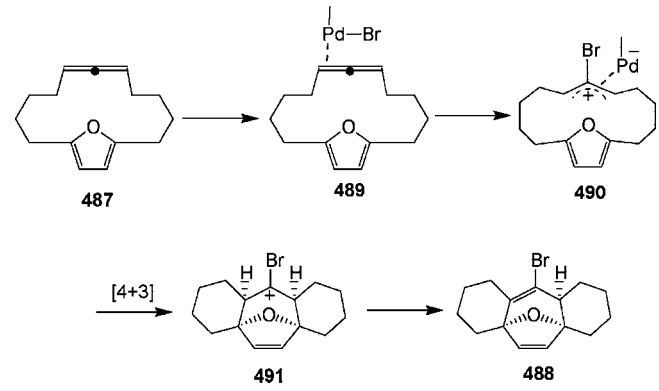
Scheme 139



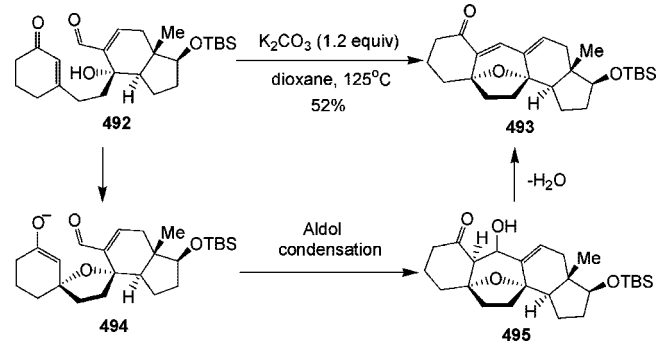
Scheme 140



Scheme 141



Scheme 142



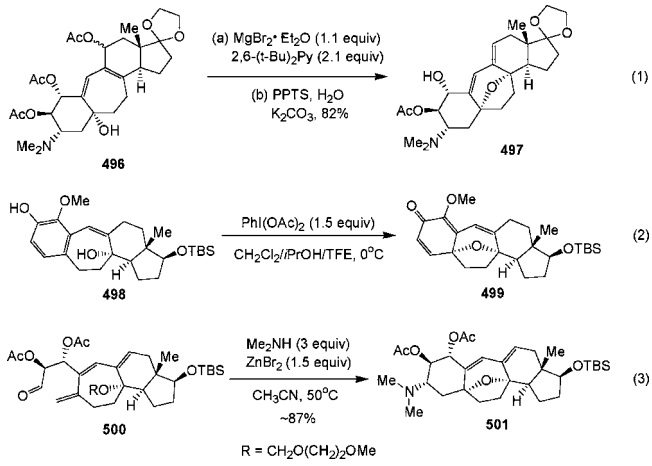
first synthesis of cortistatin A was recently achieved by Baran and co-workers.[210] Scheme 136 outlines four different synthetic pathways developed in recent years toward the construction of an ether-bridged BC ring system.

8.3.1. Synthesis of the C Ring System (Route I)

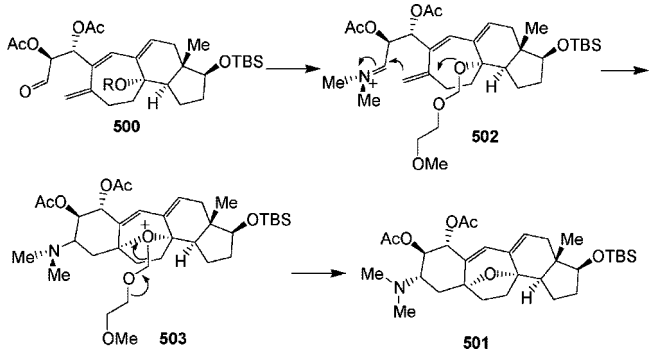
The substitute X (= OMs) in route I (Scheme 136) as a leaving group was replaced during the intramolecular alkylation, leading the desired ether-bridged tetracyclic products **480** and **482** (Scheme 137, eqs 1 and 2).[209d] Phenoxide intermediates, presumably generated by treatment of compounds **479** or **481** with TBAF at room temperature, underwent the desired alkylative dearomatization upon heating at 130 °C.

With X = Br as a leaving group, compound **483** cyclized, readily affording the ether-bridged intermediate **484** with moderate yield (Scheme 138).[209e]

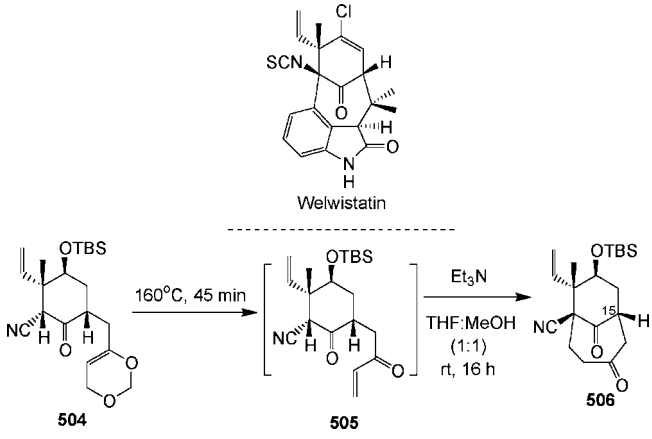
Scheme 143



Scheme 144



Scheme 145



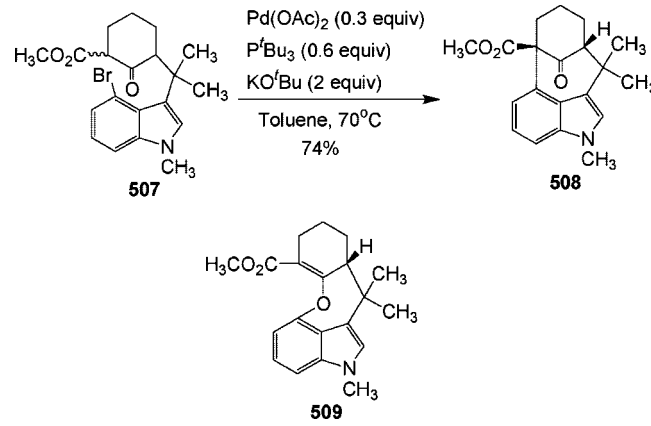
Recent studies have shown that cortistatins may protect against loss of vision.[211] Yamashita et al. employed a conjugated radical cycloaddition of iodo compound **485** to synthesize the framework of cortistatin A (Scheme 139).[212] This one-step reaction was conducted in the presence of Et_3B and $(TMS)_3SiH$ in THF, furnishing the C ring of pentacyclic compound **486**.[213]

8.3.2. Synthesis of the ABD Ring System (Route II)

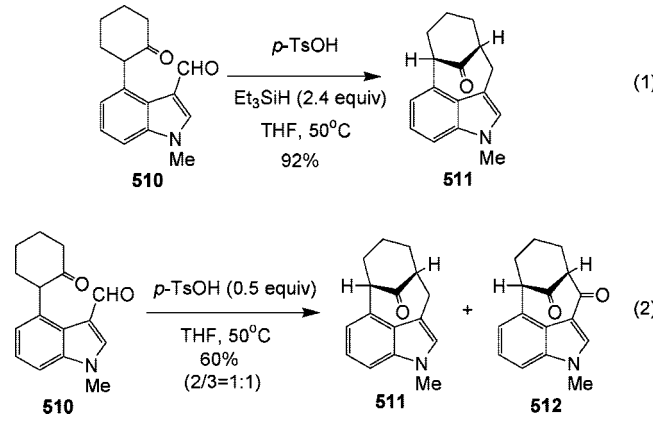
Synthesis of the ABD ring system **488** was effected by treatment of macrocycle **487** with $Pd(OAc)_2$ in the presence of LiBr in 37% yield (Scheme 140).[209h]

This palladium-mediated [4 + 3] cycloaddition occurs through a mechanism depicted in Scheme 141.[209h] The initial

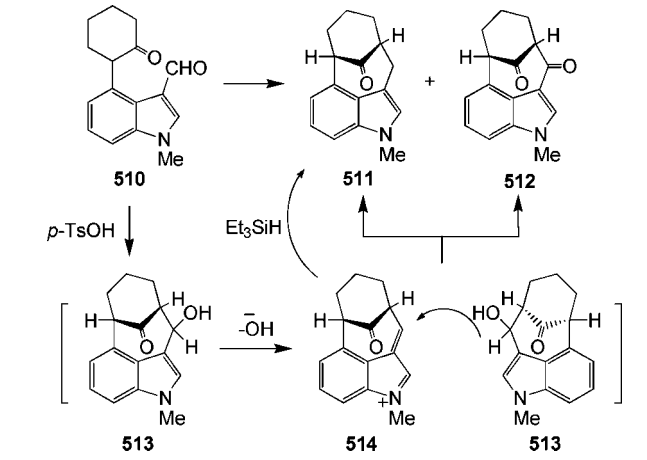
Scheme 146



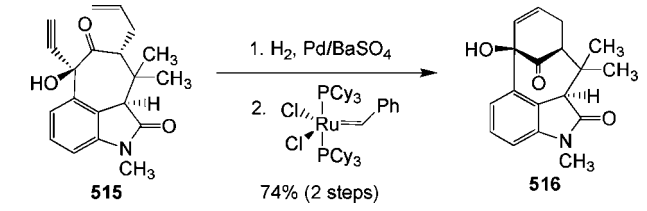
Scheme 147



Scheme 148



Scheme 149



(allene)palladium complex **489** produces a σ-allylpalladium intermediate, which rapidly equilibrates to the corresponding (π-allyl)palladium intermediate **490**. Intramolecular nucleophilic attack by the furan ring gives the [4 + 3] cycloaddition

product **491**, which loses a proton in the presence of potassium carbonate to lead to the desired ABCD ring system **488**.

8.3.3. Synthesis of the BC Ring System (Route III)

Nicolaou and co-workers designed a 1,4-hydroxy addition/aldol/dehydration cascade process providing the desired BC ring system **493** upon heating hydroxy enone−enal **492** at reflux in dioxane in the presence of K_2CO_3 in 52% yield (Scheme 142).[209a] The ether-bridged product **493** was produced through two intermediates, **494** and **495**, generated presumably from conjugate addition and Aldol condensation, respectively.

8.3.4. Synthesis of the BC Ring System (Route IV)

The BC ring system in cortistatin A can be assembled through route IV as described in Scheme 136. A mild S_N1-type cyclization mediated by Lewis acid to close the final ring of the cortistatin skeleton was accomplished by Baran's group (Scheme 143, eq 1).[210] A mild alkylative dearomatization was realized under oxidative conditions (Scheme 143, eq 2).[209b] In the event, a key pentacyclic core **499** was synthesized via a tandem oxidative dearomatization/cyclization in the presence of hypervalent iodine $PhI(OAc)_2$. An enantioselective synthesis of the ABC ring system of cortistatin A has been achieved by Shair and co-workers using a highly diastereoselective aza-Prins cyclization coupled with transannular etherification (Scheme 143, eq 3).[209g]

Scheme 144 describes the plausible reaction mechanism involving an intermediate **503**, generated by aza-Prins cyclization coupled with transannular etherification. Oxonum ion release from **503** affords pentacyclic **501**. Experimental evidence supports this sequence of events rather than MEM deprotection preceding aza-Prins cyclization.[209g]

8.4. Reactions in the Synthesis of Welwistatin and Analogues

The synthesis of welvistatin poses a significant synthetic challenge because of its unique four-ring compact chemical structure.[214] An approach to the total synthesis of the antimicrotubule agent welwistatin is described by Funk's group.[215] A key transformation of dioxin **504** into bicyclo[4.3.1] decanone **506** involves an intramolecular conjugate addition reaction with no indication of competing epimerization at C(15) (Scheme 145).

In an attempt to synthesize the *N*-methylwelwitindolinone skeleton, an efficient and convergent synthesis of the core bicyclo[4.3.1]decane ring system of welwitindolinones was developed by Rawal and co-workers.[216] A key step in the synthesis includes an intramolecular palladium-catalyzed enolate arylation of bromoindole derivative **507** to create the desired bicyclic skeleton **508** (Scheme 146). Interestingly, the *O*-arylated vinyl ether **509** was not observed.

An aldol-type intramolecular condensation in the presence of triethylsilane allows the transformation of α,β-unsaturated aldehyde **510** to the bridged indole **511**, an intermediate in the synthesis of welwitinodonlinone alkaloid skeleton (Scheme 147, eq 1).[217] In contrast, this aldol-type ring-closure reaction of **510** in the absence of triethylsilane generated a mixture of cyclohexanone-bridged indoles **511** and **512** (Scheme 147, eq 2).[217]

This acid-mediated transformation of **510** to the bridged indole **511** can be illustrated in Scheme 148.[217] Dehydration of the alcoholic intermediate **513** leads to iminium species **514**, whose subsequent interaction with **513** by hydride transfer gives product **511** along with α,β-unsaturated ketone **512** in a 1:1 ratio. In the presence of external hydride source (Et_3SiH) the iminium **514** is reduced to **511** in high yield.

In addition, a key intermediate **516** that contains the complete carbon framework of welwitindolinone was synthesized by means of RCM with Grubbs' catalyst (first generation) (Scheme 149).[218]

9. Concluding Remarks

The recent syntheses of bridge-containing organic compounds have great accomplishments as a result of the most modern synthetic methods derived from total syntheses of natural products and pharmaceutical intermediates or APIs. Subsequent transformations of bridged ring systems, in turn, have a huge impact on the organic syntheses, especially on those of asymmetric synthetic tasks. The design of general methods for obtaining enantiopure compounds and, in particular, extension of the most efficient methods described to asymmetric synthesis, with special attention on transition-metal-catalyzed reactions, continues to be of great interest for synthetic chemists. As expected, exploration of expedient and environmentally benign synthetic methods remains as the main challenge for the synthetic community.

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