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Recent applications of hetero Diels-Alder reaction in total synthesis of natural products

Majid M. Heravi*, Tahereh Ahmadi, Mahdieh Ghavidel, Bahareh Heidari, Hoda Hamidi

Department of Chemistry, Alzahra University, Vanak, P.O. Box 1993893973, Tehran, Iran

Abstract

The synthetic utility and potential power of Diels-Alder (D-A) reaction in organic chemistry is evident. These significances have been extended to the synthesis of plethora and wide variety of heterocyclic compounds via [4+2] cycloaddition reactions, so called hetero Diels-Alder (HDA) reaction. In this work we try to focus on the scope and preparative synthetic applications of HDA reaction as a key step in total synthesis of natural products.

Keywords: Hetero Diels-Alder reaction (HAD)), Intramolecular Hetero Diels-Alder reaction, (IMHDA), Natural products, Total synthesis, Asymmetric synthesis.

Contents

1. Introduction

Since the discovery of the Diels–Alder reaction (DA) by Otto Diels and Kurt Alder in 1928,[1] increasing appreciable attempts and endeavors have been made by devoted to developing this useful methodology in different features, aspects, and issues. Undoubtedly, one of the most alluring and significant development was the discovery and establishment of hetero-Diels–Alder (HDA) cycloaddition. It happens when the underlying concept is applied to other π-systems,

such as carbonyls and imines to provide the corresponding heterocyles. This reaction was first conducted between aldehydes and dienes in an asymmetric fashion.[2-5] Imines can also employed as dienophiles in hetero Diels-Alder reactions. Similar to the D-A reaction, these reactions also involve the lowest unoccupied molecular orbital (LUMO) of the imine. It means that imines bearing electron-withdrawing groups on nitrogen are the most reactive[6]. This transformation is very interesting since two newly generated bonds have the potential of being stereochemically controlled. In 1982, Danishefsky and his group discovered new types of HDA reactions using unactivated aldehyde and a diene, catalyzed by Lewis acid.[7] Since then, several research groups have been concentrating on this area since the dihydropyranone products can be obtained from the reaction of an aldehyde with appropriate dienes. Pyran derivatives as a moiety are present in several natural products. The pivotal role of HDA reactions in the construction of heterocyclic scaffold can be translated to the synthesis of wide variety of heterocycles even with moderately complex structures.[8] Noticeably, the HDA reactions generally proceed with high regio- and diastereoselectivity (generating to 4 contiguous chiral centers in a single step) and moderate to excellent de and chemical yields and.[9, 10]

In recent years, intramolecular hetero-Diels–Alder (IMHDA) reactions have been employed extensively in organic synthesis, as a matter of fact chiefly due to their and stereocontrolled nature.[11-14] These reactions allow the construction of two or more rings simultaneously in a single step, escaping sequential chemical conversions.[15] HDA reaction is a pericyclic reaction. These reactions are of especial interest due to their broad preparative importance in the chemistry of pharmaceuticals and naturally occurring compounds.[16] Intramolecular hetero Diels–Alder (IMHDA) reactions seemed to be a versatile protocol for the construction of new polycyclic systems, which were fruitfully used in the design of framework for some naturally occurring products and biologically active compounds.[17-19]

Due to these features, HDA reaction expectedly has been the subject of numerous reviews[20, 21] and books[10, 22] and have been extensively employed as key steps in the synthesis of several complex organic molecules.[23-32]

Perhaps the most important feature of HDA is its asymmetric versions. It gives chemists the power and ability to generate, up to four adjoining stereogenic centers in single step. This can be achieved via different strategies such using either optically active dienes or hetero dienophiles. Alternatively, either chiral catalysts,[33] or chiral auxiliaries.[34, 35] Asymmetric HDA reactions

provide accessibility to chiral heterocyclic compounds in a similar. These chiral heterocyclic compounds can be the desired synthetic targets themselves or being highly functionalized intermediates which can be used in the synthesis more complex molecules including natural products. In the kingdom of plants and their power to biosynthesize biologically interesting compounds, asymmetric synthesis is a rule. Very recently, the asymmetric HDA reactions have been extensively reviewed.[20] We are interested in heterocyclic chemistry.[36-44] In addition, we are also keen on asymmetric synthesis[45-49]. We recently have been engaged in reviewing the applications of name reactions in total synthesis of natural products.[50-59] Very recently, we have published on the applications intramolecular Diels-Alder (IMDA) reaction in total synthesis of natural products.[60] Armed with these experiences, herein, we try to underscore the applications of HDA reaction in total synthesis of naturally occurring compounds, exhibiting biological properties.

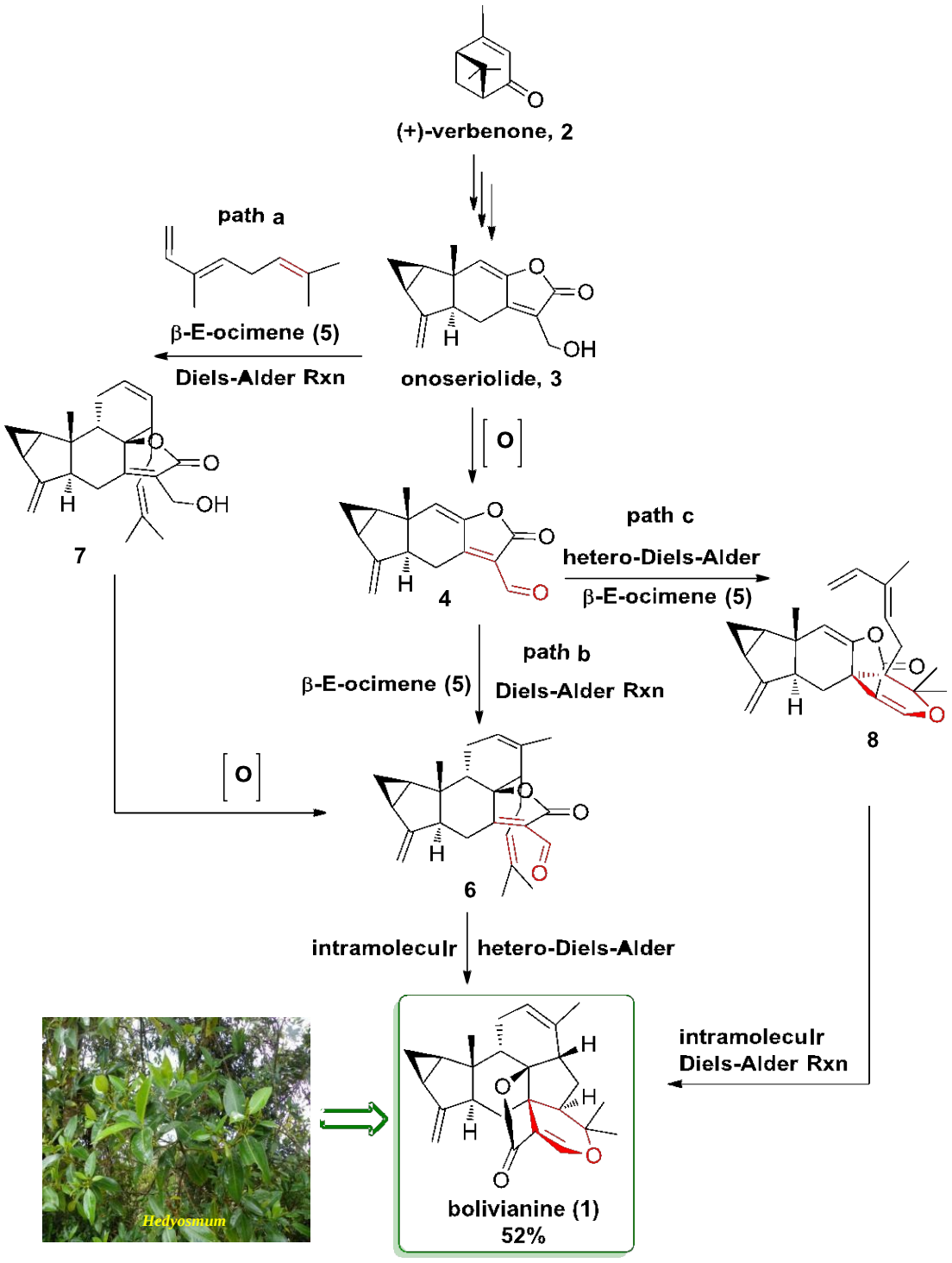
2. Applications Hetero Diels-Alder reaction in total synthesis

2.1. Intramolecular hetero Diels-Alder (IMHDA) reaction

In 2007, Jullian and his coworkers isolated the structurally complex sesterterpenoid and bolivianine, from *Hedyosmum angustifolium* (Chloranthaceae), along with another product named isobolivianine.[61] Bolivianine bears a conspicuous heptacyclic framework and nine chiral centers. The convolution of this molecule has made it a fascinating candidate for biosynthesis and chemical synthesis. Jullian's research group suggested a hypothesis for its biosynthesis. As depicted in scheme 1, the enal **4** could be provided via allylic oxidation of onoseriolide, a lindenane-type sesquiterpenoid that takes place together with bolivianine in H. *angustifolium*.[62-64] Synchronized hydrolysis of **4** followed by nucleophilic attack on geranylpyrophosphate (GPP). Ultimately, intramolecular IMHDA reaction gives bolivianine.

Encouraged by this proposition and considering its steps, the total synthesis of bolivanine in a 14-step reactions was designed. That involved the synthesis of onoseriolide **3**. Market purchasable (+)-verbenone (**2**) was chosen as stating material molecule for the synthesis of onoseriolide **3**. The total synthesis includes a Pd-catalyzed intramolecular cyclopropanation involving an allylic metal carbene followed by a DA/IMHDA tandem reaction, letting a one-step assemblage of a tricyclic system having appropriate configuration.

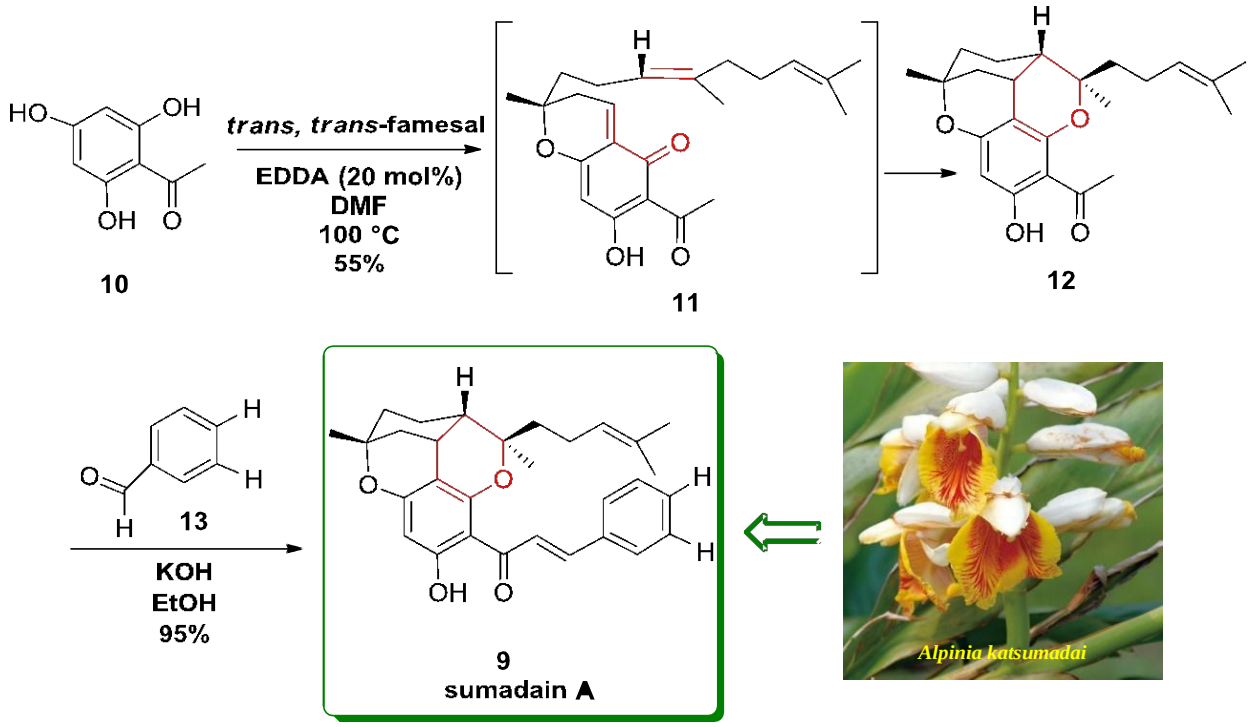
A different route has also been envisaged for the total synthesis of onoseriolide and bolivianine, based on the modification of aforementioned hypothesis (scheme 1). β-E-ocimene (**5**), a natural monoterpene created from GPP in vivo, **4** is present in H. *angustifolium*.[65] Initially, onoseriolide (**3**) was reacted with **5** to give compound **7**, which also was oxidized in vivo to compound **6** and ultimately yield bolivianine (**1**) (path a). On the other hand, initial oxidation of onoseriolide (**3**) could furnish **4**, which could couple with **5** to yield bolivianine (**1**), via either a sequential cascade DA/IMHDA, cycloaddition (path b) or a HDA/IMDA reaction pathway (path c).[66]



Scheme 1

Polycycles having citran or cyclol nuclei are wide spread in nature.[67, 68] They show a wide range of biological and pharmacological activities.[69, 70] As part of research program focused on isolation of bioactive compounds from plants in China, in 2008 a sesquiterpene-chalcone

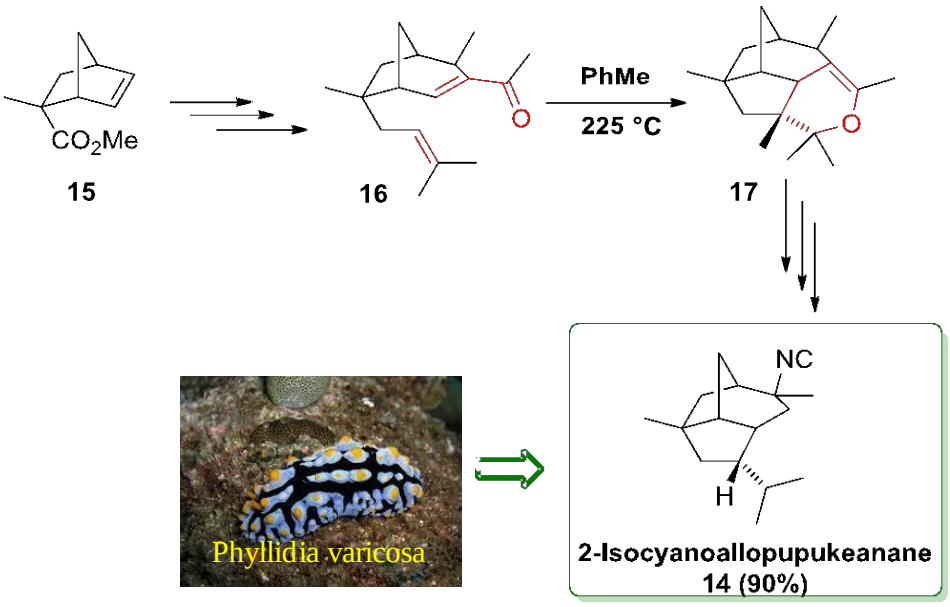
conjugated sumadains A (**9**)[71] with citran and chalcone frameworks were isolated from *Alpinia katsumadai*. This plant has been used as an antiemetic agent for centuries in folk Chinese medicine for the treatment of stomach disorders and it was remarkably has been registered and also coded in the Chinese pharmacopeia. A concise and efficient approach was reported for the total synthesis of **9**. This strategy using a sequential reaction including the domino aldol-type reaction/ electrocyclization/H-migration/HDA reaction, which eventually resulted in the fruitful synthesis of sumadain A (**9**). Using this protocol, the first total synthesis of sumadain A (**9**) was achieved. Scheme 2 illustrates a brief synthetic strategy leading to sumadain A (**9**). Treatment of 2,4,6-trihydroxyacetophenone (**10**) with trans, transfarnesal in 20 mol% ethylenediamine diacetate in DMF under thermal conditions gave adduct **12** in satisfactory yield. The transformation of **12** to sumadain A (**9**) was successfully achieved by aldol condensation.[72]



Scheme 2

The isocyanopupukeananes are classified as a new family of marine sesquiterpenes. 9-Isocyanopupukeanane was isolated from *Phyllidia varicosa* acquired.[73] 2-9-isocyanopupukeanane also possesses the same framework.[74] Shortly after these isolations 9-isocyanoneopupukeanane[75] and 2-isocyanoallopupukeanane (**14**)[76] isomers as biogenetically related to the isocyanopupukeananes were provided by rearrangement routes.

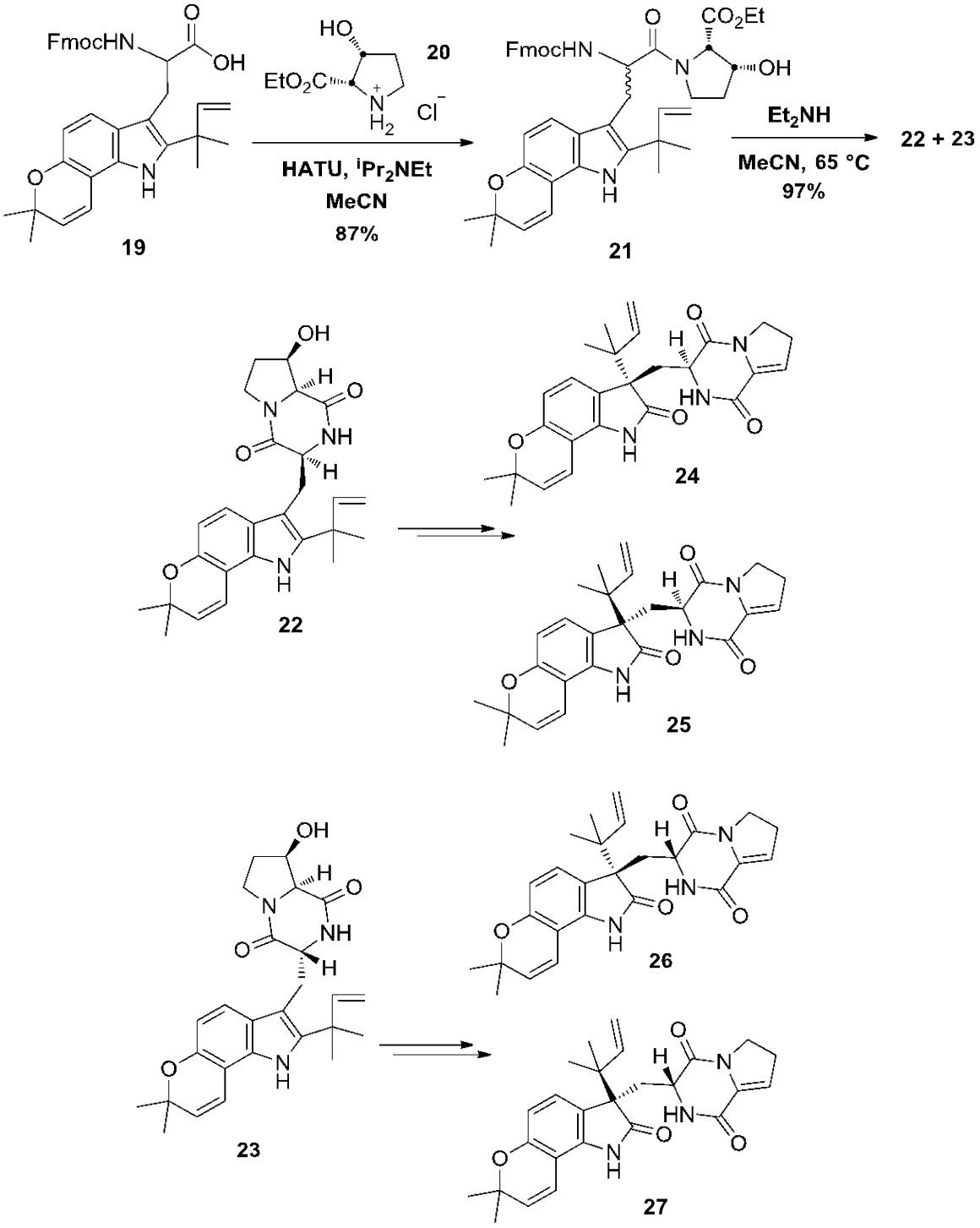
The total synthesis of 2-isocyanoallopupukeanane (**14**) has been successfully achieved. This approach gives **14** as a racemat, starting from methyl 2- exo-methylbicyclo-[2.2.1]hept-5-ene-2-endo-carboxylate **15** which is subjected to dibromocarbene addition with subsequent S_N2' substitution followed by chain elongation, to provide the unsaturated ketone **16**. The latter is subjected to an IMHDA reaction, as a key step to give, **17** which is comprising all the skeletal carbon atoms. The dihydropyran unit was then cleaved via ozonolysis to give the tricarbocyclic intermediate which in seven further steps to elaborate this sophisticated total synthesis resulting in the formation of desired target **14**.[13] The reaction pathway is illustrated in scheme 3.



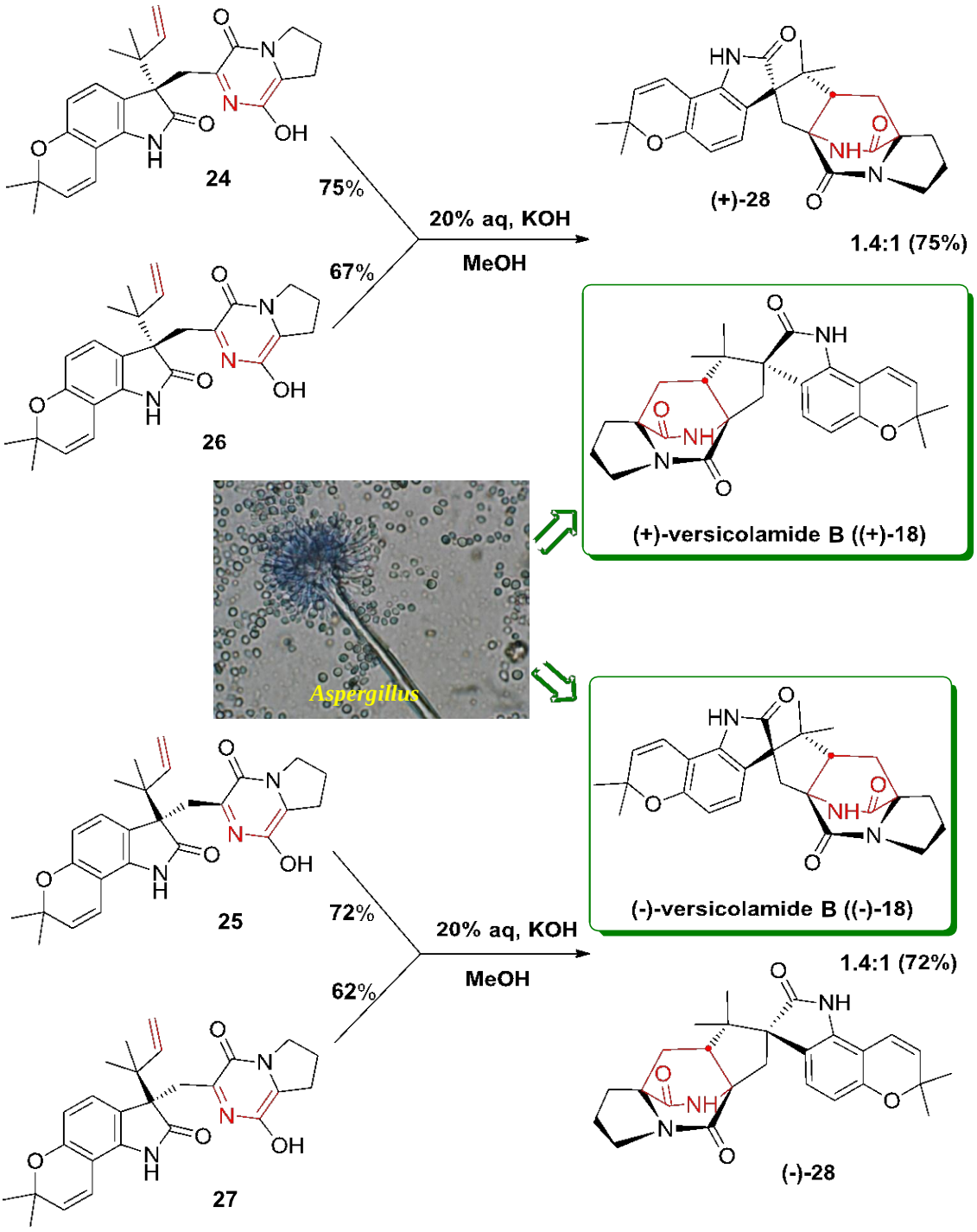
Scheme 3

Many related fungi within the *Aspergillus* genus gives several metabolites of opposite absolute configuration, such as)+(or (−)-versicolamide B. These alkaloids are proposed being produced via biosynthetic Diels–Alder reactions, entailing that each *Aspergillus* species possesses enantiomerically divergent Diels–Alder reaction product. Experimental endorsement and support of these biosynthetic proposals via employing of the IMHDA reaction as a crucial step in the asymmetric total syntheses of (+)- and (−)-versicolamide B has been investigated. Operational validation proof of the suggested biosynthetic HDA construction, combined with the secondary metabolite profile of the producing fungi, discloses that each *Aspergillus* species has grown enantiomerically discrete indole oxidases, as well as enantiomerically discrete Diels–Alderases.

In this line, the laboratory operation commenced with the already known protected amino acid **19**, Coupling reaction of **19** with (R)-cis-3-hydroxy-L-proline (**20**) afforded the amide **21**, with simultaneous cyclization gave the easily separable dioxopiperazines **22** and **23** (scheme 4). Having the compounds **22** and **23** in pure form in hand, the oxidation of the indole C2-C3 double bond and HDA cycloaddition to complete the synthesis was contemplated. The enamide **24** or **26** was simultaneously underwent HDA reaction to give a mixture of (+)-versicolamide B ((+)-**18**) and the diastereomer (+)-**28**. In the same way, the enamide **25** or **27**, under similar reaction conditions, gave a mixture of (−)-versicolamide B ((−)-**18**) and (−)-**28** (scheme 5).[77]



Scheme 4



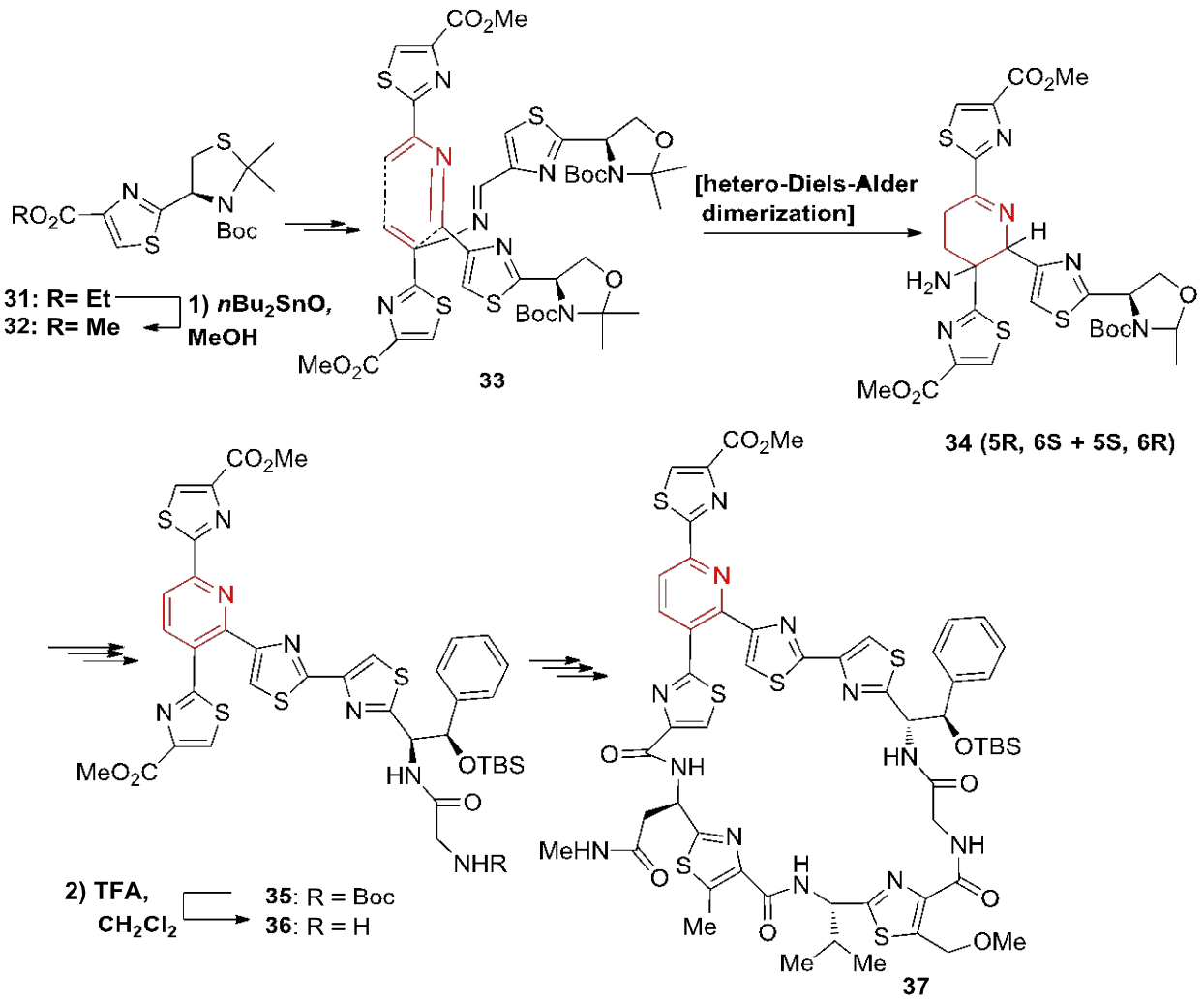
Scheme 5

The thiazolyl peptide antibiotics was initially isolated from *Planobispora rosea* ATCC53773. They showed selective anti-bacterial activity via inhibition of the bacterial elongation factor Tu, and not the eukaryote elongation factor-1 alpha.[78] The full structural elucidation of GE2270A

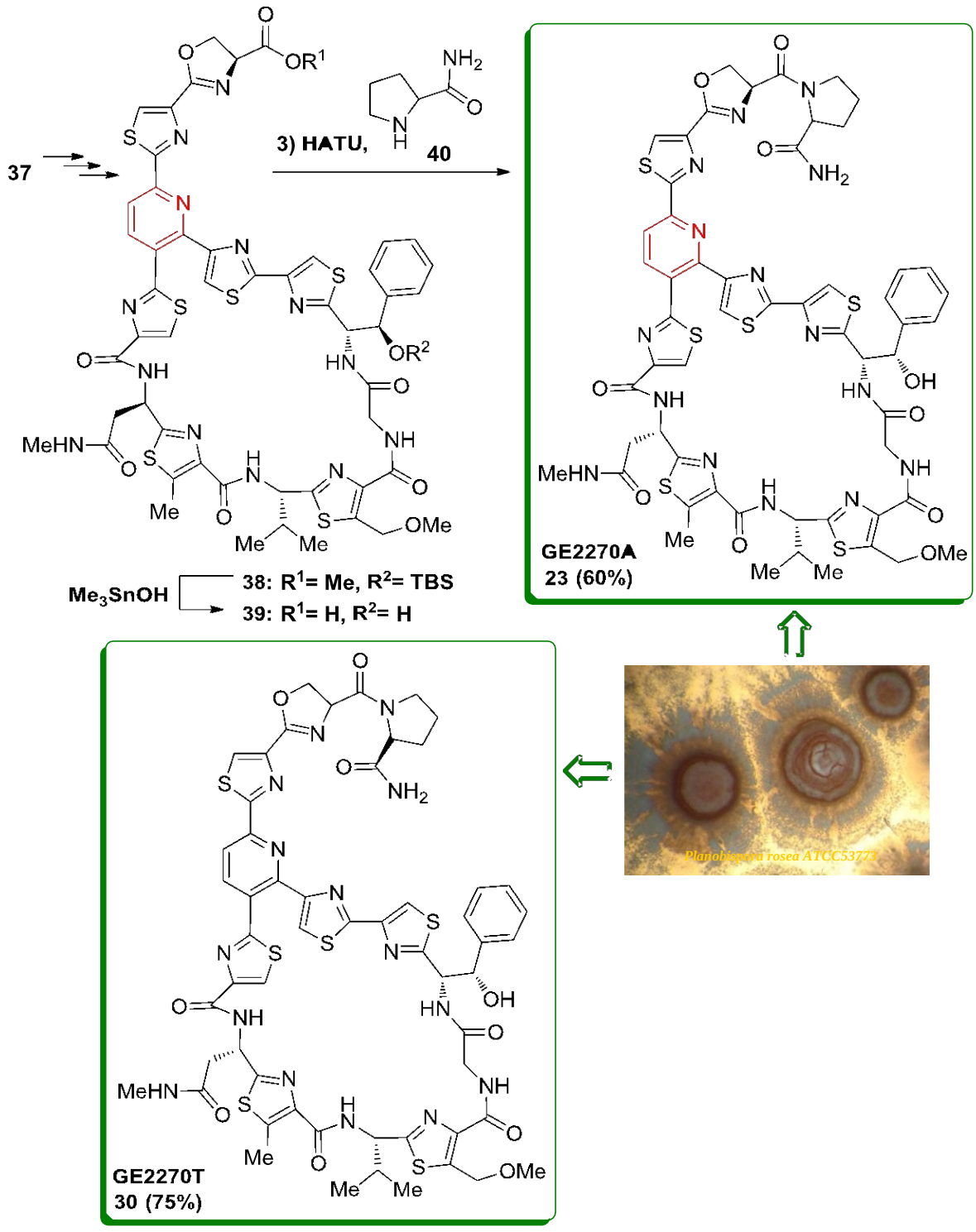
(**29**) has been revealed via the outstanding endeavors of Tavecchia et al,[79] and of Heckmann and Bach research group.[80, 81] Besides, synthetic investigation toward the GE2270 factors were also accomplished and reported by Bach[80-82] and Shin's coworkers.[83, 84]

An efficient and relatively concise total synthesis of GE2270A (**29**) and GE2270T (**30**) via a convergent protocol that utilizes a HDA/dimerization process[85, 86] as a key step to construct the trithiazolyl pyridine core of the molecule, has been achieved and reported.

In this approach, the thiazole derivative **31**, previously synthesized,[85] was transformed into its methyl ester **32** in 84% chemical yield via a facile ester exchange.[87, 88] The species **33** found being quite transitory and provided under the reaction conditions. After hydrolysis, the latter was subjected to HDA cycloaddition/dimerization to give, the amino dehydropiperidine segment **34** in satisfactory yield, albeit as a 1:1 mixture of trans diastereoisomers.[85] The Boc group was then cleaved off from this intermediate in the presence of TFA in CH_2Cl_2. This permitted its elongation to the glycine derivative **35** and **36** in 90% overall yield finally cleavage of the newly introduced Boc group (TFA), which was further extended to the macrocycle **37** (scheme 6). In fact, reaction of **39** with L-proline amide **40** mediated by HATU and iPr_2NEt gave GE2270A (**29**) in 60% overall yield staring from **38**. The generated intermediate oxazoline **38** run into along the way to form **29** which was also transformed into GE2270T (**30**) as depicted in Scheme 7.[89]



Scheme 6

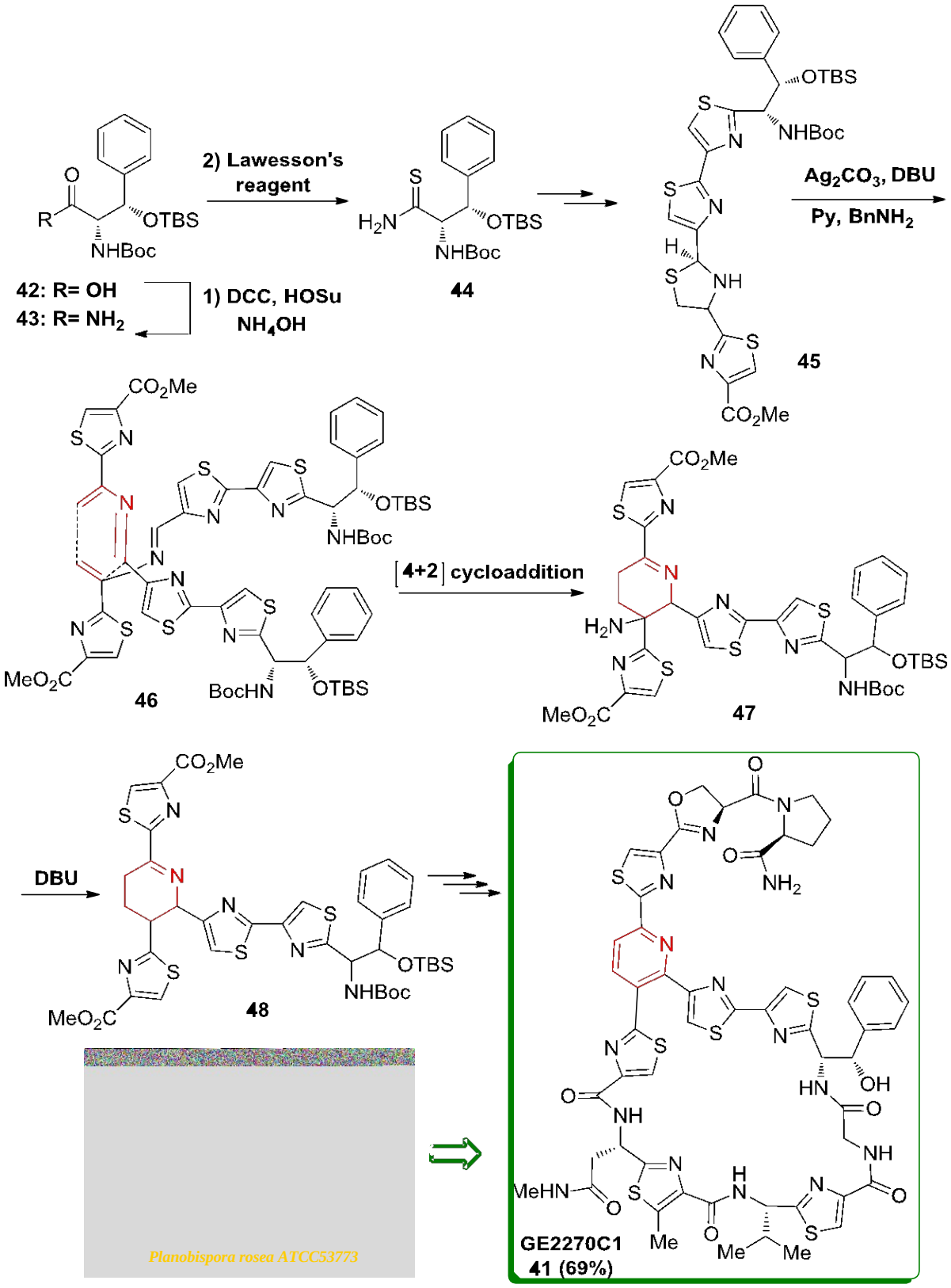


Scheme 7

The total syntheses of the thiopeptide antibiotics GE2270A, GE2270T, GE2270C1 (**41**) have been successfully by Nicolaou group in Scrript research center in San Diego Cal USA. The

innovative synthetic protocol used the HDA cycloaddition reaction for the construction of the pyridine core of the desired molecules and based on a macrolactamization process to build up the macrocycle.[90]

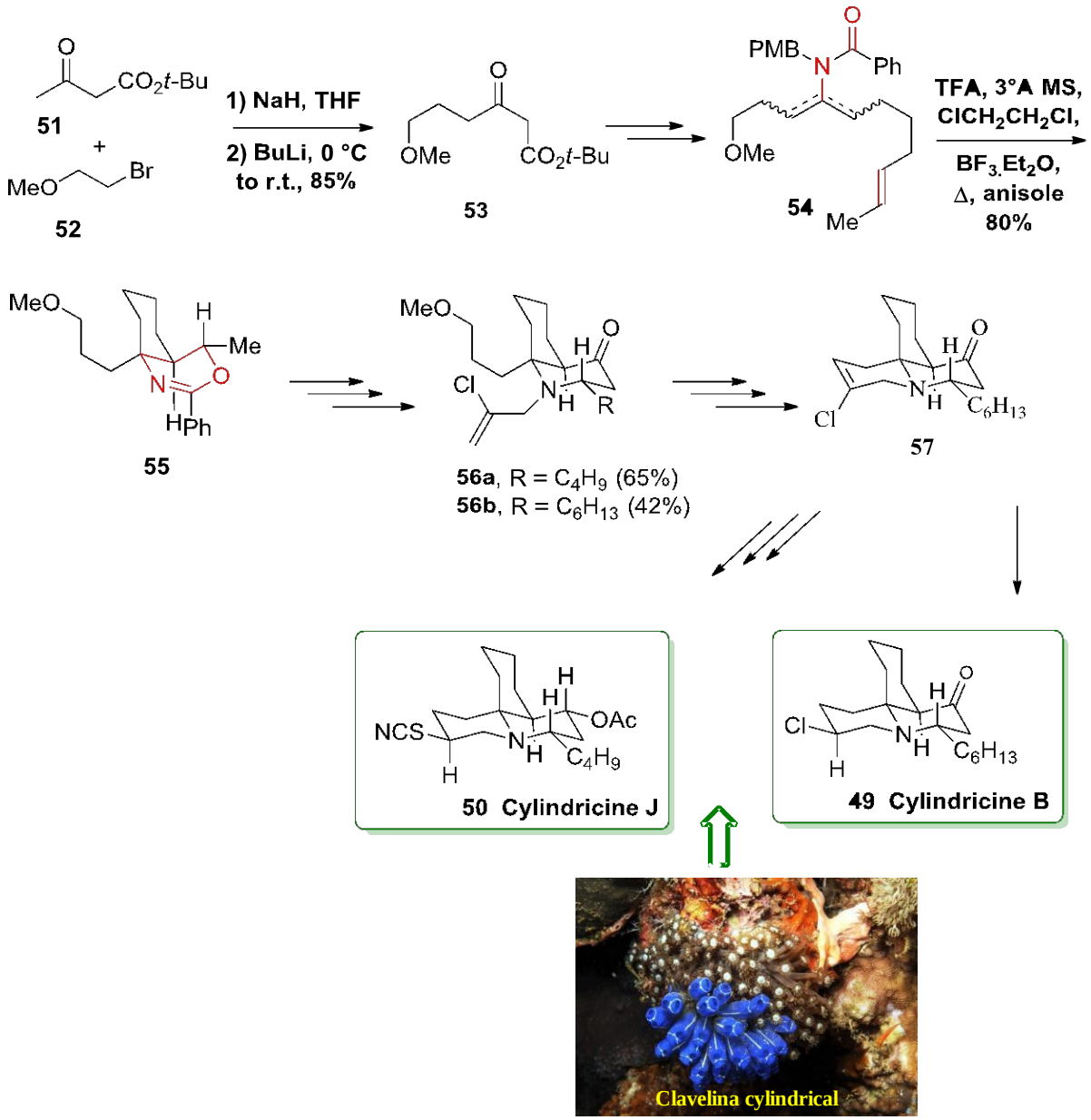
Of especial interest it was the possibility of modifying the HDA reaction downstream in order to shorten the sequence for the total synthesis of the tetrathiazole pyridine core segment **48** by several steps. In particular, an approach involving introduction of the hydroxyl phenylalanine subunit into the HDA precursor resulted in a strategy with more diversity. In this way the [4 +2] dimerization step could be conducted on such a particularized system. In fact, this idea was examined in the laboratory (Scheme 8). Therefore, conversion of phenylalanine derivative **42** into its amide **43** (DCC, HOSu, NHOH) with treatment of the latter with the Lawesson reagent resulted in thioamide **44** in excellent yield over the two steps. After several steps thiazolidine **45** in 78 % was obtaine from **44**. Delightfully, precursor **45** underwent into the desired D-A/dimerization cascade under optimized conditions (Ag_2CO_3, DBU, BnNH, py), thus giving the desired dehydropiperidine system **47** via the intermediacy of heterodiene **46**. Ultimately, sequential deamination/aromatization of dehydropiperidine **47** was promoted with DBU in refluxing ethyl acetate to complete the total synthesis of tetrathiazole pyridine **48** (33 % yield). The total synthesis of GE2270C1 (**41**) by these modified protocols, are called, complex HDA dimerization (synthesis of compound **48**; Scheme 8).[90]



Scheme 8

In the 1990s, Blackman and his coworkers reported the isolation of a small family of structurally related tricyclic alkaloids from the ascidian *Clavelina cylindrica*, which was found and collected from the east coast of Tasmania.[91-93] The major components of the alkaloidal extracted and isolated were identified as cylindricines A and B (**49**). Their structures were unambiguously elucidated by spectral analysis, and secured by X-ray crystallography of the corresponding picrates. Accordingly, it was found that cylindricine B have a C-ring-extended pyrido-[2,1-j]quinoline system.

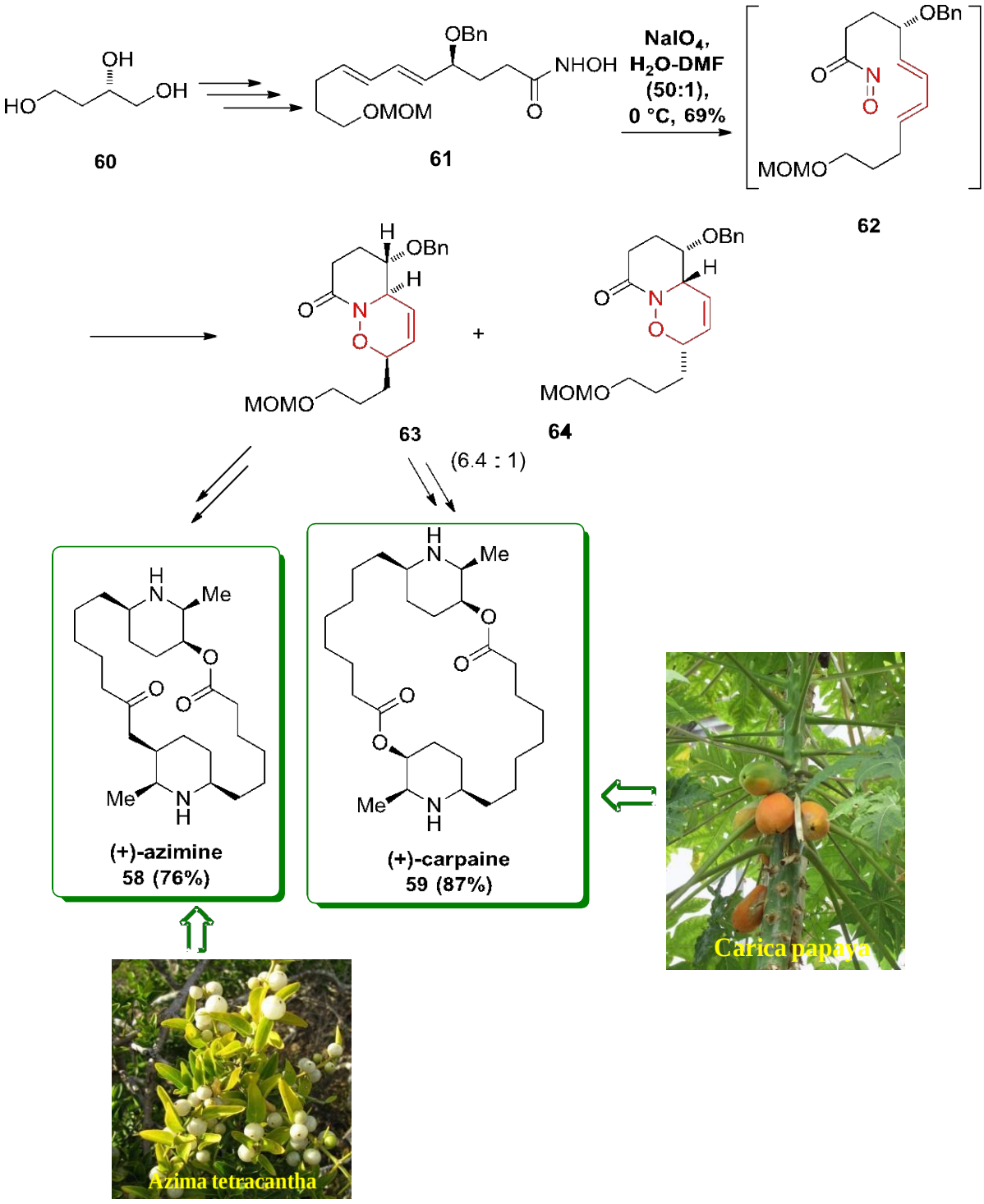
For total synthesis, the required precursor for the crucial HDA step, tert-butyl acetoacetate, was chosen which was transformed to the Weiler dianion with subsequent alkylation with bromoethyl methyl ether to give **53** in satisfactory yield.[94] The latter was then converted intermediate **54**, in two steps using following the previously procedure.[95] In the following was treated enamide **54** with TFA in dichloroethane at ambient temperature for relatively long period of time, with subsequent heating mediated by BF_3/Et_2O and anisole, resulting in the expected 3,5-dihydrooxazine cycloaddition product **55** as a single diastereoisomer in satisfactory chemical yield. In 2003, a strategy for the construction of the tricyclic pyridoquinoline framework of cylindricines B (**49**) and J (**50**) has been established based on use of HDA[95] and vinyl chloride RCM protocols.[96] Now determination of the C(2) stereochemistry of the key bicyclic intermediates **56a** and **56b** was intended. Ultimately, this diene was exposed into the second generation Grubbs ruthenium catalyst resulted in RCM product **57** in 36% yield over unoptimized conditions (Scheme 9). When the configuration was found correct for the cylindricines, the conversion of these compounds into the natural products via appropriate functional group manipulations was contemplated, designed and successfully achieved.[97]



Scheme 9

Azimine (**58**)[98] and carpaine (**59**),[99, 100] were initially isolated from *Azima tetracantha* L. and *Carica papaya* L., respectively and being the new family of macrocyclic dilactones comprising a 2,3,6-trisubstituted piperidine scaffold, and carpaine is reported to show a wide scope of biological activities as well as antitumor activity at even low concentrations.[101] Synthetic potency in this field has led into the preparation of azimic acid[102, 103] and carpamic acid[104, 105] both as racemat and enantiomeric forms. However, there has been only a single report

concerning with the synthesis of the macrocyclic dilactone family of alkaloid, carpaine (**59**), developed, and present jointly by Corey and Nicolaou.[106, 107] In connection with studies on natural product, synthesis on the acylnitroso-DA protocol,[108-110] the enantioselective total syntheses of (+)-azimine and (+)-carpaine have been developed and reported. The synthesis started with (*S*)-1,2,4-butanetriol (**60**) as a single source of chirality (Scheme 10). Oxidation of **61** using $NaIO_4$ in aqueous medium[111] at 0 °C, the in situ created acylnitroso compound **62** which underwent IMHDA reaction afforded a 6.4:1 mixture of the trans and cis adducts (with respect to H4a and H5) **63** and **64** in 69% overal yield. The trans stereochemistry given to the major isomer **63** was relied on the ^{1}H NMR coupling constant of 8.8 Hz for two vicinal protons at C4a and C5 in an axial-axial organization. The final reactions resulted in the target azimine (**58**) and (+)-carpaine (**59**).[112]

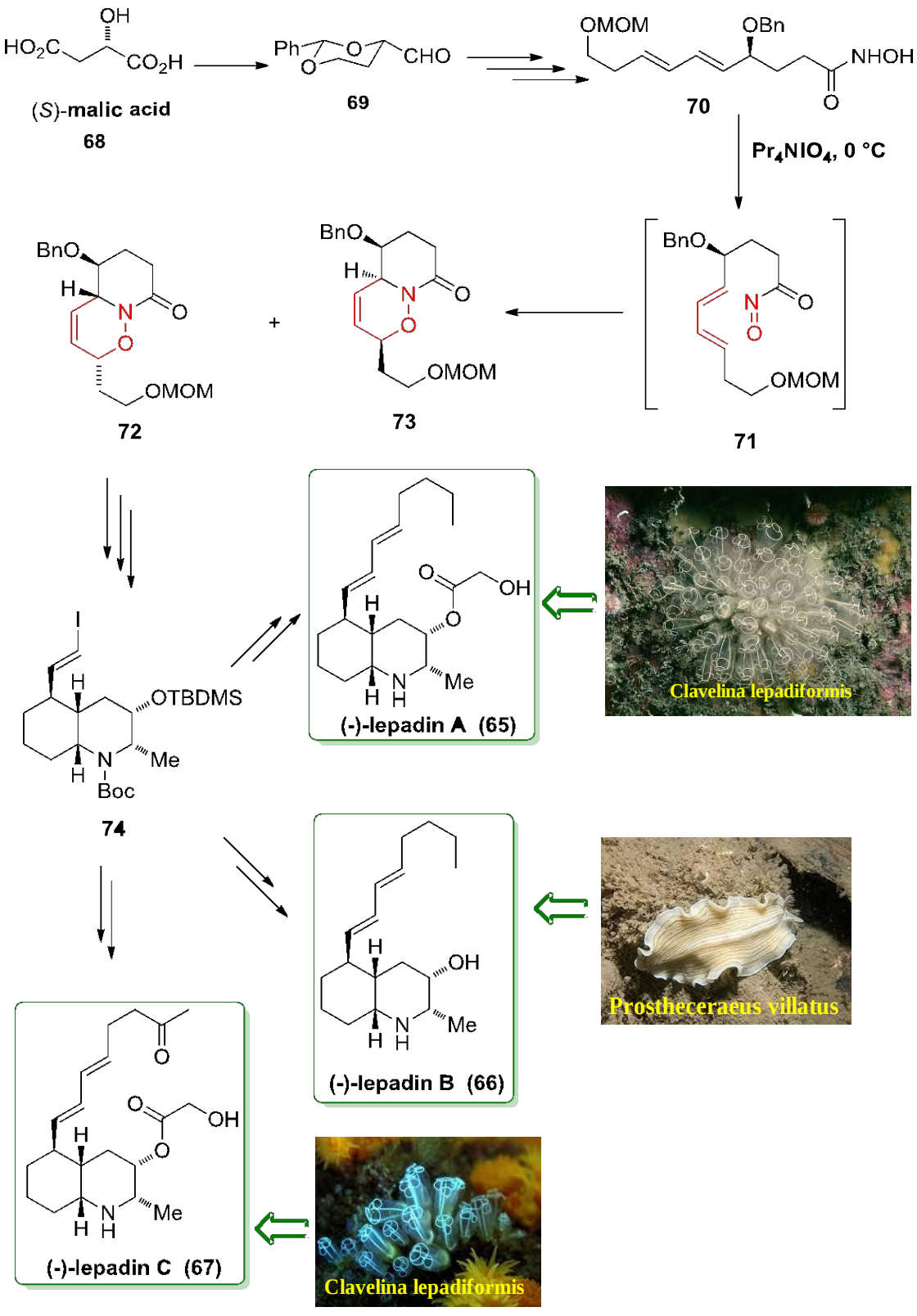


Scheme 10

Lepadin A (**65**) was initially isolated by Steffan[113] and his coworkers in 1991 from the tunicate *Clavelina lepadiformis* collected in the North Sea. As a matter of fact, this is the first species of a

decahydroquinoline alkaloid from a marine natural source. Later, similar related compounds, lepadins B (**66**) and C (**67**), along with lepadin A have been observed in the predatory flatworm *Prostheceraeus villatus* and its tunicate prey C. *lepadiformis*.[114] Lepadins A (**65**) and B (**66**) have demonstrated remarkable in vitro cytotoxicity toward human cancer cell lines.[114] Literature survey showed no reports regarding the total synthesis of lepadins A and C. However, in 1999 Toyooka and Takahata research group[115] has successfully accomplished and reported the total synthesis of the natural enantiomer of lepadin B, which resulted in approval of the suggested relative configuration and confirmed the absolute stereochemistry of this aforementioned alkaloid.

As depicted in the scheme 11, the synthesis commenced from Horner-Emmons reaction of **69**. Oxidation of **70** using tetrapropylammonium periodate (Pr_4NIO_4) under common nonaqueous conditions led to, in situ creation of acylnitroso compound **71**. The latter was subjected to IMHDA cycloaddition reaction to afford the *trans*-oxazino lactam **72** as a chief isomer, albeit in very low diastereoselectivity of 1.7:1. The obtained (E)-alkenyl iodide **74**, after several steps imposed on **72**, played a key role as intermediate in the synthesis of the lepadin alkaloids. (-)Lepadin C (**67**) can undergo coupling reaction whereas (-)-lepadins A (**65**) and B (**66**) can be subjected into the Suzuki cross-coupling reaction.[116]



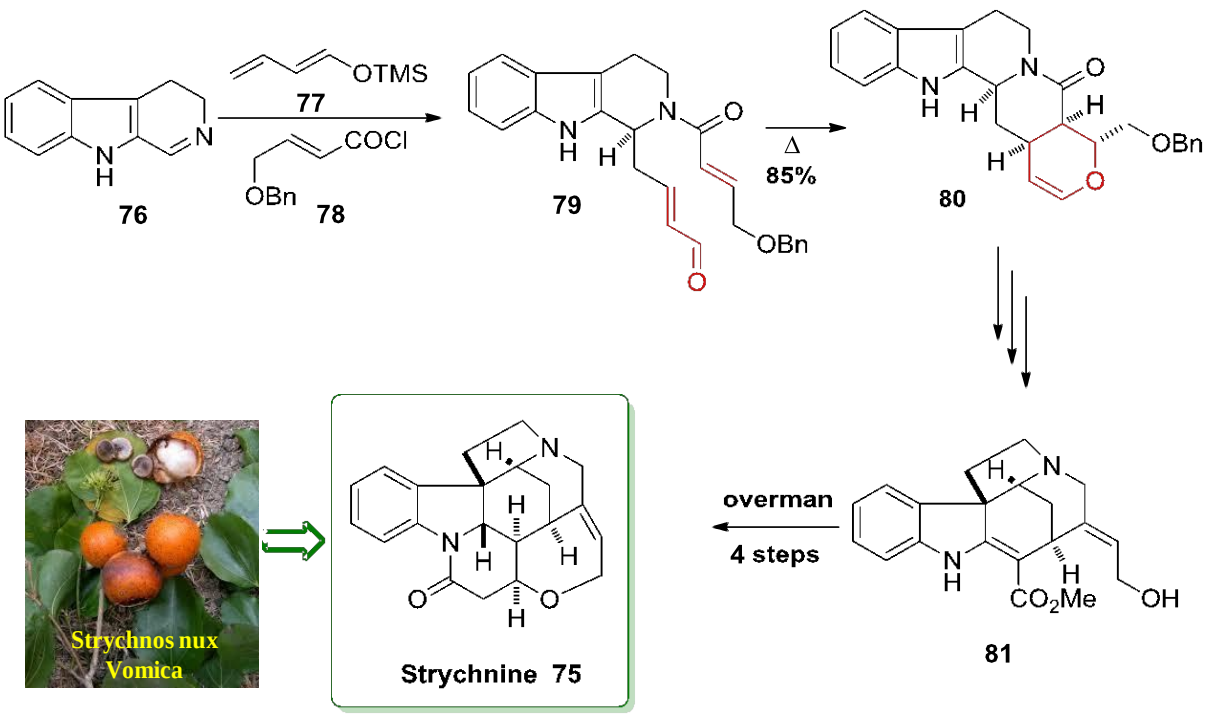
Scheme 11

Strychnine (**75**), which is found in abundantly in the Indian poison nut (*Strychnos nux Vomica*) and Saint Ignatius' bean (*Strychnos ignatii*), is one the most notorious indole alkaloids.[117-119] The well-known toxicity of strychnine is consequences of its interaction with the strychninesensitive glycine receptor in the lower brain stem and the spinal cord, hence disorderly normal nerve cell signaling and leading to overexcitation. Socrates, the renowned philosopher was forced to commit suicide by syrup of *Strychnos nux Vomica*. In 1818, strychnine was initially isolated in pure form by Pelletier and his coworkers.[120] Robinson, in 1946 initially suggested the actual structure of strychnine via an extensive degradative analysis.[121, 122] A year Woodward also independently proposed the same structure and announced strychnine as the most complex compound known for its molecular size.[123, 124]

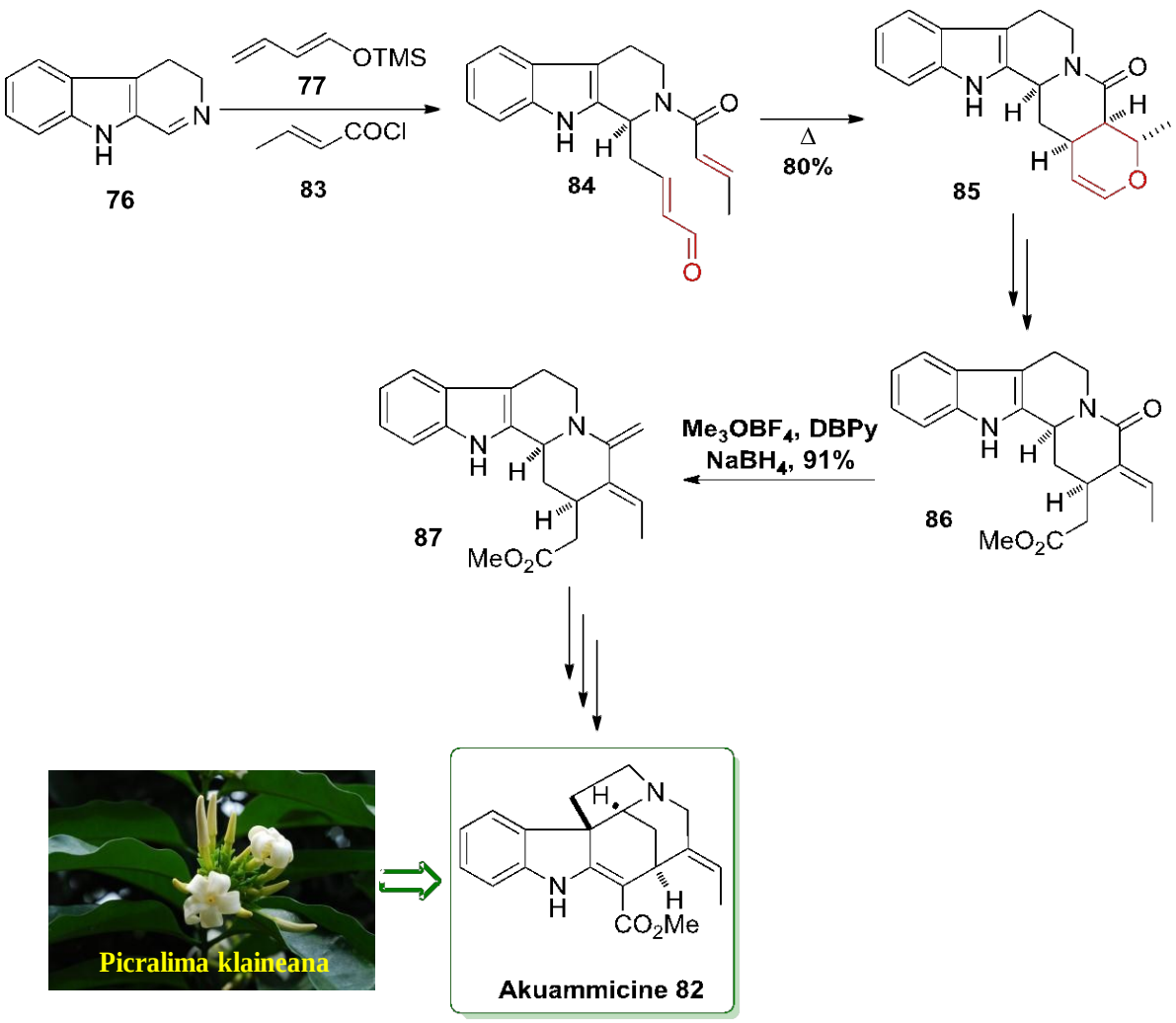
IMHDA reaction of **79** gave **80** which was transformed into **81** in four steps,[125, 126] The synthetic **81** thus can be converted into **75**, which its spectral data (^{1}H NMR, ^{13}C NMR, IR) was compared to those of identical an authentic sample and found being identical (scheme 12).

The related alkaloid akuammicine (**82**) was initially isolated from the seeds of *Picralima klaineana*,[127] and its structure shortly was elucidated.[128, 129]

The total synthysis of **82** has been accomplished and reported. The strategy involves the vinylogous Mannich reaction of **76** with 1-trimethylsilyloxybutadiene to afford **84** which subjected into the IMHDA reaction of **84** provide **85**. In this way, thereby assembling the pentacyclic heteroyohimboid framework was assembled in just four steps starting from tryptamine (Scheme 13).[130] Before, to test of the feasibility of mimicking biosynthetic routes in accordance to Scheme 1, it was initially essential to convert **85** into **86** and **87**. In fact, deformylgeissoschizine (**87**) is a key intermediate in several syntheses of the *Corynanthe* alkaloids. Accordingly, the feasibility of converting **87** directly into **82** was evaluated.[131]



Scheme 12



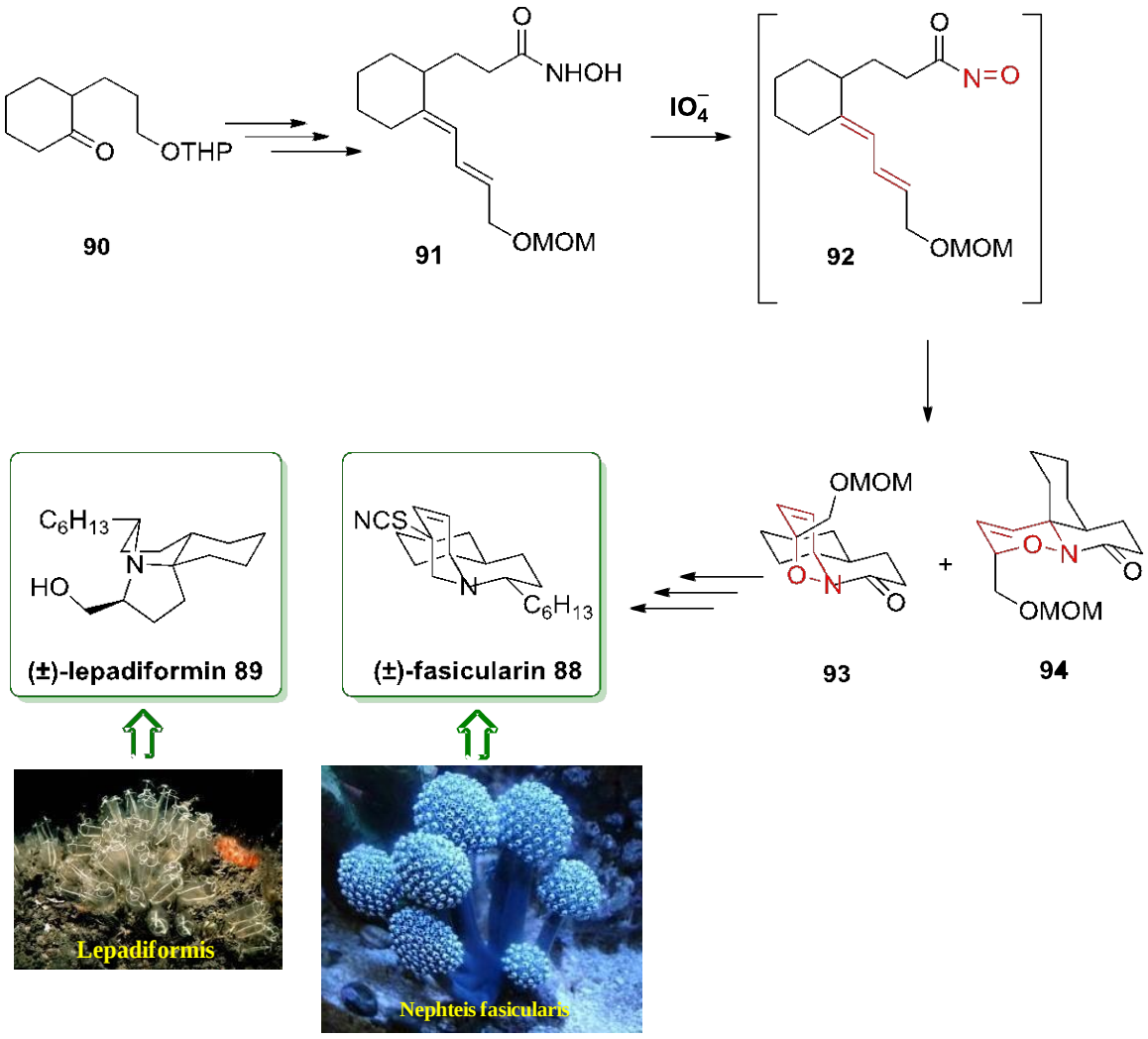
Scheme 13

A tricyclic alkaloids, fasicularin (**88**) has been isolated in 1997 by Patil and his coworkers[65] from the Micronesian ascidian *Nephteis fasicularis*, it has been found in being selective toward a DNA repair-deficient organism. Weinreb et al[132] attempted the synthesis of the presumed structure **95** for lepadiformine. Unexpectedly, they obtained a synthetic material, which was found being vividly and clearly, different from natural lepadiformine and it exists in a nonzwitterionic form as **95**. In this line, Pearson et al.[133] have reported synthesis of the three other possible diastereomers of **95** at C(3) and C(5) and have declared that none of these three stereoisomers is actually, lepadiformine.[134]

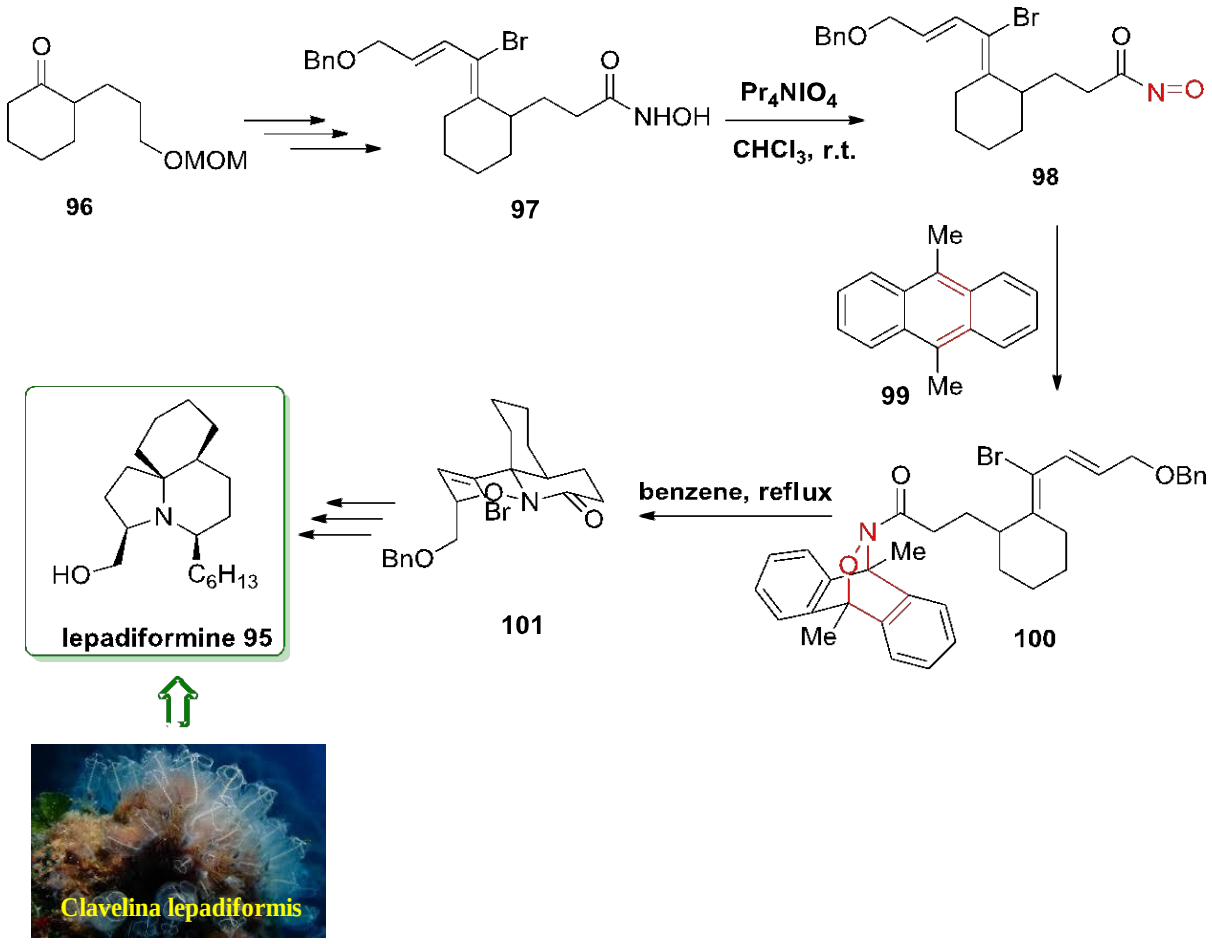
Shortly after (in 2000), the total synthesis of tricyclic marine alkaloids (±)-fasicularin (**88**) and (±)-lepadiformine (**89**) were claimed by Hideki Abe, and coworkers[109] In this approach, the

decisive strategic element actually is the stereocontrolled IMHDA cycloaddition reaction of an N-acylnitroso moiety to an exocyclic diene, both with or without bromine substitent to control the syn-facial or anti-facial selectivity, resulting in formation of the trans- or cis-fused decahydroquinoline ring systems **93** or **94** respectively. This is a key and crucial step in the multi-step total synthesis provides a golden opportunity for the simultaneous introduction of the nitrogenated quaternary center in a single step. For further expansion of the six-membered or five-membered ring A, the trans-fused adduct **93** afforded either (±)-fasicularin (**88**) or (±)-lepadiformine (**89**). The comparison of physical and spectroscopic data revealed that the hydrochloride salt of synthetic compound is identical to (±)-**89**, isolated from natural source, and identified as lepadiformine. In this strategy initially, the synthesis of hydroxamic acid **91** required for the IMHDA cycloaddion to study the facial selectivity, was contemplated and designed. As illustrated in Scheme 14, the Horner-Emmons reaction of ketone readily obtainable **90**[135] was conducted to afford the desired precursor **91**, after several steps. The latter was oxidized using Pr_4NIO_4 under the common nonaqueous conditions to create the corresponding acylnitroso compound **92** which was in situ underwent IMHDA cycloaddition reaction to afford the B/C trans-fused and cis-fused tricyclic lactams, **93** and **94**, albeit in low diastereoselection of 2.1:1 and in 58% total yield.

However, the tricyclic amino alcohol **95** having the suggested structure of lepadiformine in a nonzwitterionic form, obtained from the cis fused adduct **101**, was established being totally dissimilar from lepadiformine via physical and spectral comparison. Thus the ketone **96**[135] was submitted to Horner-Emmons olefination to afford **97** after several steps. Subsequently, **97** was oxidized to give acylnitroso-diene **98** which in situ underwent to IMHDA cycloaddition reaction. This IMHDA reaction in the presence of 9,10-dimethylanthracene, proceeded smoothly to afford the corresponding adduct **100** in 84% yield (Scheme 15).[109]



Scheme 14

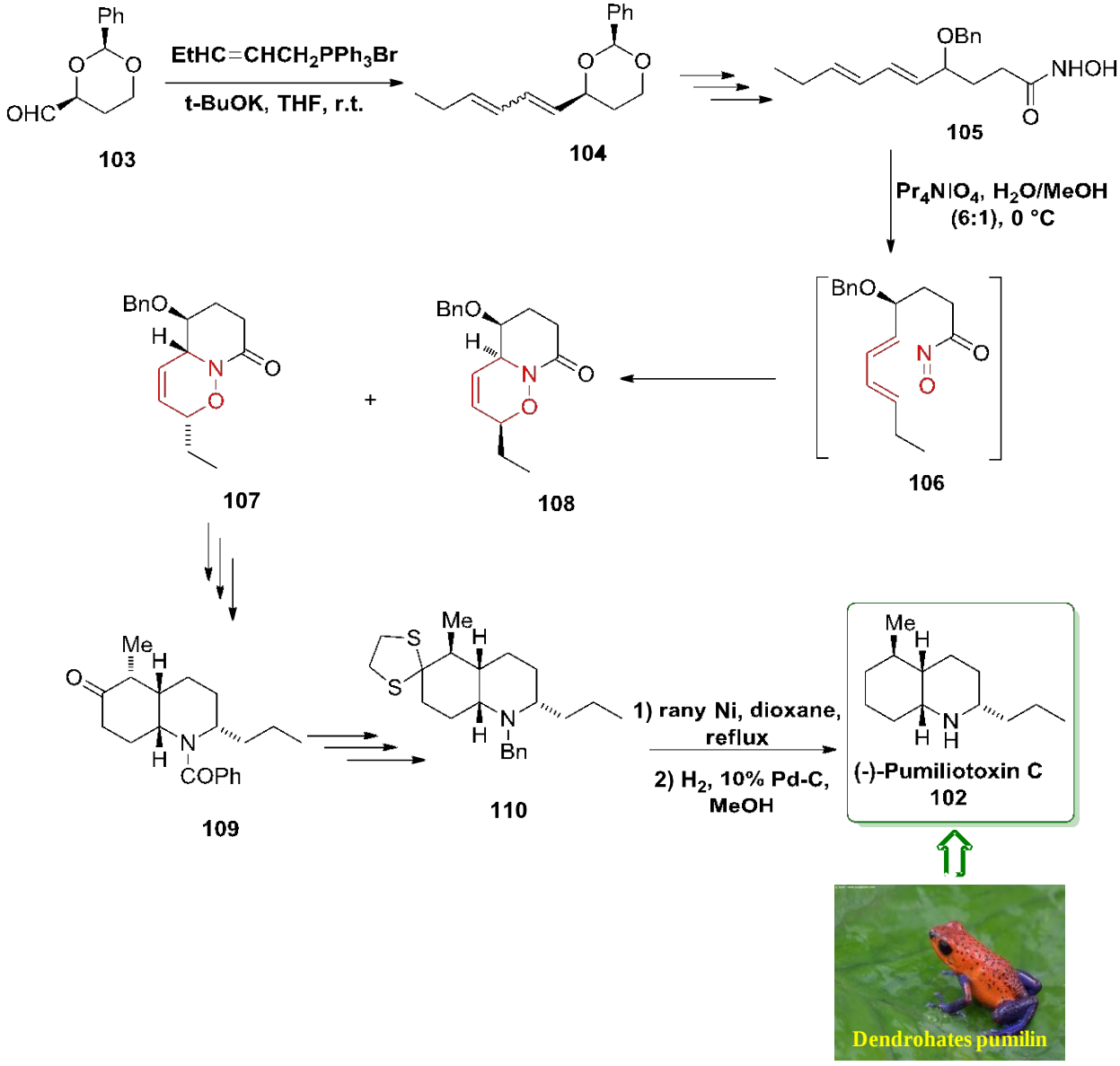


Scheme 15

The asymmetric synthesis of (-)-pumiliotoxin C (decahydroquinoline cis-195A) has been achieved and reported (**102**),[136-141] The latter was initially was isolated from skin extracts of the Panamanian poison-frog *Dendrohates pumilin*[142, 143] as the first member of dendrobatid alkaloids.[144]

This approach started from Wittig reaction of (2S,4S)-4-formyl-2-phenyl-1,3-dioxane (**103**) which afforded a mixture of (E)- and (Z)-dienes **104**. Subsequently, **105** was oxidized using periodinate under nonaqueous conditions led to in situ formation of the intermediate acylnitroso diene **106** which simultaneously underwent IMHDA cycloaddition reaction to provide poor diastereoseiectivity (1.4:1) of the trans (regarding to 4a-H and 5-H) vs. cis adducts (**107** and **108**). Compound **107** affords N-benzoyl-cis-decahydroquinolone **109** after several steps reaction. Ultimately, **110** with the precise oriented side chains at C-2 and C-S was subjected to

desulfurization with Raney Ni with subsequent hydrogenolytic removal of the benzyl protecting group to afford (-)-pumiliotoxin C (**102**) (scheme 16).[145]



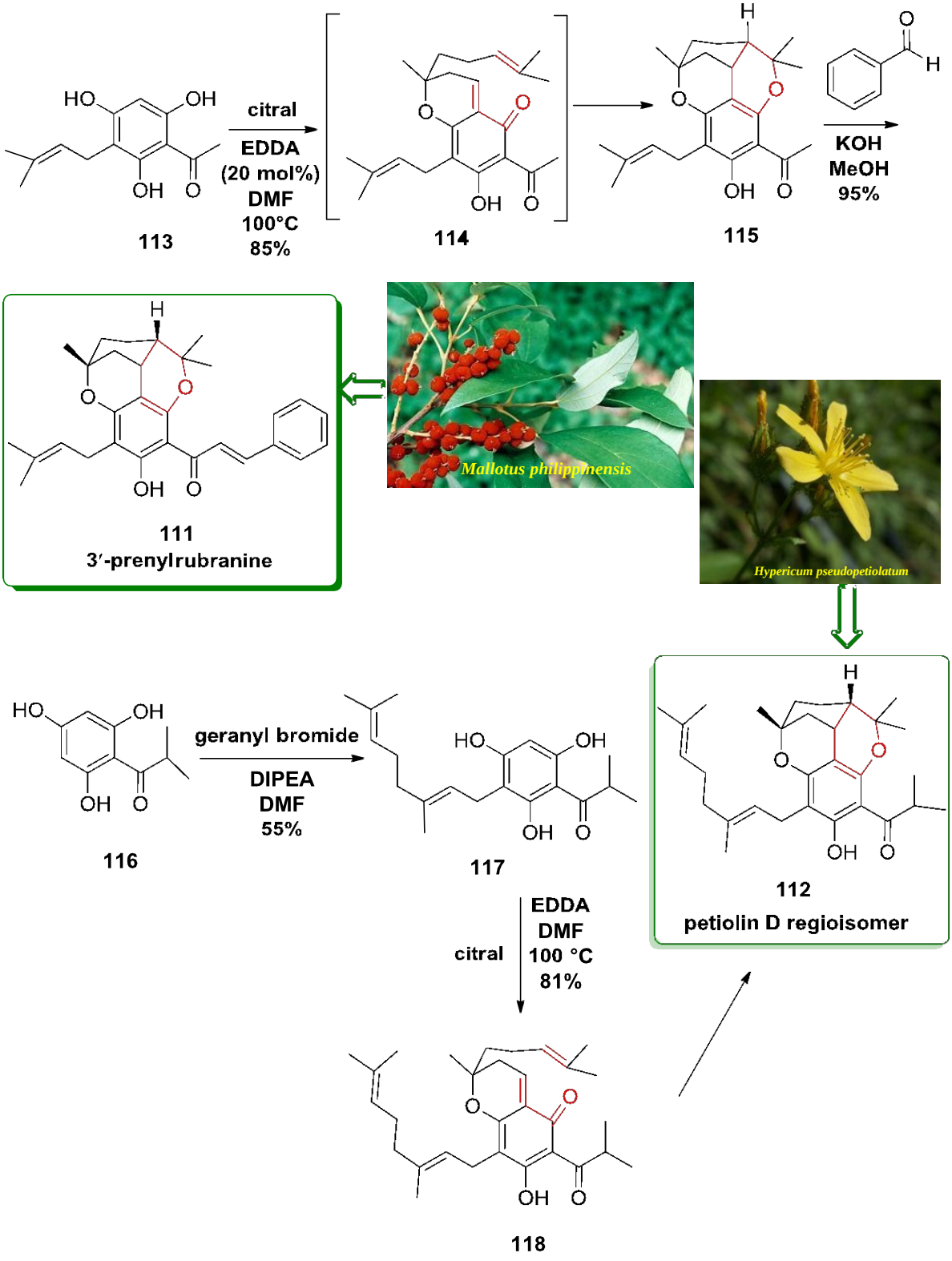
Scheme 16

3′-prenylrubranine (**111**) bearing prenyl groups on citran rings were isolated from *Mallotus philippinensis*.[146, 147]. The extract obtained from *Mallotus philippinensis* showed anti-bacterial potency.[147]

Polycycles having citrans are wide spread in nature[67, 148, 149] and show a broad range of biological and pharmacological potencies.[69, 70] In this approach compound **113** was provided in satisfactory

yield via treatment of 2,4,6-trihydroxyacetophenone with prenyl bromide Reaction of **113** with 1.2 equiv citral at 100 °C for relatively long time in DMF gave tetracyclic adduct **115** in high yield. This protocol was also employed in one-step synthesis of natural 3'-prenylrubraine (**111**) from prepared adduct. Treatment of **115** with benzaldehyde afforded 3'-prenylrubraine (**111**) in excellent yield. This strategy is actually based on domino aldol-type reaction/electrocyclization/H-migration/HDA cycloaddtion reaction.

This protocol was also employed in the first synthesis of unnatural petiolin D regioisomer (**112**) (Scheme 17).[150] Treatment of **116** with geranyl bromide mediated by N,N-diisopropylethylamine in DMF at ambient temperature for long period of time afforded **117** in satisfactory yield. Reaction of **117** with citral in the presence of 20 mol % ethylenediamine diacetate at 100 °C in DMF for relatively long reaction time gave adduct **112** in high yield. The structure and stereochemistry of **112** were suggested and approved via comparison of its spectral and physical data with those of previously reported for petiolin D which found being identical.[151] A new synthetic approach for biologically interesting polycycles carrying prenylated, geranylated, and farnesylated citrans has been developed and reported. This strategy commences from substituted trihydroxybenzenes with prenyl, geranyl, and farnesyl groups on the benzene ring. This methodology based on cascade type sequential reaction including aldol-type reaction/electrocyclization/H-migration/HDA cycloaddtion reaction. This approach was also employed in the synthesis of biologically important 3′-prenylrubranine (**111**) and petiolin D regioisomer (**112**).[150]

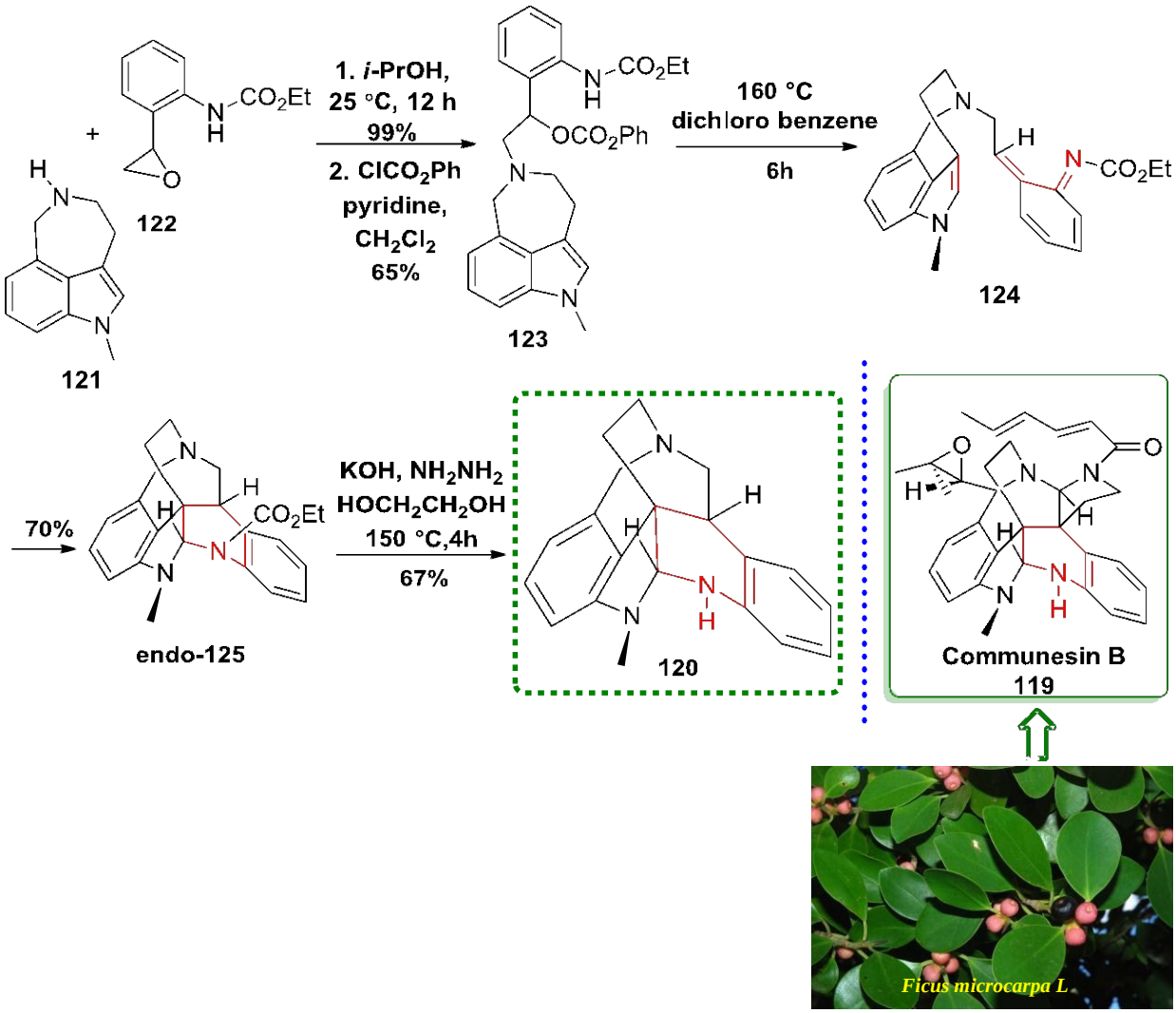


Scheme 17

In 2002 Hemscheidt and his research group accomplished the discovery of a structurally important polycyclic natural product from an endophytic fungus utilizing a bioassay designed to perceive antimicrotubule/antimicrofilament agents.[152] The unknown fungus was isolated from the bark of *Ficus microcarpa* L. which subsequently has been lost. Consequently, this natural product was called nomofungin (figure. 1). Inquiringly, it was found that a structurally very similar natural product, communesin B **118** (Scheme 18), which has an NH instead of the suggested pyran oxygen for nomofungin,[153] HDA already been disclosed and remaind relatively disregarded by the synthetic organic chemists. In addition, communesin B affords ^{1}H and ^{13}C spectra closely similar to those revealed for nomofungin. In 2003 this divergence was disclosed by Stolz et al who suggested a biosynthetic pathway to communesin B via the oxidative coupling of tryptamine with the ergot alkaloid aurantioclavine.[154] Initially, experimental work validated this speculation and pressed the denial of the nomofungin structure.[155]

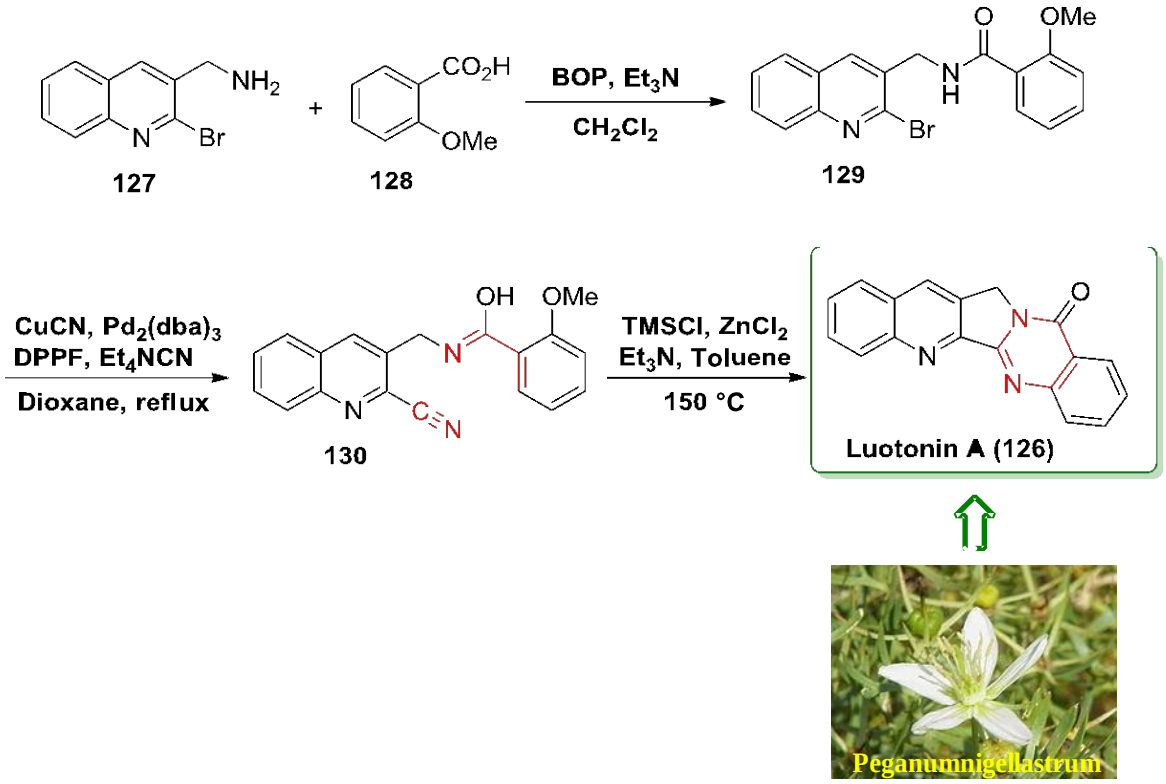
Delightfully, this general synthetic design illustrated in Scheme 18, was easily adapted which now required the creation of an aza-*ortho*-xylylene as a desired intermediate.[156] Expectedly, this reactive intermediate underwent the intramolecular cycloaddition with the indole heterodienophile and in this way introduce the "southern" aminal substructure of communesin B.[157] Pursuant to the purpose, ring opening of the already known epoxide **122**[158] with the benzazepine **121** afforded a mixture of regioisomer of amino alcohols that could be easily separated via conversion to the corresponding phenyl carbonates. The major carbonate **123**[159] was found to be an appropriate precursor to N-acyl-aza-*ortho*-xylylene **124** under thermolysis condition in dichlrobenzene which afford a single cycloadduct, aminal endo-**125** as sole product. The stereochemical assignment was tenable upon hydrolysis of the carbamate motif of endo-**125** to the aminal **120**. More significantly, the chemical shift of the resonances for the aminal proton and aminal carbon of aminal **120** were identical to those reported for communesin B, previously.

Figure 1



Scheme 18

A brief total synthesis of luotonin A, isolated from *Peganum nigellastrum* has been achieved and reported by Nomura and his coworkers in 1997.[160] Initially, the cyanide **130** was prepared via condensation of the amine **127** and 2-methoxybenzoic acid **(128)** mediated by BOP. Introduction of a nitrile group into **129** afforded the amide **130** in high yield. With the compound **130** avialable in hand, it was submitted into the vital IMHDA cycloaddtion reaction. Treatment of **130** with TMSCl and Et_3N at 150 °C in toluene under pressure, mediated by $ZnCl_2$ gave luotonin A **(126)** in 46% yield (scheme 19).[161] The synthetic **126** was found identical with that reported, by comparison of its physical and spectroscopic data.[162]

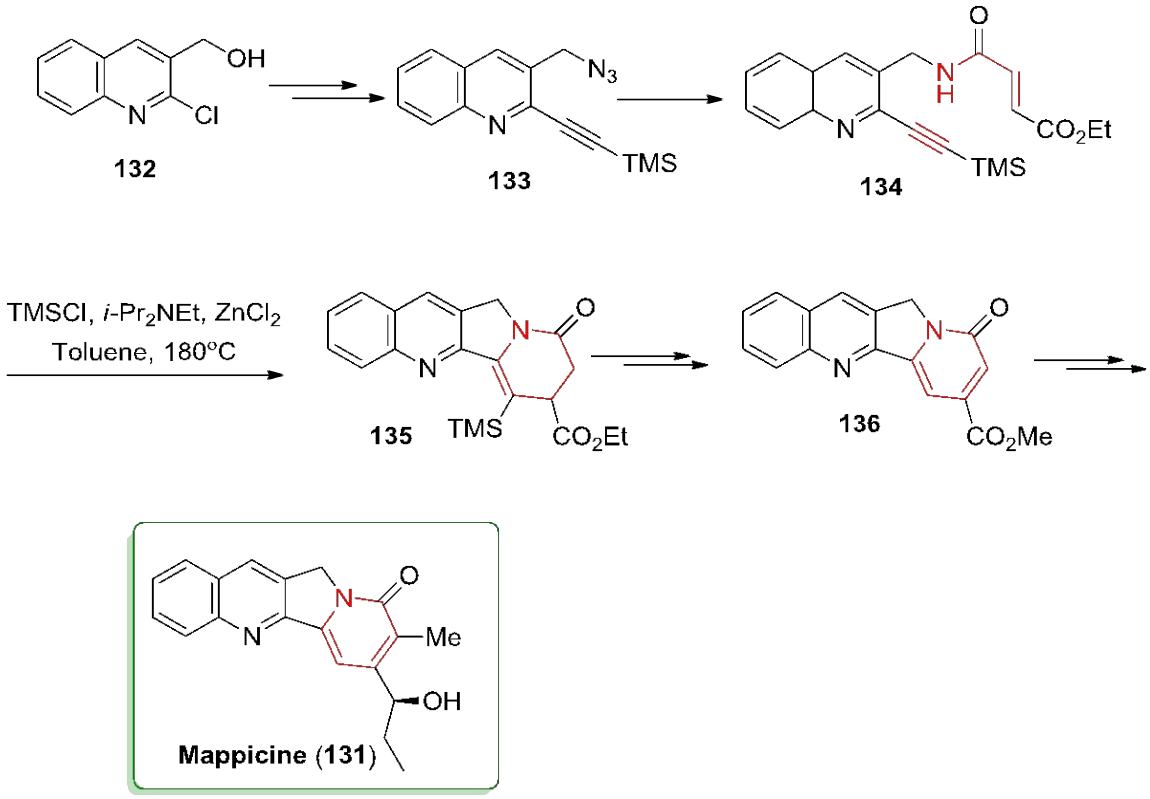


Scheme 19

Mappicine is an analog of camptothecin which was initially isolated from *Mapia Foetida*.[163] Since the transformation of the ester **136** into mappicine (**131**) has been achieved by Kametani et al[164] the synthesis of **136** completes the task. A novel synthetic route to mappicine (**131**) applying the IMHDA reaction as a key step has designed and being practiced.[165]

The appropriate 2-chloroquinoline **132**, was used as starting material being converted to the corresponding azide **133** via a two steps processes. However the formal synthesis of mappicine (**131**) began with compound **133** which was transformed to the unsaturated amide **134.** IMHDA

reaction of the latter resulted in the cycloadduct **135** (76%). At last, compound **135** was transformed into methyl ester **136** after several steps. The latter was then converted to mappicine (**131**) (scheme 20).[165] This successful total synthesis was achieved and reported by Kametani et al in 1975.[164]

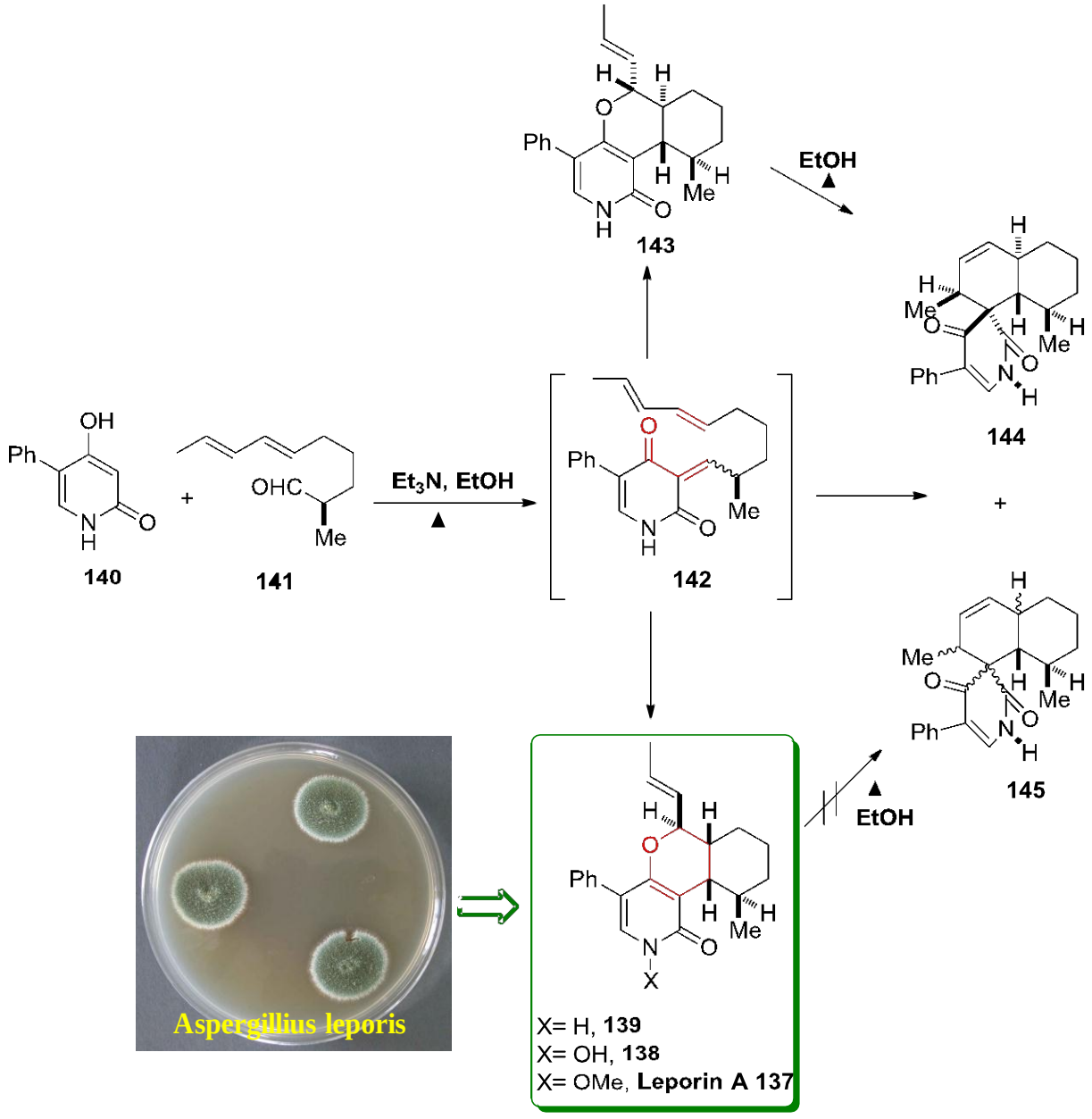


Scheme 20

Gloer and his coworkers in 1996 isolated the Antiinsectan leporin A (**137**), which has been isolated from the sclerotia of *Aspergillius leporis* (NRRL 3126) by Gloer and his research group and its structure has been assigned, chiefly, based on 1D- and 2D-NMR experiments and studies.[166]

The total synthesis of (±)-leporin A (**137**) has been achieved successfully and reported. This efficient approach involves a domino Knoevenagel condensation-inverse electron demand along with IMHDA cycloaddtion reaction for construction of the key tricyclic **139** from pyridone **140** and dienal **141** via generation of intermediate **142** in one pot fashion to afford in overall 35% yield. The condensation of **140** and **141** in EtOH in the presence of piperidine and pyridine[167, 168] gave variable quantities of the desired cis fused tricyclic inverse electron demand IMHDA

adduct **139**, along with the trans fused diastereomer **143**, and two spiro fused DA adducts **144** and **145**. Upon hydroxylation with subsequent methylation of **139** hydroxypyridone, **138** was obtained to complete the first total synthesis of (±)-leporin A (**137**) (scheme 21).[169]

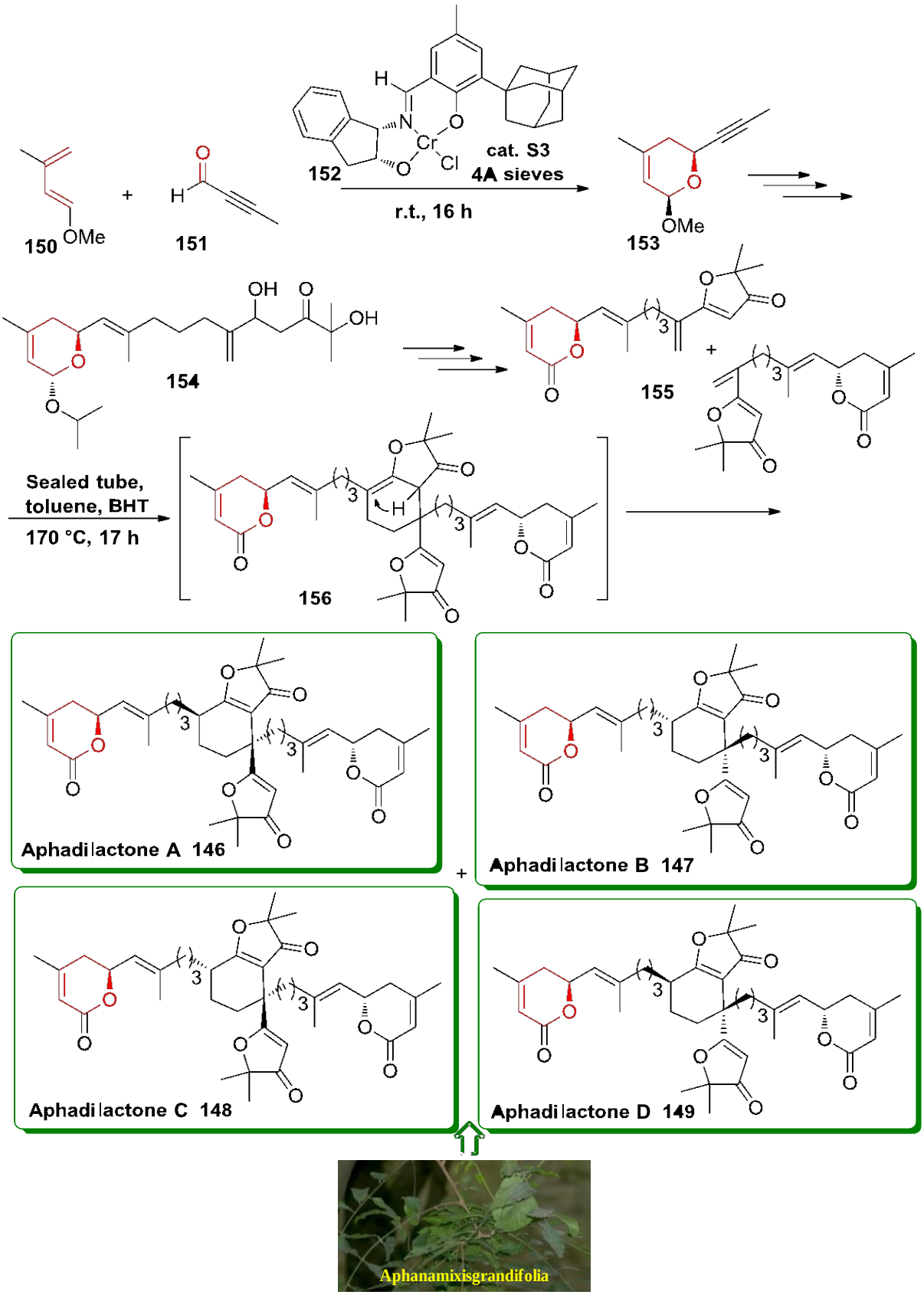


Scheme 21

2.2. Hetero Diels-Alder (HDA) reaction

Aphadilactones A−D (**146**−**149**), a new family of diterpenoid dimers, were initially isolated from the leaves of *Aphanamixis grandifolia*, an arbor tree that grows chiefly in the tropical and subtropical areas of Asia, by Yue and his colleagues.[170] The total synthesis involves a catalytic asymmetric HDA cycloaddtion reaction to construct the dihydropyran ring, along with simultaneous assemblage of the lactone and furan moieties via a cascade acid-catalyzed acetal cleavage/oxidation/cyclization process, and an IMHDA cycloaddtion reaction to obtain the desired target products.

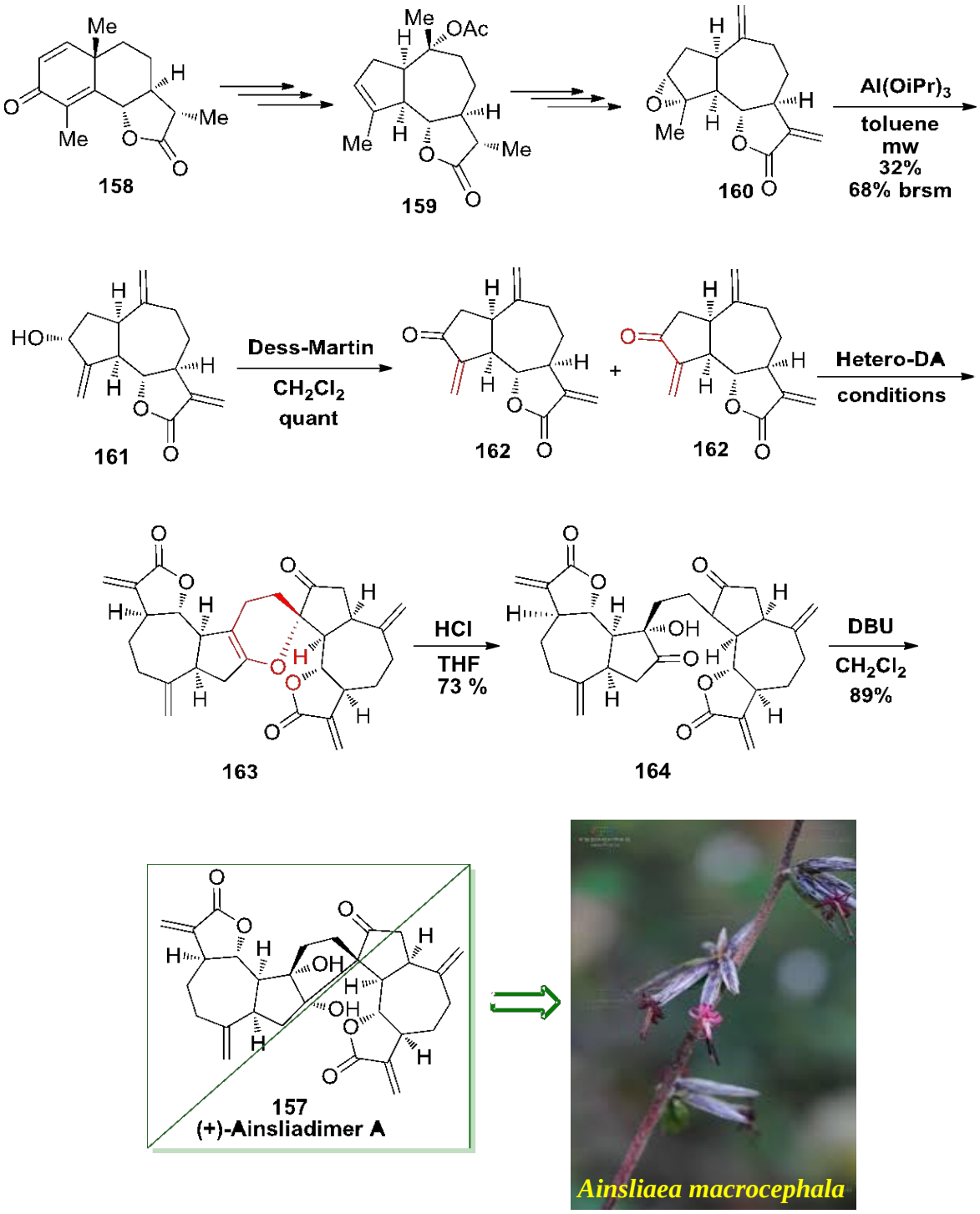
The reaction of alkoxybutadiene derivatives **150** with 2-butynal **151**, was studied, revealing that **151** was actually an efficient partner in the stereoselective HDA reaction, giving cycloadducts **153** in high yield and excellent enantioselectivity (98% ee). Intermediate **154** was obtained in gram quantities. With key precursor **154** avialable in hand, the synthesis of **155** was then attempted which achieved in a three-step cascade sequence. Now, having monomer **155**, available in hand, the stage was set to perform the bioinspired [4+2] dimerization/1,3 σ-hydrogen migration sequence to obtain the desired target. Aphadilactones A−D were produced in an approximate 1:1:1:1 mixture in satisfactory yield (scheme 22). The synthetic samples obtained, had the identical ^{1}H and ^{13}C NMR spectra with those of natural aphadilactones A−D.[171]



Scheme 22

Zhang et al in 2008 isolated and elucidated the structure of a new sesquiterpene lactone dimer, (+)-ainsliadimer A (**157**), with an exceptional carbon skeleton from *Ainsliaea macrocephala*. It has been used in folk Chinese medicine for the treatment of different diseases, including angina and rheumatoid arthritis.[172]

A protecting group free and biomimetic total synthesis of (+)-ainsliadimer A has been achieved in 14 steps starting from α-santonin. This synthetic approach based on a hydrogen bonding promoted HDA dimerization to provide the key homodimer intermediate, which shows the feasibility of employing nonenzymatic conditions to accomplish the suggested biosynthesis. The synthesis of dehydrozaluzanin C (**162**) started from α-santonin **158**, a market purchasable material. Photolysis of **158** with a high-pressure Hg lamp (500 W), provided alkene **159** in satisfactory yield over two steps. Reaction of **160** with aluminum isopropoxide in toluene under microwave irradiation gave the R-allylic alcohol 3-epizaluzanin C (**161**), which upon oxidation by Dess-Martin procedure gave dehydrozaluzanin C (**162**). While this monomer **162** was avialable HDA dimerization could be examined to confirm the suggested biosynthetic process (Scheme 23). Worthy to mention here that hydrogen bonding catalysis that can mimic the effectiveness of enzymes or antibodies has recently attracted much attention as a significant progress in organic synthesis.[173] Encouraged by the sophisticated work of Rawal and his coworkers in hydrogenbond-promoted HDA cycloaddition reactions,[174-177] an extensive studies have started and going on.[178]

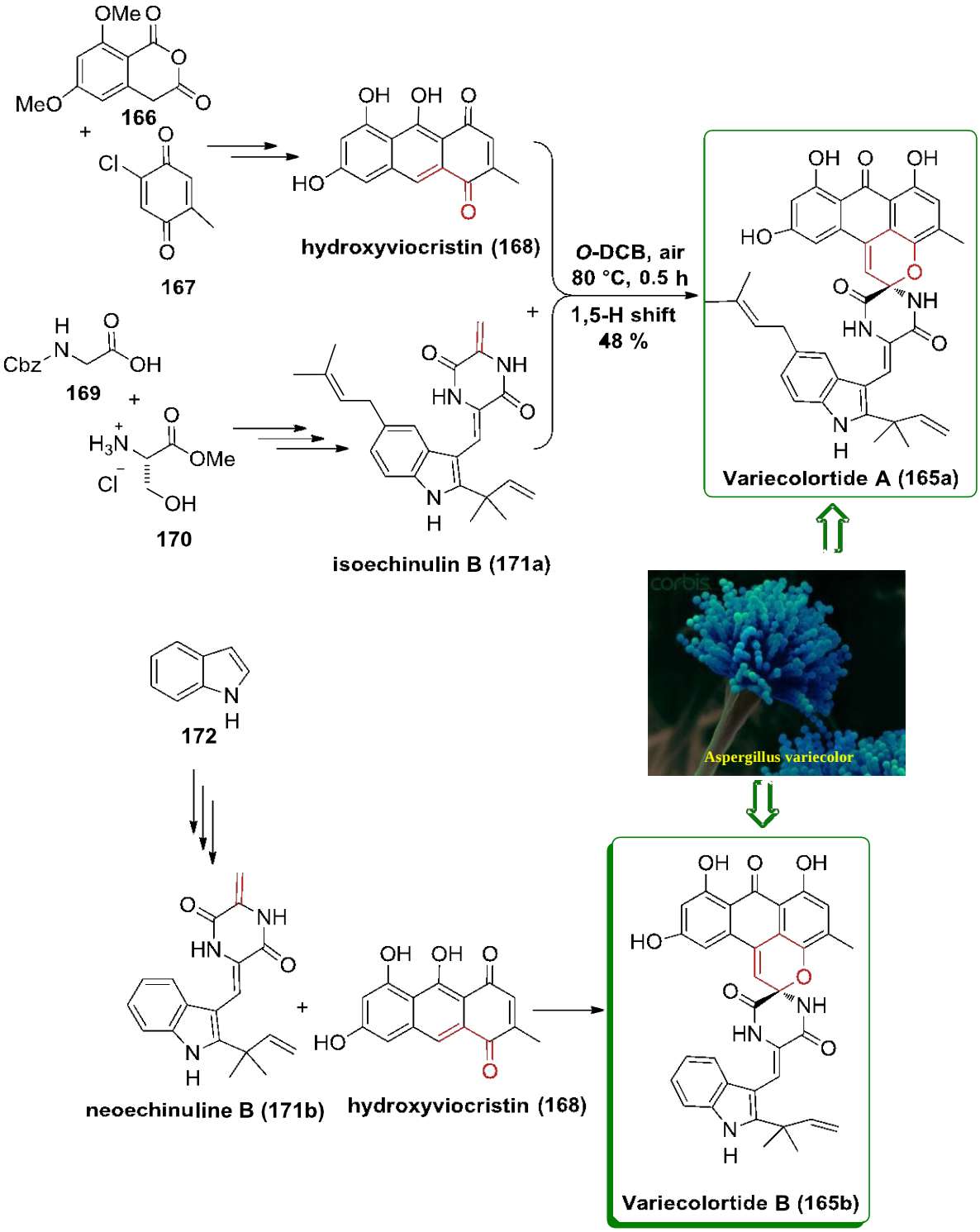


Scheme 23

Synthesis of the dopamine derived alkaloids exiguamine A and B based on a biomimetic pericyclic reaction and oxidation cascade has been recently published (Scheme 24).[179]

Exceptionally, the exiguamines generated in nature as racemic mixture and feature a spirobicyclic N,O-acetal as an important structural moiety. Thus the variecolortides (**165a–b**), a newly revealed family of racemate N,O-acetals, has stirred up, much interest.[180] These rarely occurring fungal natural products were isolated from a halotolerant strain of the fungus *Aspergillus variecolor* and exhibited moderate cytotoxic effects.[180]

A brief total synthesis of **165a** and **165b** has been successfully achieved. This strategy presents a remarkably facile approach resulted in linkage of the anthraquinone and diketopiperazine components by employing new type HDA reaction.[181] This approach could be mimic of biosynthesis. The total synthesis of the variecolortides commenced with the providing of hydroxyviocristin (**168**; Scheme 24). Upon deprotonation the already known orsellinic acid was converted into anhydride **166**,[182] with subsequent addition of the resultant benzylic anion to chloro para-benzoquinone **167** which was transformed to hydroxyviocristin (**168**). For the incorporation of amino acid segment, carbobenzoxy-protected glycine **169** was condensed with serine methyl ester (**170**) to provide isoechinulin B (**171a**) as a sole single isomer via four steps.[183] A similar sequence beginning from indole **172** afforded neoechinulin B (**171b**; Scheme 24). Delightfully, HDA reaction of hydroxyviocristin (**168**) and isoechinulin B (**171a**) in ortho-dichlorobenzene under thermal conditions furnished variecolortide A in 48% yield. Analogously, variecolortide B was provided from building blocks **171b** and **168**.[184]

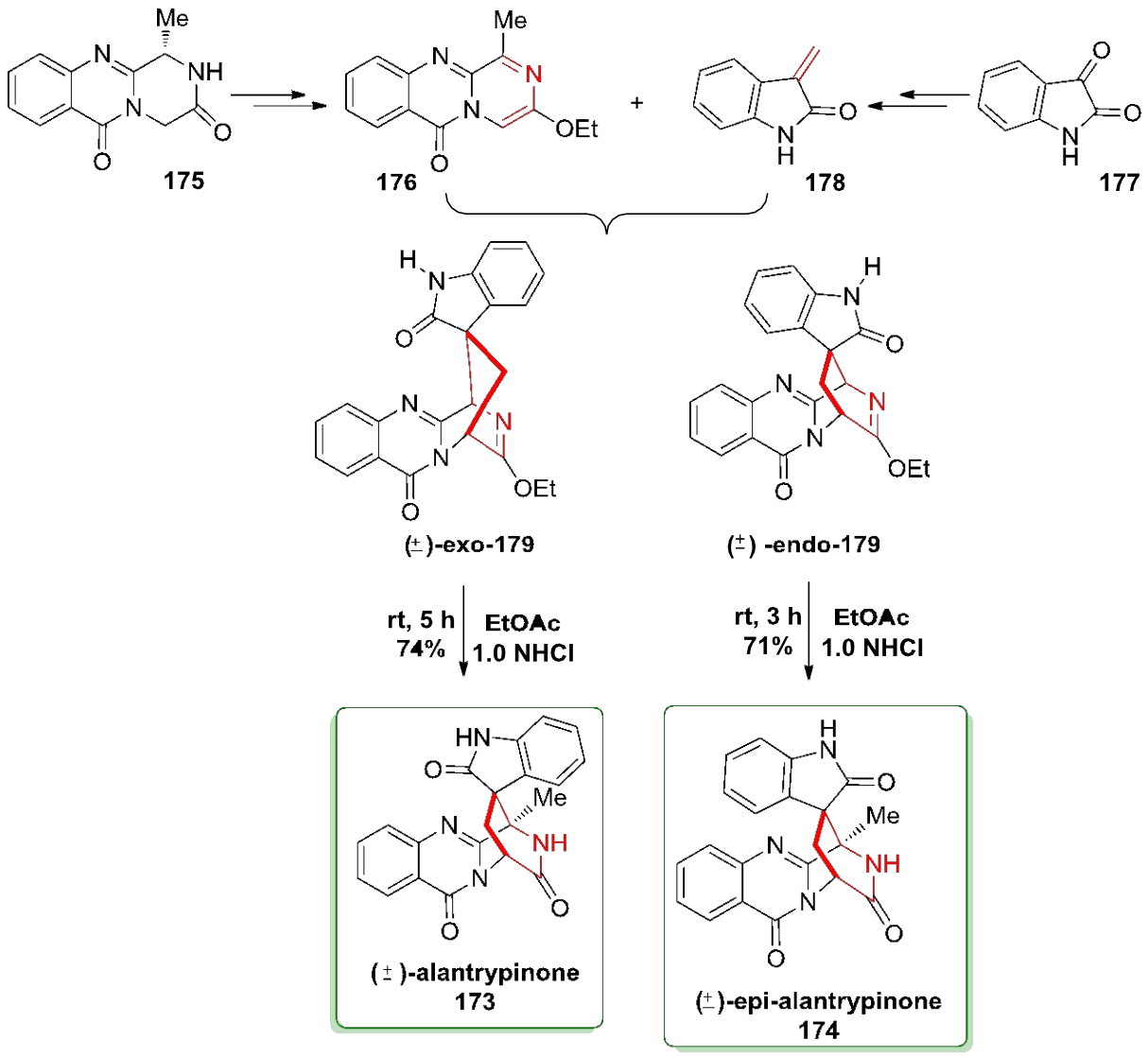


Scheme 24

Alantrypinone[185-187] (+)-**173**, is a polycyclic alkaloid. It has been found that is most probably biosynthetically derived from anthranilic acid and tryptophan. It was initially isolated from

Penicillium thymicola in 1998. Its biological activities were evaluated at the isolation stage. In 2004, it was found that (+)-**173** and (+)-serantrypinone,[188, 189] which were isolated during binding assay based screening of fungal culture extracts, were insecticides. It was shown that this alkaloids are highly selective for insect (vs mammalian) c-aminobutyric acid (GABA) receptors.[190] The design, synthesis, and biological properties of (±)-**173** and these types of analogues were reported. For the total synthesis an approach for the synthesis of (±)-**173** developed by Kende and coworkers was used.[186, 187] Their strategy the synthesis of (±)-**173** includes a HDA reaction between azadiene **176** and dienophile **178** as key step.

Kende"s protocol includes the transformation of, **175** to **176**. Primarily dienophile **178** was provided via the Peterson olefination of isatin (**177**). In a key step, HDA reaction of **176** with **178** took place regioselectively, to give desired (±)-exo-**179** and undesired (±)-endo-**179** in 52% and 18% respectively. By decreasing the amount of **176** in the reaction down to 1.5 equiv, (±)-endo-**179** was provided in 43% yield together with 34% of (±)-exo-**179**. The same reactions under gave (±)-endo-**179** with higher stereoselectivity under thermal conditions. These results reveal that (±)-endo-**179** is a thermodynamically stable product. As a result (±)-exo-**179** and (±)-endo-**179** were converted to (±)-**173** and (±)-**174**, respectively, using Kende protocol, reported hitherto. The synthetic pathway and results are illustrated in Scheme 25.[191]



Scheme 25

Brevetoxins secreted by the dinoflagellate *Ptychodiscus brevis* may cause wide-ranging natural catastrophe.[192] Nakanishi et al in 1981 reported the elucidation structure of brevetoxin B, as a first member of a new family of structurally unique marine toxins.[193] Brevetoxin has 11 adjoining trans-fused cyclic ether rings, fabulously arranged in a "ladder-like" rigid background.[193] Nakanishi et al suggested an interesting biogenetic scheme showing that brevetoxins may be biosynthesized via a polyepoxide tandem cyclization.[194] An extensive investigation for ladder-frame polyethers resulted in the elucidation structure of brevenal (**180**) isolated from *Karenia brevis* (figure 2).[195, 196] Delightfully, this smaller polyether was found to be an antagonist of brevetoxins. Recently, Wright et al reported the isolation of a new marine

alkaloid, brevisamide (**181**), from *K. brevis* (figure 2). Apparently it is the biogenetic template for the polyepoxide tandem reaction resulted in brevenal.[197] Satake and co-workers achieved and reported the first total synthesis relied on a multi-step build of the substituted tetrahydropyran ring as well as Suzuki-Miyaura coupling of the segments.[198] Lindsley et al has recently reported their achievement to discover another approach to brevisamide.[199]

An asymmetric total synthesis of brevisamide relied upon a strategic easy installation of the highly substituted tetrahydropyran ring employing Jacobsen‟s asymmetric HDA reaction.[200, 201] The protocol reduces high junction and flexibility to structural modulation. Initially aldehede **182** [202] is transformed to enone **183** through addition of ethylmagnesium bromide with subsequent Swern oxidation to give **183** in high yield over two steps. The latter was reacted with TESOTf mediated by Et_3N to provide triethylsilyl diene **184** in high yield. Upon Jacobsen‟s asymmetric catalytic HDA cycloaddtion reaction of diene **184** and aldehyde **185** in the presence of **152** mol % Jacobsen‟s chromium catalyst **152**,[200] and in the presence of molecular sieves the desired cycloadduct **186** in satisfactory yield was obtained. Scheme 26 shows the synthesis of brevisamide via installation of tetrahydropyran **187** and vinyl iodide **188** employing a Suzuki-Miyaura coupling reaction as the crucial step as used by Satake et al.[200, 201] The cross-coupling of the resultant alkylborane and iodide **188** employing a catalytic quantity of $PdCl_2$-(dppf)·in dichloromethane afforded a TBS-ether as an intermediate. This intermediate was then desilylated to afford **189** in moderate yield over two steps. Upon selective oxidation of the allylic alcohol in **189** gave synthetic brevisamide **181** in pure form and 87% chemical yield.[203]

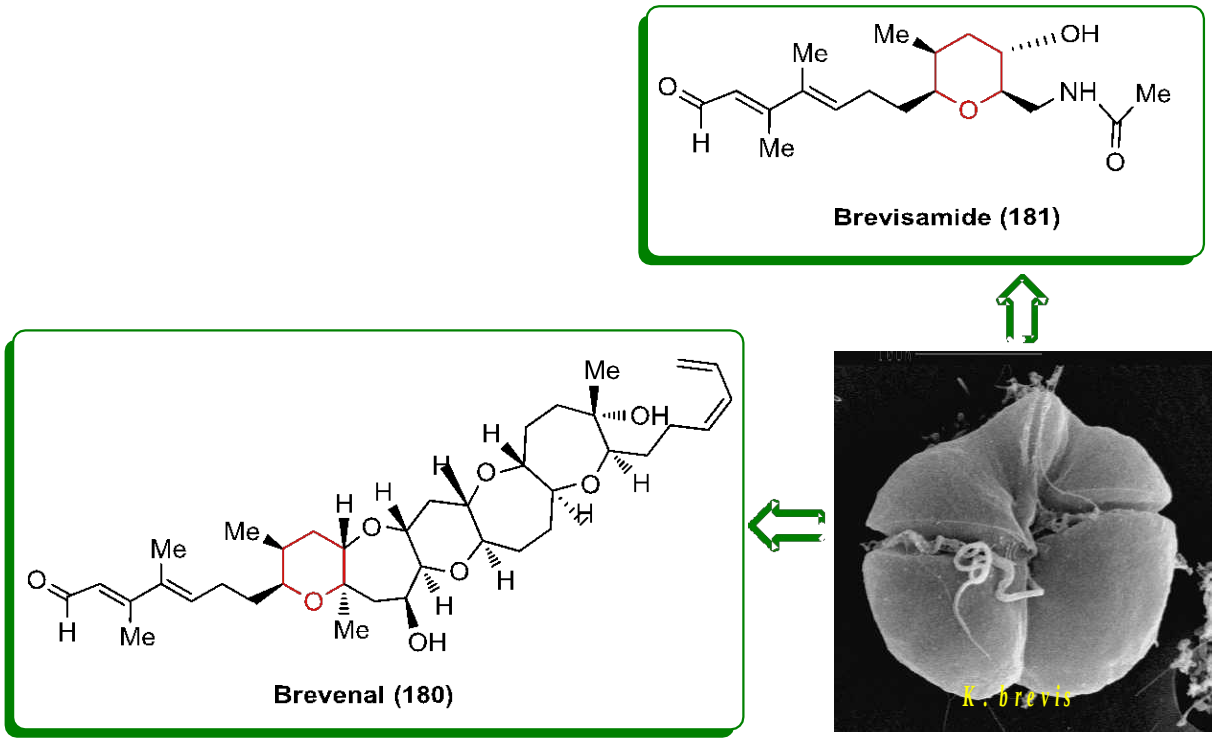
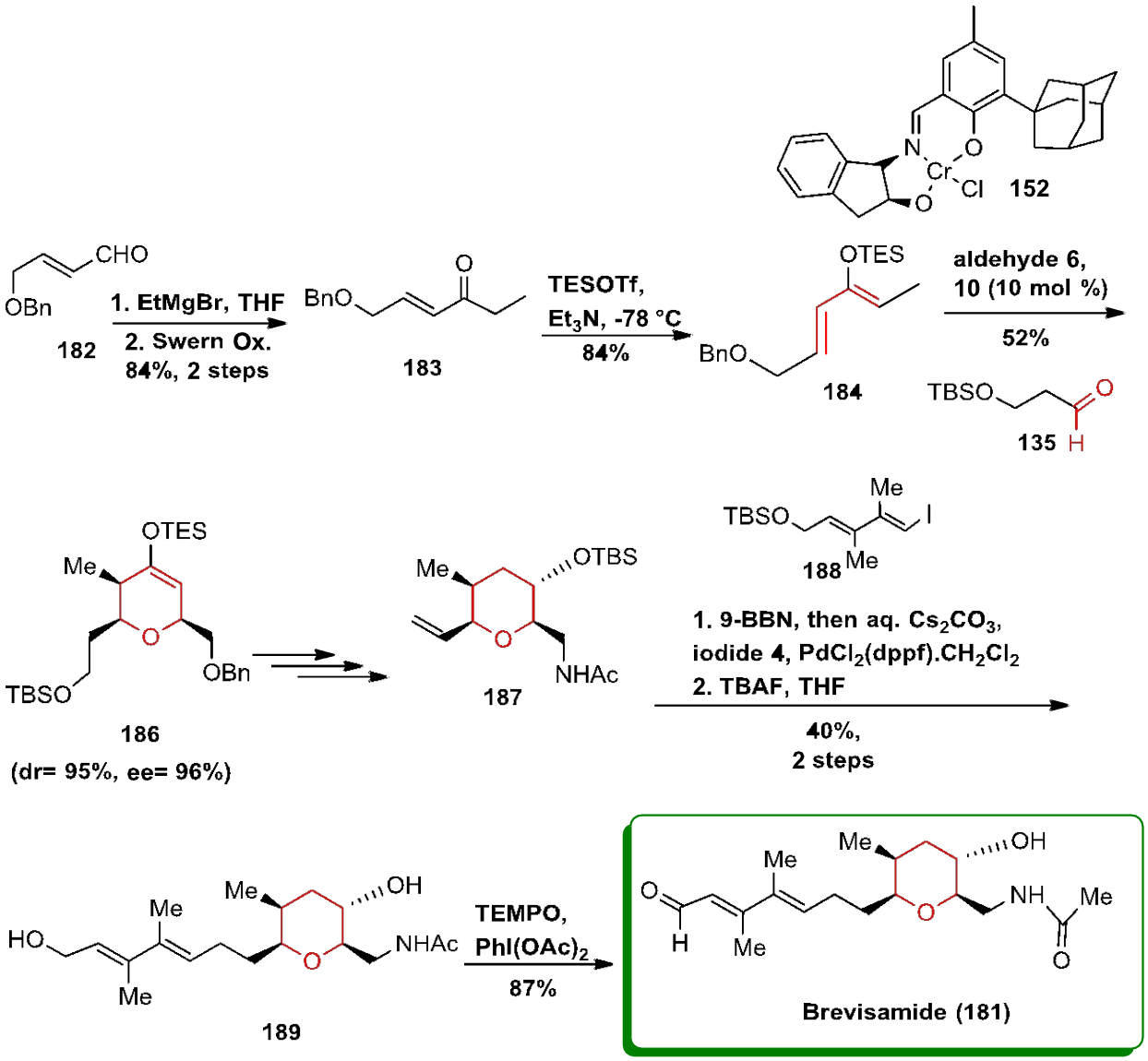


Figure 2

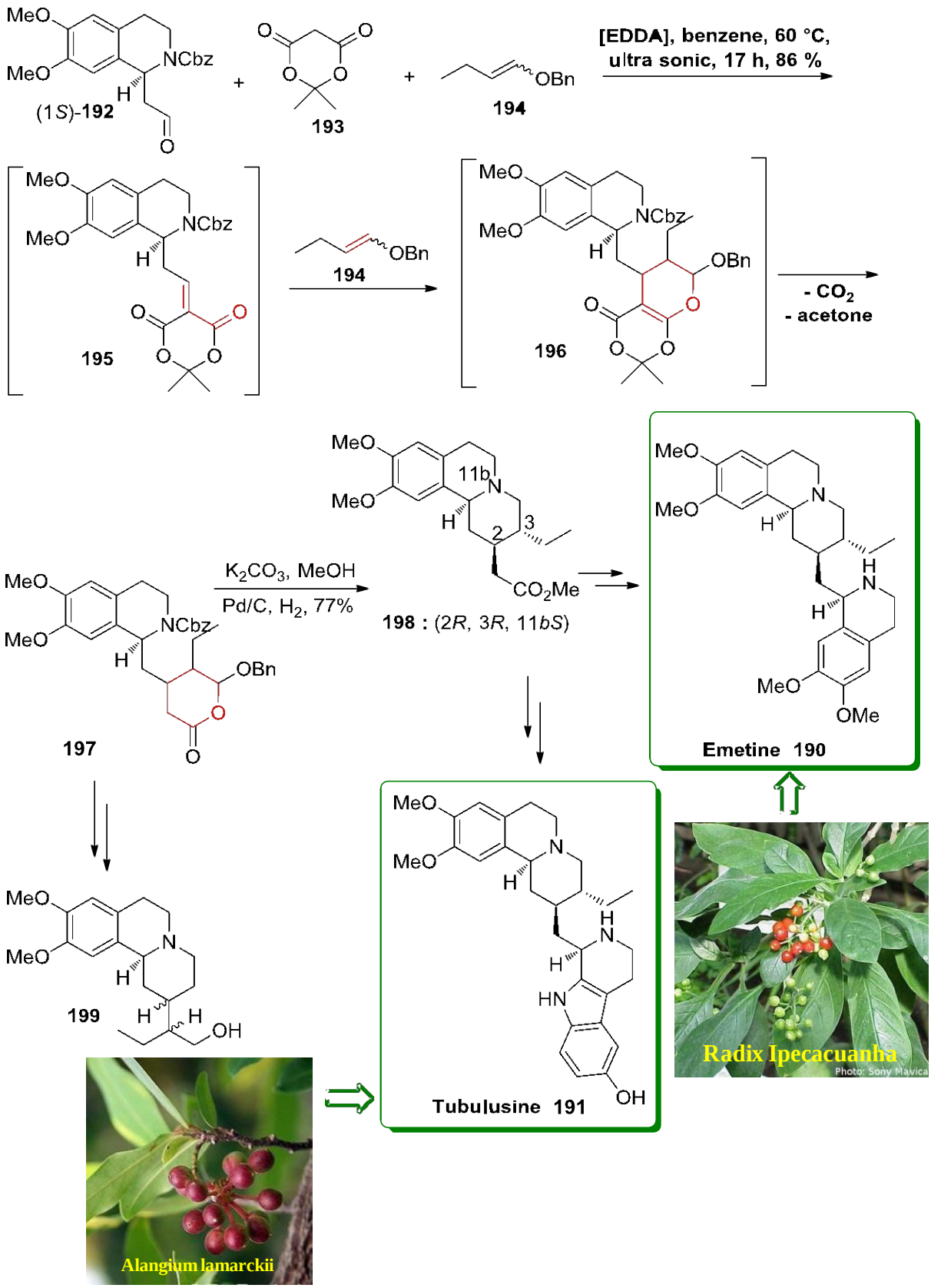


Scheme 26

The Ipecacuanha alkaloid emetine (**190**) and the Alangium alkaloid tubulosine (**191**) are placed in the group of tetrahydroisoquinoline alkaloids. It is suggested that they are created in nature from dopamine and the monoterpene secologanin. Emetine (**190**) was initially isolated from *Radix Ipecacuanha* and the roots of *Psychotria Ipecacuanha* and *Cephalis acuminata*[204, 205] and possesses multifold remarkable biological and biological potency. It exhibits antiprotozoic properties[206] and is used in the treatment of lymphatic leukaemia[207]. At the present time, emetine (**190**) is a banned drug due to its substantial toxicity. Tubulosine (**191**) was initially isolated from the dried fruits of *Alangium lamarckii*[208] and the sap of *Pogonopus speciosus*.[209] It is

significantly active towards several cancer cell lines[209] and has been investigated for different biological properties, acting as inhibitor in protein biosynthesis[210] and inhibition of HIV reverse transcriptase.[211]

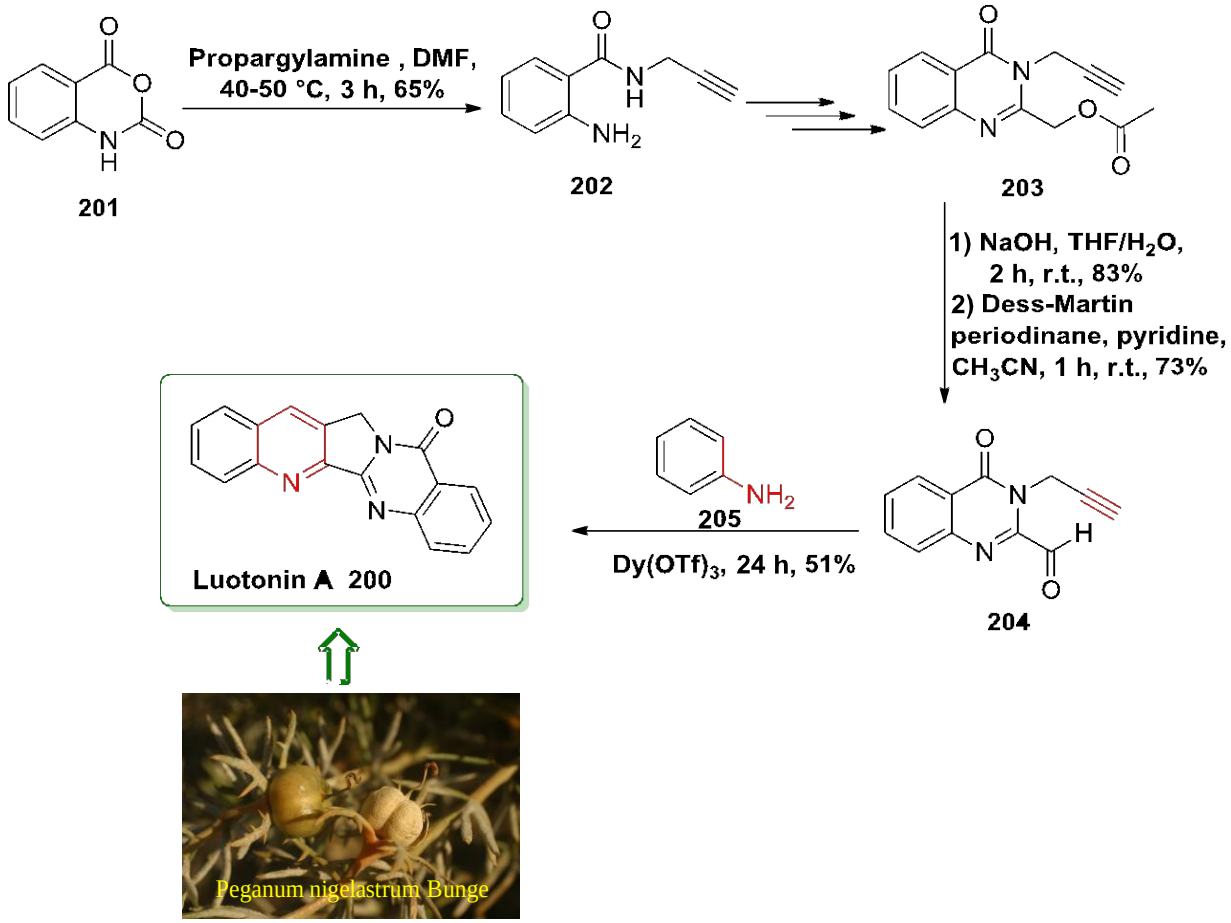
Protection of the secondary amino group along with CbzCl, deprotection of the TIPS group combined with oxidation of the generated primary hydroxy group resulted in the aldehyde (1S)-**192**. The domino reaction of (1S)-**192**, Meldrum's acid **193** and enol ether **194** was conducted under catalysis of ethylene diammonium diacetate. Initially, the 1-oxa-1,3-butadiene **195** is generated, which is converted **196** in a HDA reaction with inverse electron demand; under the reaction conditions **196** CO_2 is lost and acetone to give **197** as the desired product. The latter was then gave the benzoquinolizidine **198**. Further conversion of **198** afforded enantiopure emetine (**190**) and tubulosine (**191**), respectively (Scheme 27). Besides, commencing from **197** the new benzoquinolizidine alkaloid **199** was prepared.[212]



Scheme 27

Luotonin A is a structurally related cytotoxic alkaloid. It was initially isolated in 1997 from the aerial parts of *Peganum nigellastrum Bunge*.[162] This plant has been used for a centuries in Chinese folk medicine for the treatment of various conditions, including rheumatism and inflammation. Luotonin A has attracted the attentions of several research group.[213-216] Particularly worthy to mention is an intermolecular Povarov approach to the synthesis of luotonin A, which has been reported by Stevenson et al.[214]

Pyrrolo[3,4-b]quinolines could be provided via the coupling of anilines with N-propargylic substituted heterocyclic aldehydes mediated by mild Lewis acid catalysts such as ($Ln(OTf)_3$). The coupling proceeds via sequential reaction involving imine generation/ a proper intramolecular aza-DA (Povarov) reaction. This strategy was employed in a total synthesis of luotonin A. The synthesis of luotonin A employing similar strategy requires the use of a quinazolinone aldehyde **201** as precursor. Ring-opening of market purchasable isatoic anhydride using propargylamine provided 2-amino benzamide **202** in satisfactory yield.[217] The latter was transformed to **203** in several step. Removal of the acetate group from **203** afforded the aldehyde precursor **204**. HDA (Povarov) reaction between **204** and aniline took place in the presence of 10 mol % $Dy(OTf)_3$ in CH_3CN only in relatively long reaction time to afford luotonin A (Scheme 28). Apparently further oxidation of the initially generated 1,2-dihydroquinoline occurs in situ, resulted in isolation of impure luotonin A which after purification by flash column chromatography gave the pure desired natural product in 51% yield.[218]

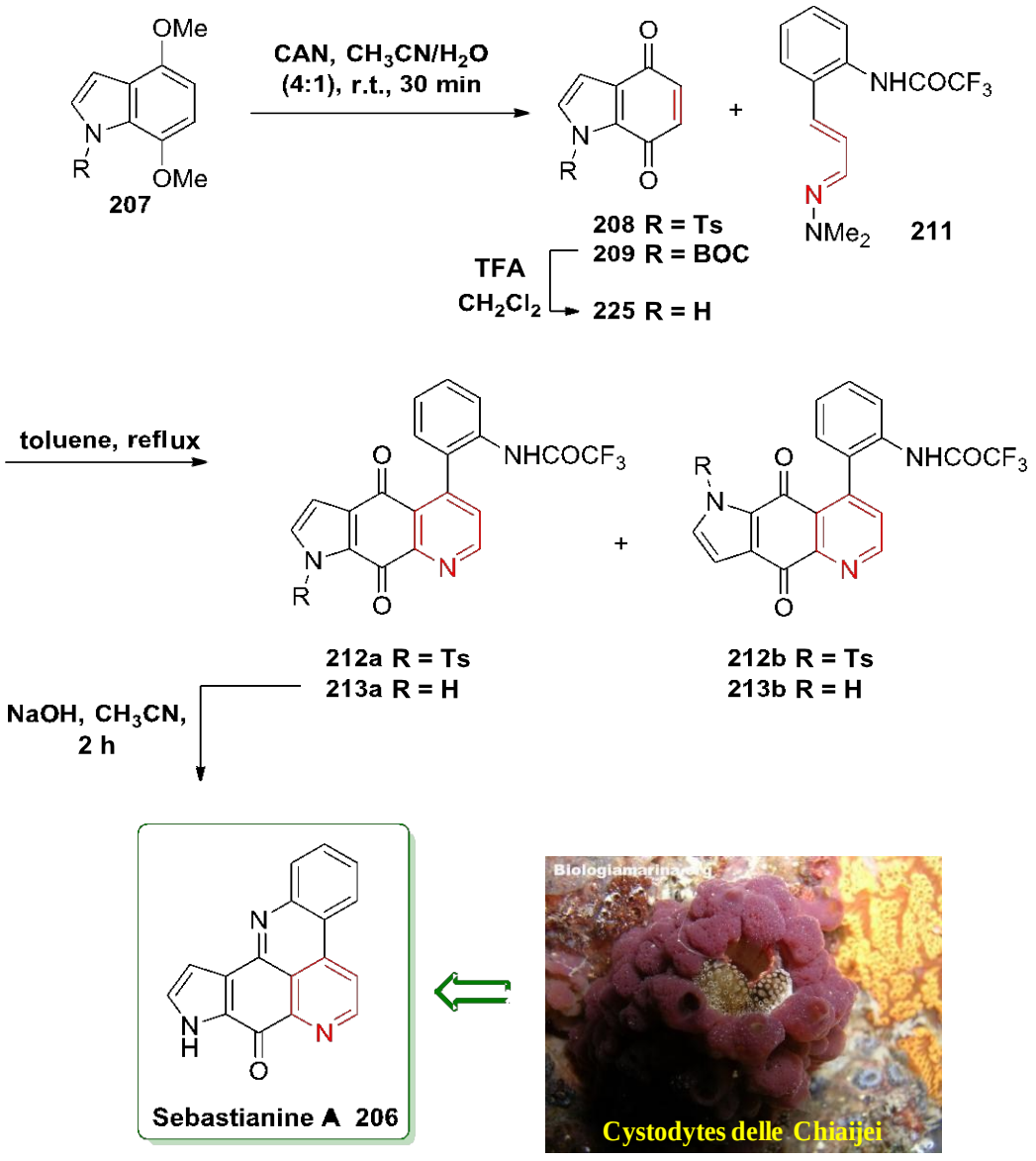


Scheme 28

Pyrido[4,3,2-*mn*]acridine alkaloids is a representative in a group of naturally occurring compounds, isolated from marine source. It have shown several remarkable biological potencies, such as tumor toxicity and are acting as fungal growth inhibitors. The isolation and structural elucidation of arnoamines A and B, as the first members of the pyridoacridine family that bears pyrrole fused to the pyridoacridine ring system, has been reported by Plubrukarn and Davidson[219] in 1998. Their total synthesis has been successfully achieved and reported.[220] In 2002, the total synthesis of pyridoacridine alkaloid, sebastianine A (**206**) were accomplished and reported by Torres *et al*., from the ascidian *Cystodytes delle Chiaijei*.[221]

In this strategy, the two dienophiles **208** and **210** were prepared commencing, from 4,7-dimethoxyindole **207**. The HDA cycloaddtion reactions with both aforementioned dienophiles **208** and **210** in toluene under reflux conditions gave **212a**/**212b** and **213a**/**213b** in low yield upon oxidative aromatization using MnO_2 (8 and 6%, respectively) as a mixture of the two

regioisomers **212a/212b** and **213a/213b** (Scheme 29). The HDA adducts **213a** were then cyclized in the presence of aqueous sodium hydroxide to afford the corresponding pentacyclic compounds **206** in high yield.[222]

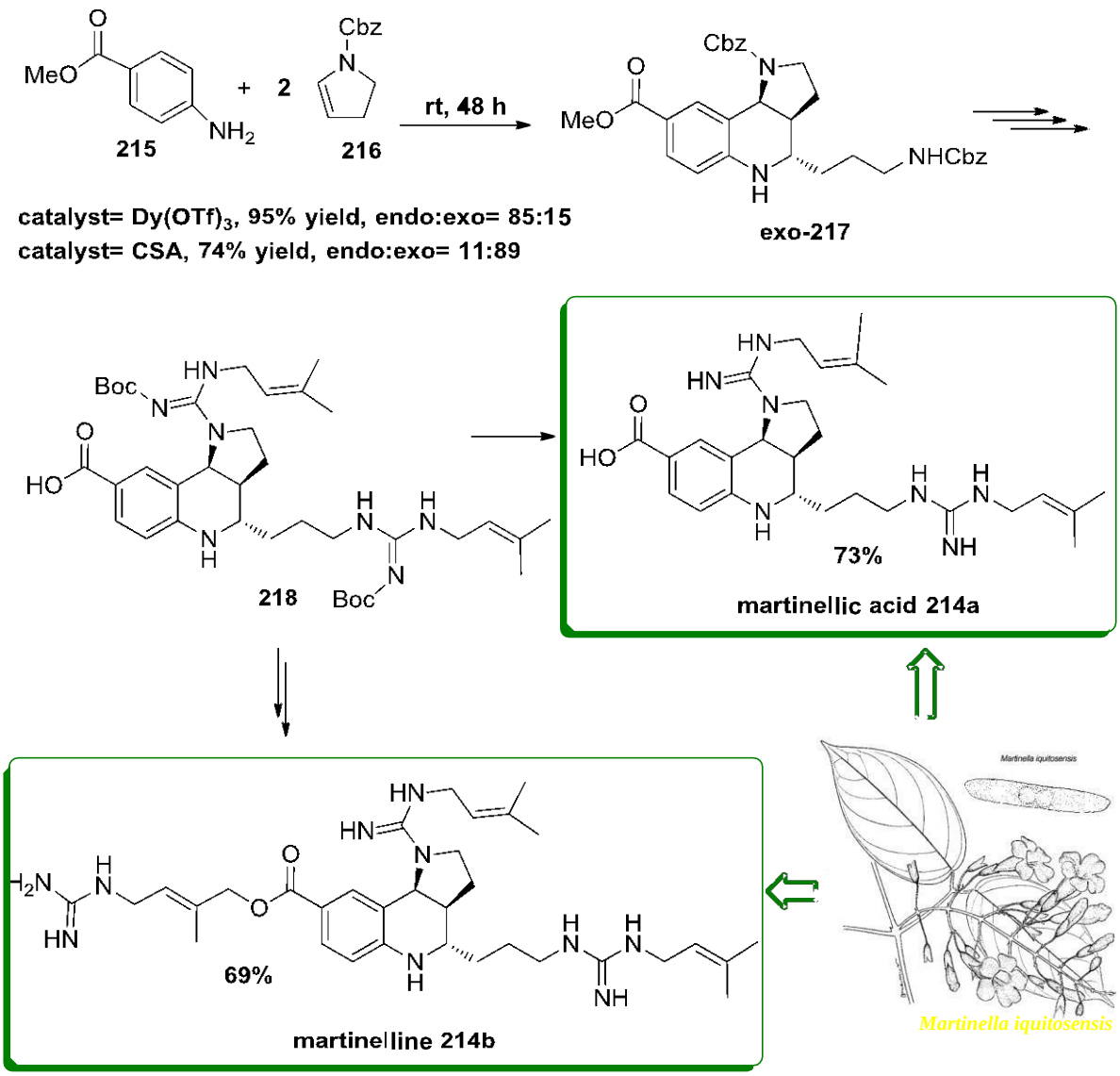


Scheme 29

Native people in Amazonian lowland, used to treat different types of eye ailments, such as inflammation and conjunctivitis with the extract obtained from root of the *Martinella iquitosensis*.[223] It has been realized, that, two new guanidine alkaloids, martinellic acid **214a** and martinelline **214b**, present in extract are probably responsible for such medicinal usefulness.

214a and **214b** have been screened, showing moderate antibiotics activity and also they micromolar binders of several G-protein coupled receptors.[224]

The total synthesis of **215** has been accomplished and reported. The total synthesis starts from methyl 4-aminobenzoate **215** which upon reaction with *N*-Cbz-2-pyrroline **216** gives the hexahydropyrrolo[3,2-*c*]quinoline core **217** of martinelline as a diastereomeric mixture with the ratio of 85:15 unfortunately in favor of the undesired *endo* substance (Scheme 30). A brief total synthesis of the guanidine alkaloids, (±)-martinelline and (±)-martinellic acid have been designed, operated and successfully achieved. In a key step a protic acid catalyzed HDA cycloaddition/ coupling reaction between *N*-Cbz 2-pyrroline **216** and methyl 4-aminobenzoate **215**, 2:1 was employed. Interestingly it was the use of protic acid catalysis, instead of Lewis acid catalysis, was compulsory to obtain the desired mode of diastereocontrol in the coupling reaction. This strategy caused the fast synthesis of (±)-martinellic acid and the biologically more important (±)-martinelline in 10% overall yield over nine steps via the longest linear sequence. **217** were then transformed into **218** in several steps using different functional group conversions. Deprotection of the two Boc groups which still remained in the molecule using TFA/CH_2Cl_2 with subsequent HPLC purification gave (±)-martinellic acid **214a** in 14% overall yield in eight steps. On the other hand, After 2 steps martinelline **214b** was obtained via deprotection of the Boc groups using TFA in dichloromethane, with subsequent reversed-phase preparative HPLC.[225] This product showed identical spectroscopic data with those of the original natural products.[224]

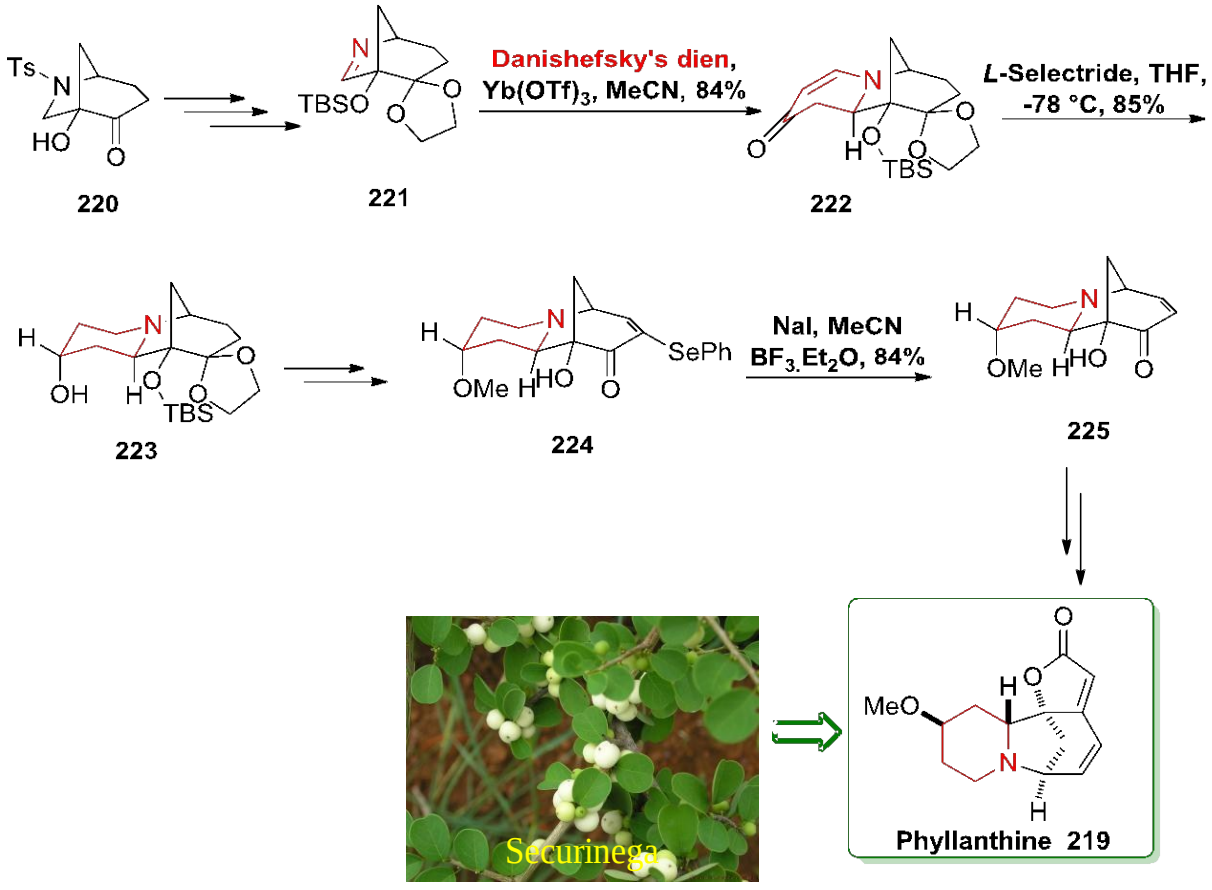


Scheme 30

Several plants of the Euphorbiaceae family, especially those of the *Securinega* and *Phyllanthus* genera, provide a group of tetracyclic compounds classified as the *Securinega* alkaloids.[226] Securinine, the main alkaloid which was isolated from the leaves of *Securinega suffructicosa*. Its structure elucidated in the 1960s.[227] Subsequently, several other *Securinega* alkaloids were isolated. They contain the A-ring methoxylated compound phyllanthine (**219**).[228, 229]

The A-ring of phyllanthine (**219**) was successfully, synthesized from hydroxyketone **220** via a stereoselective $Yb(OTf)_3$-catalyzed HDA reaction of the imine **221** with Danishefsky"s diene employing various common Lewis acid catalysts such as $SnCl_4$, $TiCl_4$, providing adduct **222**.

Conjugate reduction combined with asymmetric equatorial ketone reduction of vinylogous amide **222** gave tricyclic intermediate **223**, which could be subsequently transformed in a few to stable hydroxyenone **225** in few steps, via the generation of R-selenophenylenone intermediate **223** (scheme 31). Then D-ring was constructed, again employing an intramolecular Wadsworth-Horner-Emmons olefination reaction to afford phyllanthine (**219**).[230]

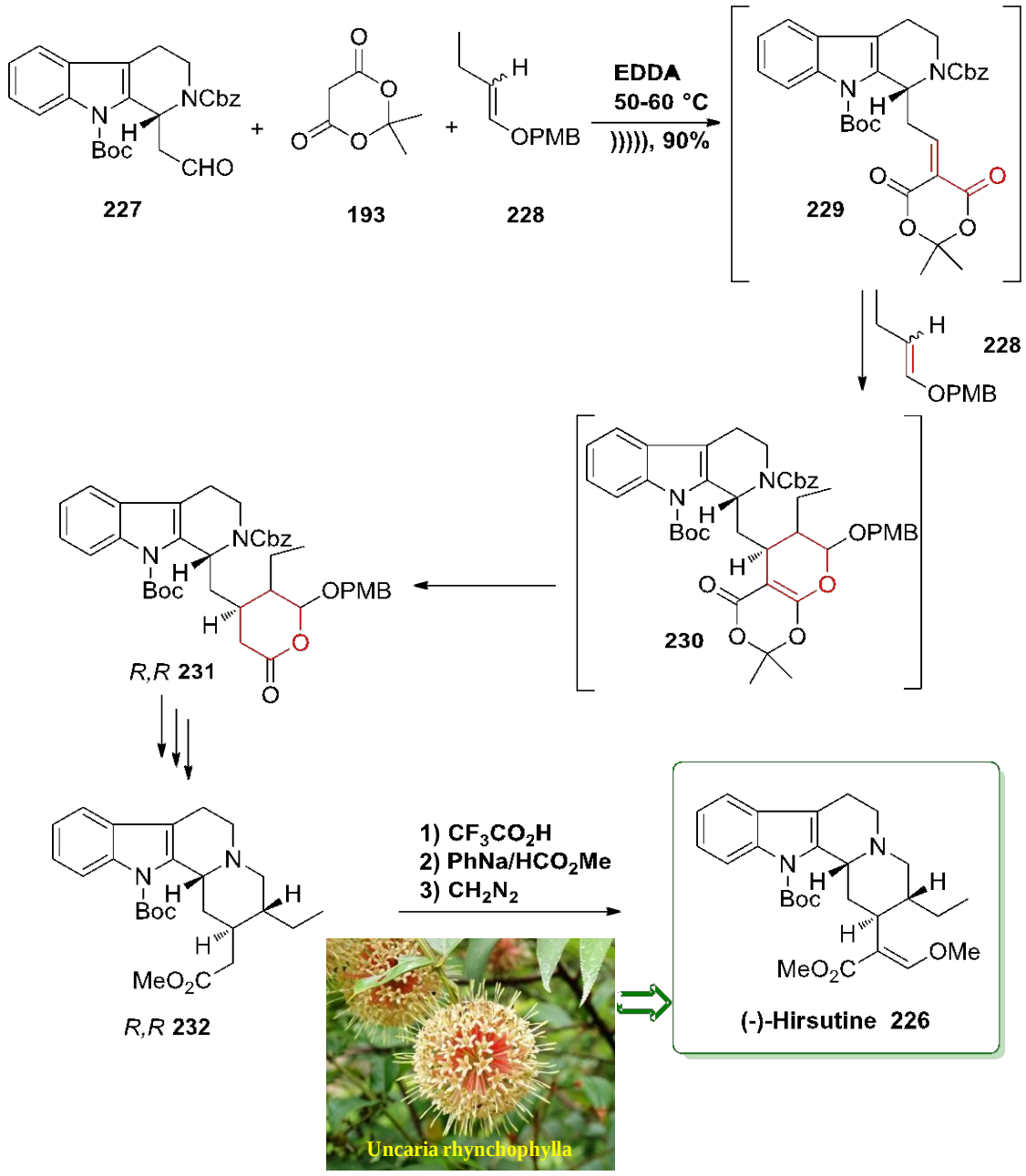


Scheme 31

The indole alkaloids[231, 232] hirsutine **225**[233-235] and dihydrocorynantheine both are classified in the corynanthe family. They were isolated from the plant *Uncaria rhynchophylla* MIQ. This plant has been used in the preparation traditional Chinese medicine "Kampo." for centuries.

In 2002, hirsutine **226** has tremendous attention in medicine, since it has been found showing to inhibit the growth of the influenza A virus. The total synthesis of hirsutine **226** has been accomplished successfully and reported. In this approach the enantiopure tetrahydro-β-carboline (3R)-aldehyde **227** was reacted with a mixture of Meldrum's acid **194** and the enol ether **228** (E/Z: 1:1) promoted by a catalytic amount of EDDA (ethylenediammonium diacetate) to afford

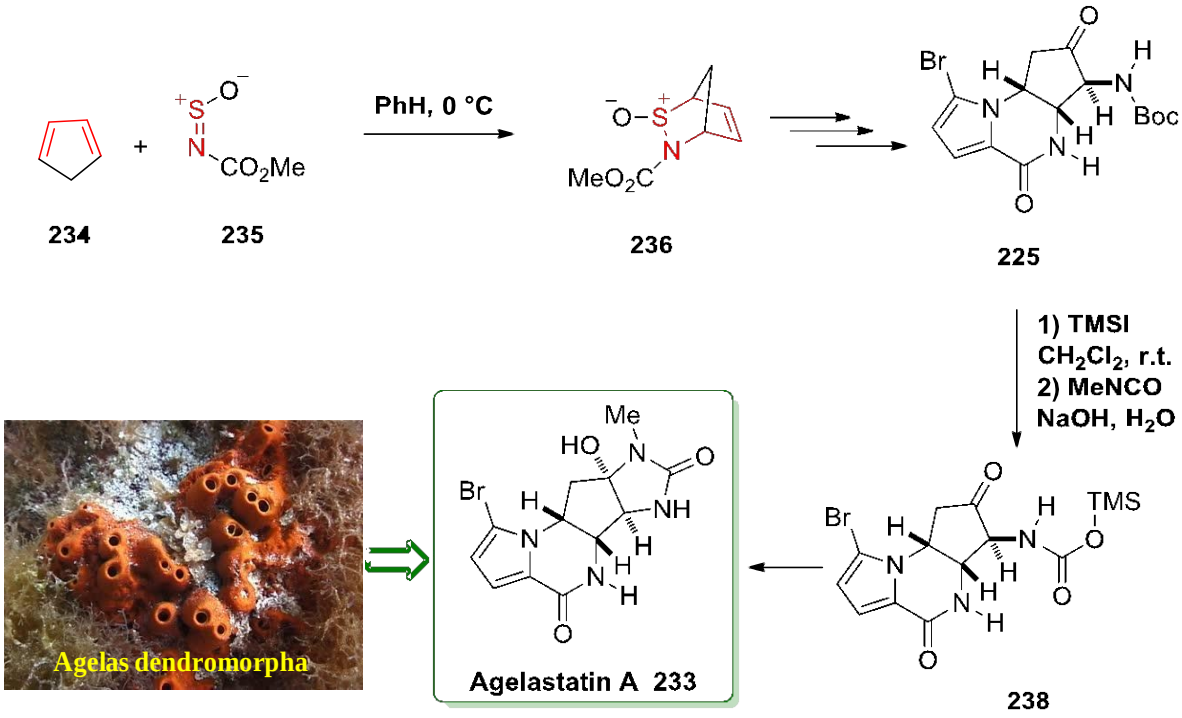
231 in high yield. It is proposed that this transformation occurs via a domino Knoevenegl –HDA. A 1,3 induction of >20:1, generates the Knoevenegl product **229** as an intermediate. This followed by transformation of **230**, via HDA reaction which upon loss of CO_2 and acetone by reaction with water gives **231** (Scheme 32). The latter was transformed to the desired natural product (−)-hirsutine **226** via formation of **232** in several steps.[236]



Scheme 32

Agelastatin was initially isolated in 1993 from the deep water marine sponge *Agelas dendromorpha* by Piertro and his research group. The sample for isolation had been collected from deep water from the Coral Sea near New Caledonia.[237-239]

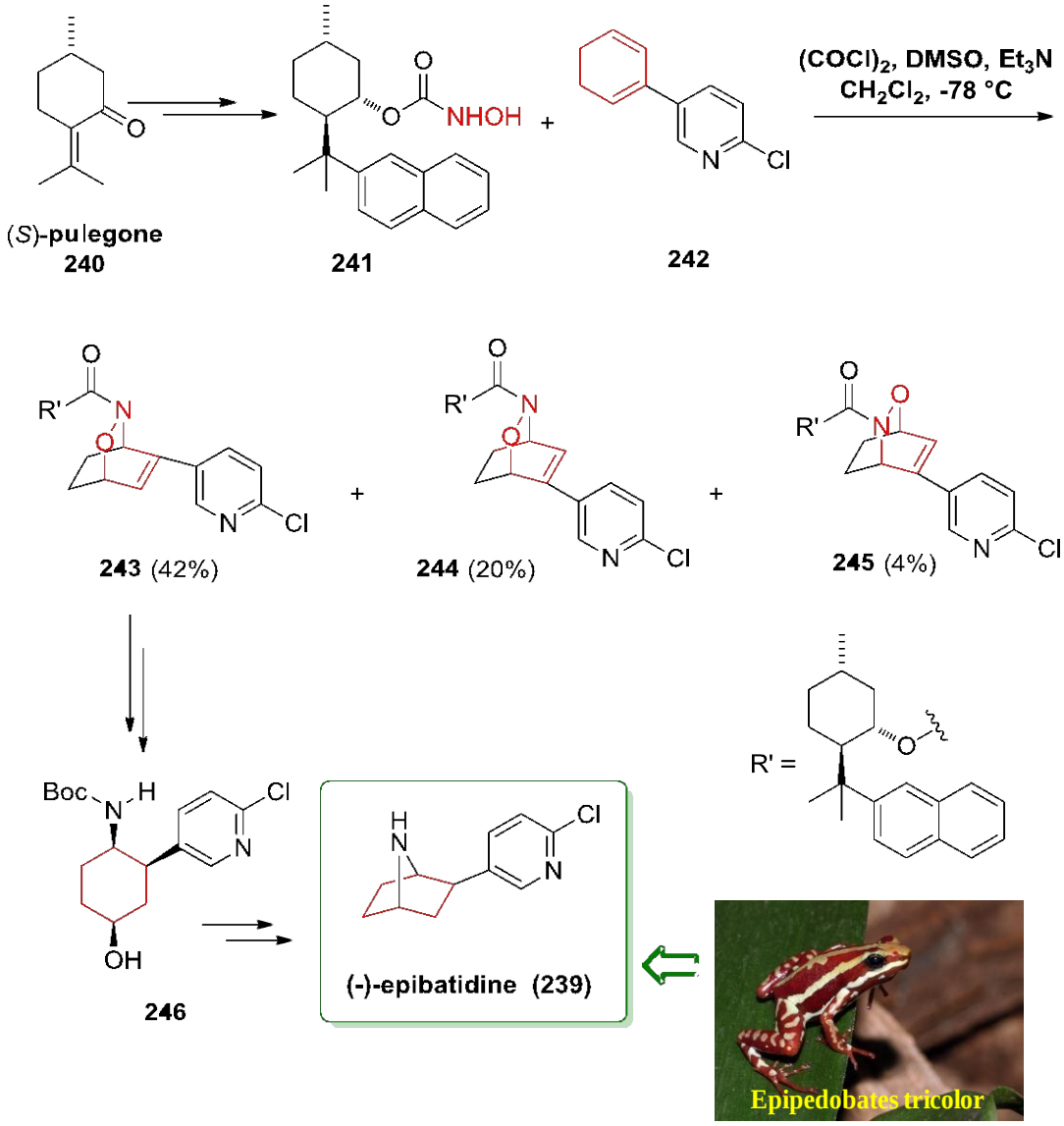
A relatively concise total synthesis of agelastatin A (**233**), a cytotoxic marine metabolite, has been accomplished and reported. This approach interestingly starts from cyclopentadiene which upon HDA cycloaddtion reaction with N-sulfinyl methyl carbamate (**235**) gave cycloadduct **236**. The latter in several steps was transformed to silylpyrrole **237**, which could be transformed to bromopyrrole **238**. At last, the D-ring could be annulated onto an R-amino ketone derived from **238** employing methyl isocycanate, to afford racemic agelastatin A (**233**) (scheme 33). This total synthesis has been completed in 14 steps, conducted in 12 operations giving the desired natural product 1in about 0.7% overall yield.[240]



Scheme 33

In the mid-1970s a new class of amphibian alkaloid epibatidine was initially isolated only in a trace quantity from the skin of the Ecuadorian poison frog, *Epipedobates tricolor*, of the family Dendrobatidae by Daly and his research group.[241] It took long time when in 1992 its structure **239** was elucidated.[242] This structure elucidation disclosed the relative stereochemistry and exceptional feature having a strained nitrogen-bridged six-membered carbon ring system (7-

azabicyclo[2.2.1]heptane) carrying an exooriented 3-(6-chloropyridyl) substituent. Due to obtaining the very tiny amounts of the natural product (less than 1 mg can be isolated and collected from about 750 frogs), the assignment of absolute stereochemistry was difficult. However in 1994 Fletcher et al[243, 244] disclosed the absolute configuration, establishing it as 1R, 2R and 4S as illustrated in scheme 34. Because of the shown unprecedented biological properties, interesting structure, and insufficiency in nature, epibatidine has attracted enormous attention of synthetic organic chemists worldwide,[245] and shortly a plethora of synthetic strategy has been practiced and some of the successfully were accomplished.[246-251] Among these synthetic strategies, nevertheless, only two stereoselctive total syntheses of (-)-epibatidine (**239**), a naturally occurring enantiomer, have been reported: a) via Pd-catalyzed desymmetrization reported by Trost and co-workers[249] and b) via stereoselective protonation revealed by Kosugi et al.[248] A stereoselective total synthesis of (-)-epibatidine (**239**) has been accomplished via development of stereoselective HDA cycloaddition with an *N*-acylnitroso dienophile carrying the optically active 8-arylmenthol as a chiral element. Therefore, upon in situ oxidation of the hydroxamic acid *ent*-**241** incorporating the (1*S*,2*R*,5*S*)-8-(2-naphthyl)menthyl auxiliary was conducted applying the Swern conditions to produce the acylnitroso dienophile, which reacted rapidly with 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**242**) to afford the (1*S*,4*R*)-*meta-aza* cycloadduct **243** as a major diastereoisomer. The resulted facial diastereoselectivity is consistent with a transitional state model with the naphthyl group in "stacked" position along with the acylnitroso group standing in the *s-cis* conformation, whereas π attractive interaction between the naphthyl and nitrosocarbonyl groups could control the facial stereoselectivity. In the following, compound **244** upon hydrogenation with subsequent of removing of the chiral auxiliary using LiH_2NBH_3 followed by reductive cleavage of the N-O bond using $Mo(CO)_6$ afforded the amino alcohol derivative **246**. The latter was then transformed to (-)-epibatidine **239** through bromination with subsequent cyclization.[252]

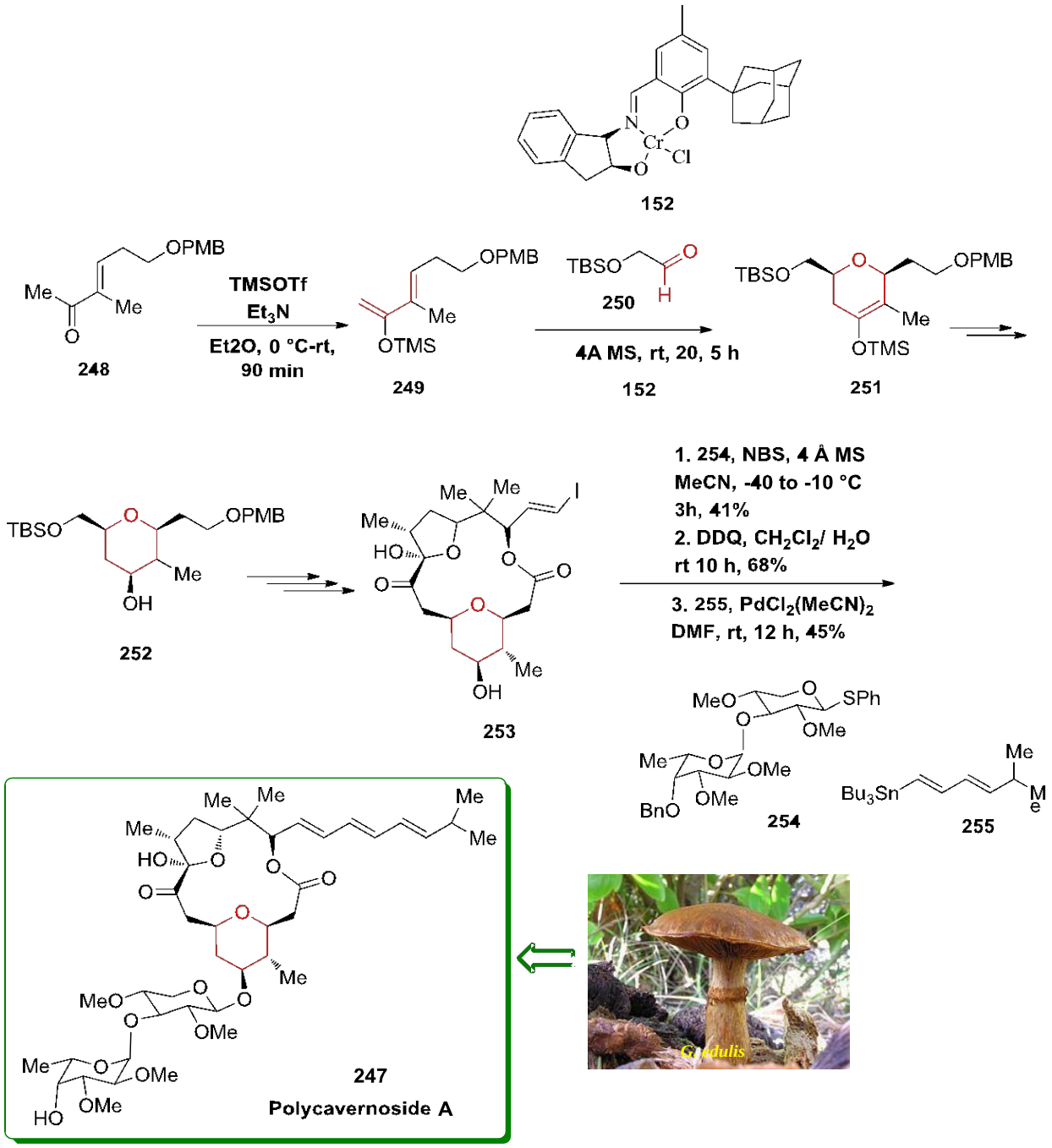


Scheme 34

In 1993 polycavernoside A (**247**(was isolated by Yasumoto research group, along with a small amount of analogue polycavernoside B, as relevant toxins for the lethal human poisoning which happened in Guam in 1991 and in the Philippines in 2002−2003. The fatal cause was recognized being to the ingestion of the comestible red alga *Gracilaria edulis* (*Polycavernosa tsudai*).[253, 254] In a total synthesis achieved by Sasaki group initially (−)-polycavernoside A converted to the THP (tetrahydropyran) ring via catalyzed asymmetric HDA cycloaddition, occurred between silyloxy diene **249** and aldehyde **250**, in the presence of **152** to give the desired product **251** The

latter was converted to desired tetrahydropyran **252** excellent yield in two steps including reduction (Scheme 35).[255]

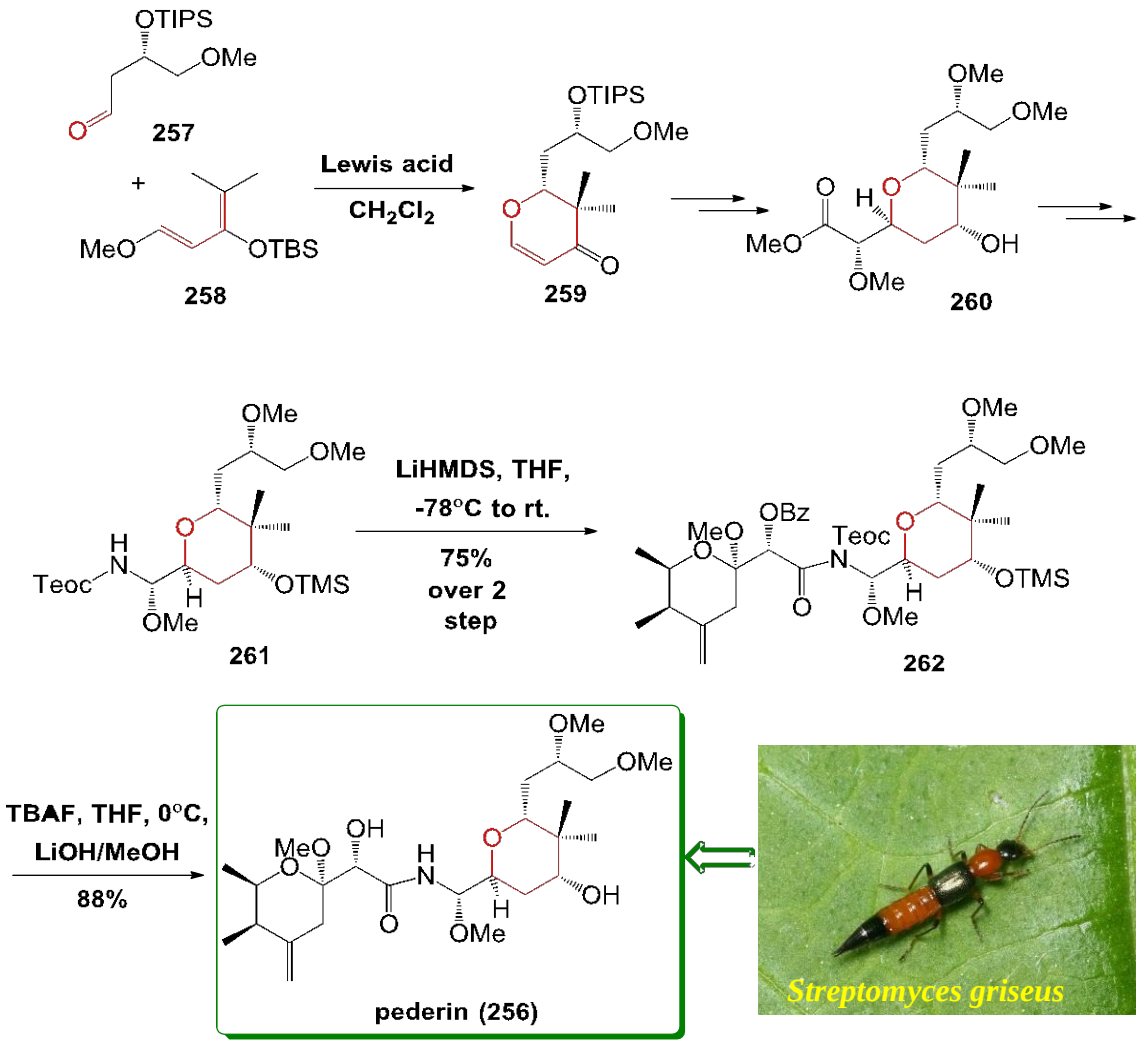
At last, glycosylation of **253** with thioglycoside **254**[256, 257] in the presence of NBS[258] (41%), was subjected into oxidative cleavage of the benzyl ether using DDQ (68%), followed by Stille coupling with the already known dienylstannane **255**[259, 260] (45%) to achieve the synthesis of (−)-polycavernoside A (**247**).[52, 261, 262]



Scheme 35

Pederin (**256**) historical among bioactive natural products.[263] Its presence in the haemolymph of rove beetles of the genus *Paederus*, has been recognized[264] Initially it was isolated in 1919 as a crystalline compound by Netolitzky. It was screened and found to be an active vesicant.[265] Interestingly, Pavan and Bo collected massive *Paederus fuscipes* beetles, to be certain to isolate an appreciable amount of pure pederin, for further elucidation of its structure. In 1965 its structure was determined and reported by to allow its chemical formula and provisional structure to be determined by Quilico et al.[266] Remarkably, Matsumoto et al. independently suggested a marginally modified structure for pederin,[267] This modified structure latter was confirmed and validated by single crystal X-ray analysis.[267, 268]

The total synthesis of pederin was also claimed by Rawal group which also employed a HDA cycloaddition reaction as a vital step. Pyranone **259** initially was prepared reaction between **257** and **258** mediated by Al(2,6-diphenylphenol)$_2$Me and TMSOTf. In the last step of reaction again HDA reaction was performed affording THP ring **260** in excellent yield (Scheme 36).[262, 269] The addition of this acid chloride in toluene gave to the lithium anion **260** which was converted to protected pederin **262** in satisfactory yield over two steps. Upon deprotection via initial treatment with TBAF with subsequent hydrolytic quench afforded pederin (**256**) in 88% yield.



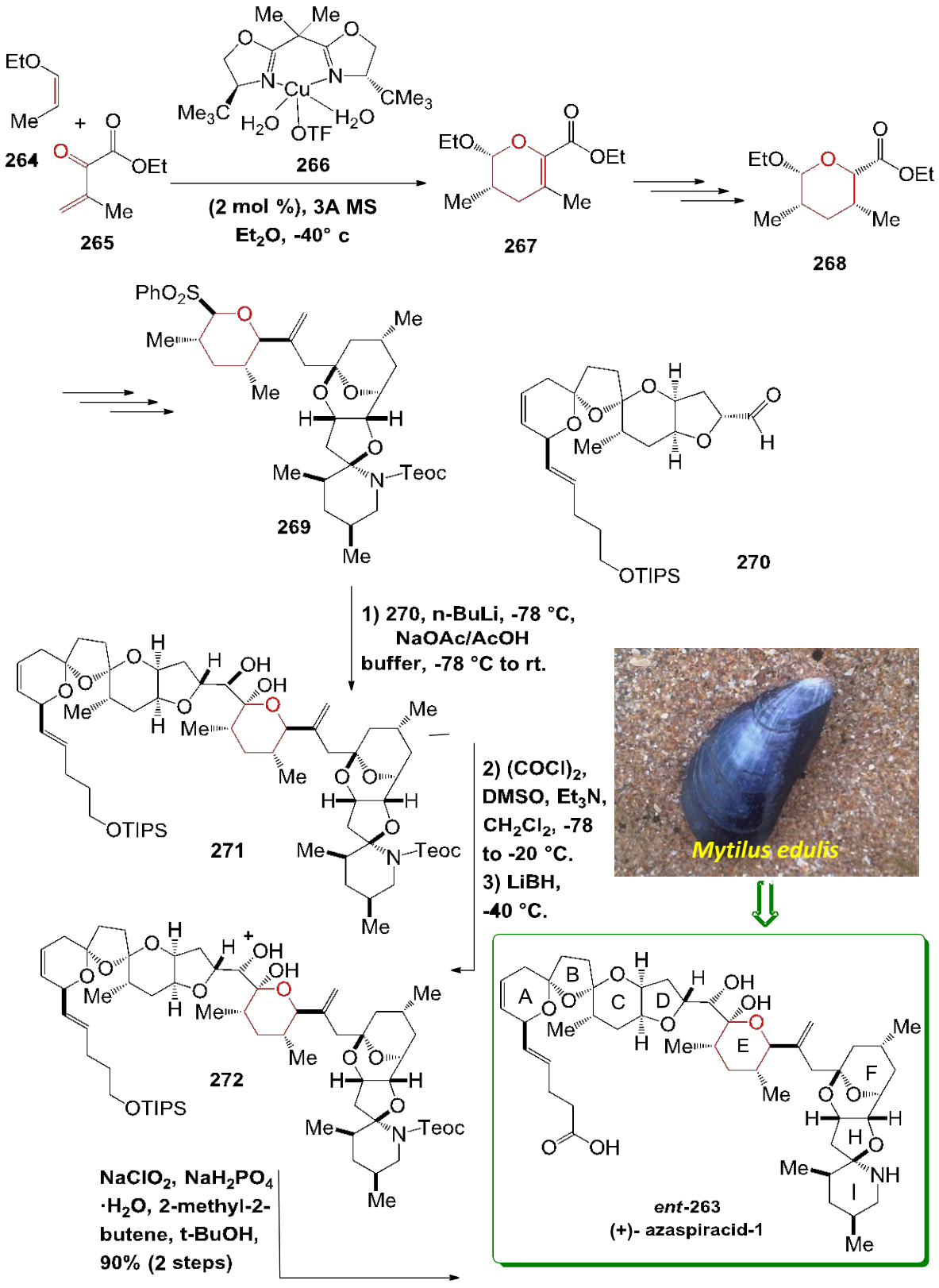
Scheme 36

Azaspiracid poisoning is a recent toxic syndrome initially discovered and revealed in 1995. In one instance, at least 8 people became dizzy in Netherlands after overwhelming blue mussels (*Mytilus edulis*) harvested.[270] The intoxications due to azaspiracid poisoning were also observed in several other countries. Due to these observations and incidents, natural product chemists were motivated for isolation of this compound. In 1998 Satake group proposed[271] marine dinoflagellate,[272] as the origin and their occurrence has assumed in multiple shellfish species involving mussels, oysters, scallops, clams, and cockles.[272] The interesting structure of this toxin has stimulate several research group worldwide and particularly motivated Nicolaou,[273] Carter,[274] Forsyth,[275] research groups as well as some others.[276] Eventually in 2003 it was Nicolaou group

accomplished a fruitful synthesis of the suggested structure **263**, and confirmed clearly the structure suggested for isolated natural product.[277-279]

During the total synthesis, this group prepared THP rings in (+)-azaspiracid via HDA cycloaddtion reaction. The THP E-ring **268** was constructed from dihydropyran **267**. The latter in turn synthesized via a HDA reaction between **264** and **265** in the presence of copper box-complex **266**. However this reaction afforded a mixture of cis and trans diastereomers in a total yield of 84% (Scheme 37).[277]

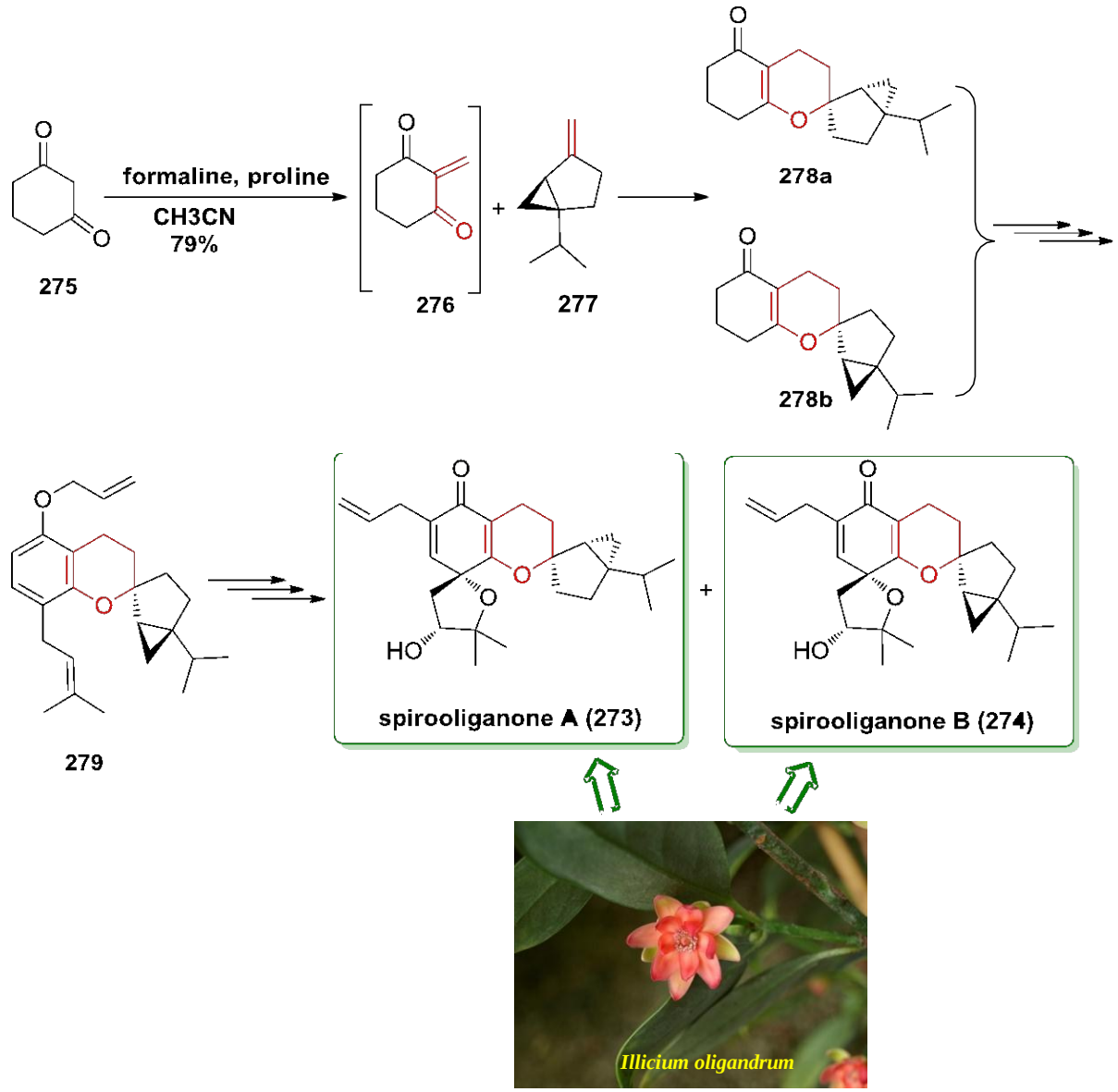
The sulfone anion obtained from **269** was created using n-BuLi followed by addition to aldehyde **270** which subsequently quenched at -78 °C in pH 5 buffer. Delightfully, this approach gave a 50% overall yield. Noticeably, the lactol diastereomers **271** and **272** were easily separated in virtually equal amounts by flash column chromatography.[280] This step actually successfully completed the total synthesis of (+)-azaspiracid-**1** (ent-**263**).[277]



Scheme 37

Illicium oligandrum has been for long time, as long as centuries, used as Chinese traditional medicine mostly for the treatment of rheumatoid arthritis. Yu et al initially isolated a pair of spiro carbon epimers, spirooliganones A and B, from the roots of I. *oligandrum* and revealed their results in 2013.[281]

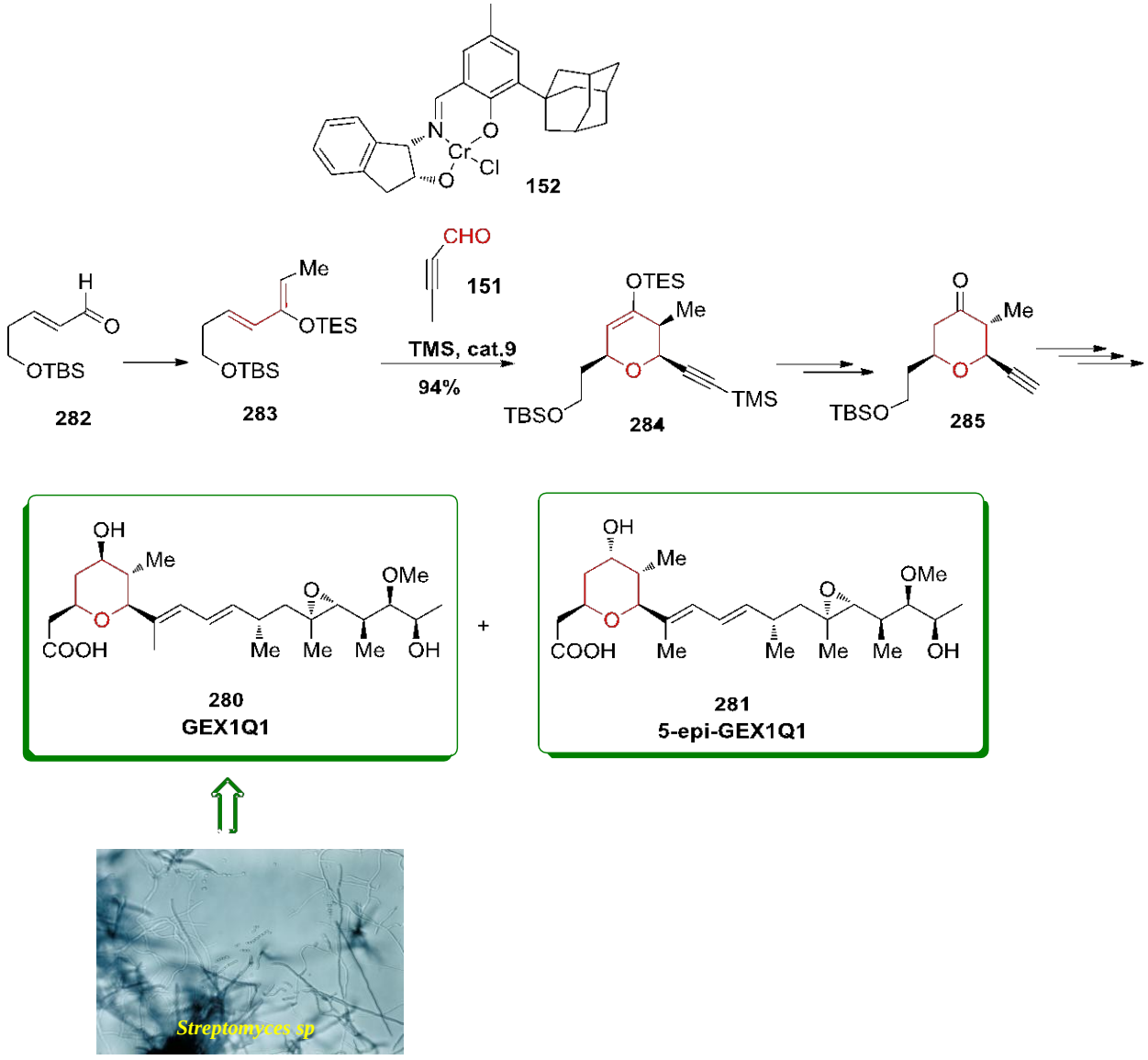
A facile and efficient approach to achieve the stereoselective total syntheses of (−)-spirooliganones A and B in 8 steps has been disclosed. This strategy uses market purchasable 1, 3-cyclohexanedione, formalin, (−)-sabinene, prenyl bromide, and allyl bromide. As shown in Scheme 38, the synthesis commenced with preparation the tetracyclic intermediate **278a** and **278b**. Upon Hoffmann conditions,[282-285] 1, 3-cyclohexanedione was reacted with formalin and (−)-sabinene in acetonitrile as solvent, along with HDA cycloaddition reaction which occurs monotonously in one pot to give a 1:1.2 mixture of epimeric tetracyclic adducts in high yield. Allyl ether **279** were also provided in several steps in high yield. Spirooliganone B (**274**) and (−)-spirooliganone A (**273**) was obtained in 15% overall yield.[286]



Scheme 38

In 2002 Yoshida and co-workers isolated GEX1Q1 **280** as one of the six natural occurring compounds including GEX1A (herboxidiene) from a culture broth of *Streptomyces* sp.[287] The stereoselective synthesis of tetrahydropyranone derivative **285** is illustrated in Scheme 39. Silyloxy diene **283** was provided using aldehyde **282** as precursor according to the procedure reported previously.[288] A stereoselective HDA cycloaddition reaction of diene **283** with market purchasable aldehyde **151** under catalysis effect of Jacobsen"s catalyst **152**[289, 290] gave

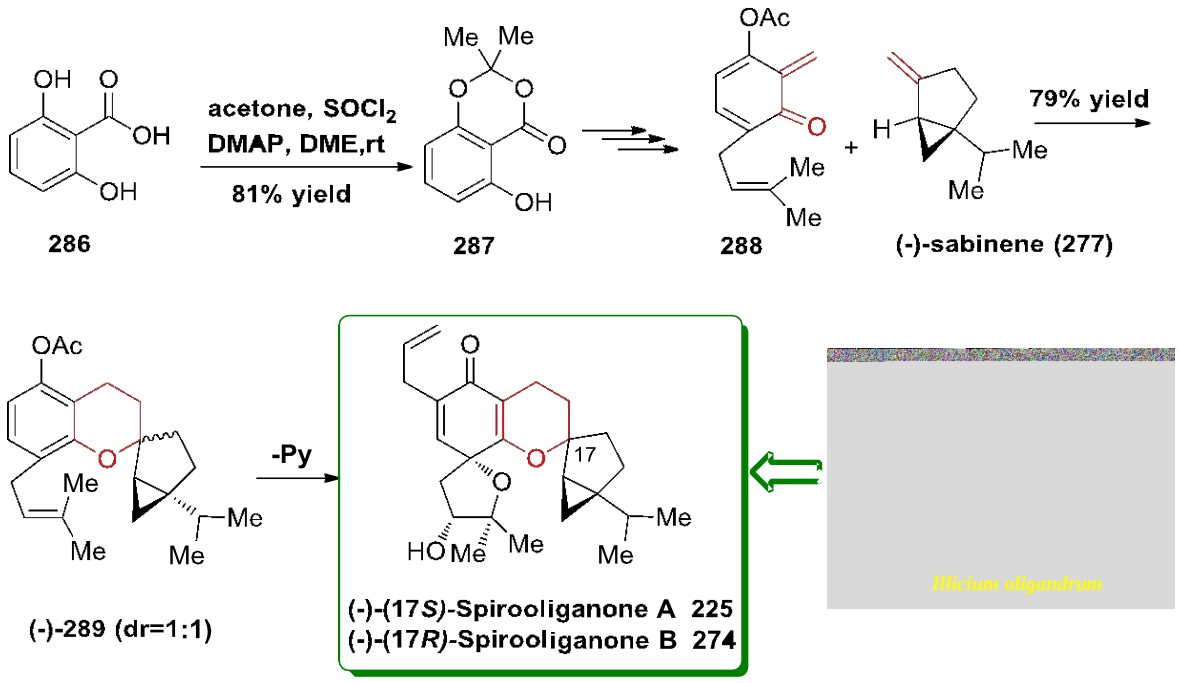
cycloadduct **284** in excellent yield, finally leading to synthetic GEX1Q1 (**280**) in high yield along with 5-epi-GEX1Q1 **281**.[291]



Scheme 39

In 2013 Yu[292] and other co-workers isolated the two structurally novel antiviral spirooliganones A and B from the roots of *Illicium oligandrum*. They were found, showing a wide range of antiviral activities and has been extensively used for centuries in Chinese traditional medicine for treatment of rheumatoid arthritis.

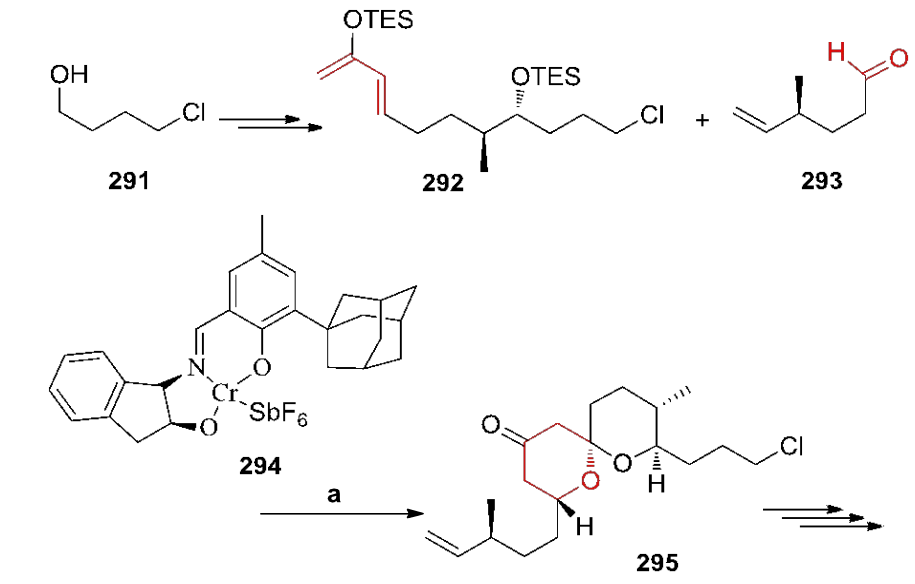
Biomimetic total syntheses of potent antiviral spirooliganones A and B were accomplished and reported in 3% and 2% yield, respectively, in 12 steps starting from market purchasable materials. This relatively concise total synthesis (Scheme 40) commenced with the synthesis of acetonide **287** from market purchasable or readily available 2,6-dihydroxybenzoic **286** in which the spiro-fused AB rings of spirooliganones can be provided via the phenol oxidative dearomatization.[293-297] The assemblage of the key tetracyclic scaffold (BCDE rings, **289**) could be obtained in a biomimetic manner after several steps including a HDA reaction of (−)-sabinene (**277**) and o-quinone methide **288**. The desired spirooliganones A and B can be obtained in several steps.[297]



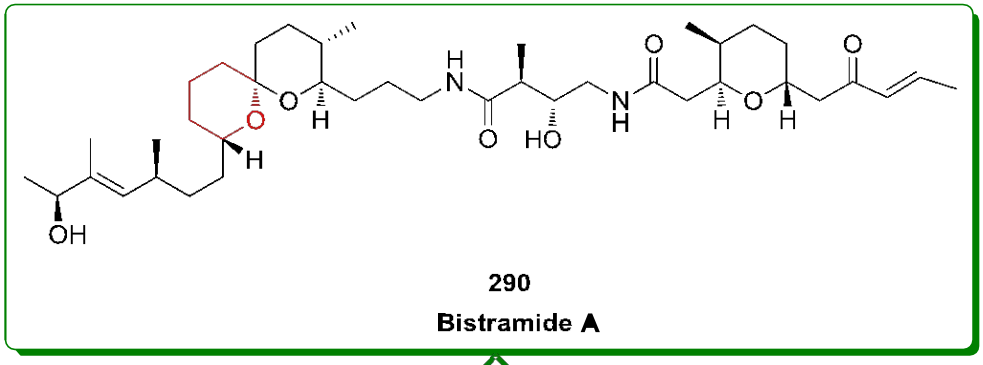
Scheme 40

Verbist and co-workers in 1988 disclosed the isolation of a novel marine metabolite of *Lissoclinum bistratum* named bistramide A.[298, 299] Initially it showed prompt active cytotoxicity, and then bistramide A (**290**) to have a deep effect on cell cycle regulation, resulted in growth arrest, diversity, and apoptosis in some cell lines.[300, 301] A concise impressive sequential involving asymmetric HDA cycloaddtion reaction and oxidative carbon–hydrogen bond functionalization to access spiroacetals achieved.

Initially,4-choloro-1-butanol **291** was transformed into the silyloxy diene **292**. In turn the spiroacetal was provided via HDA coupling/ cycloaddtion of **292** with the aldehyde **293**, which can be accessed in one step from (+)-b-citronellene,[302, 303] in the presence of ent-**294**. With subsequent DDQ treatment combined with acid-catalyzed ring closure provided the spirocycle **295** in 58% yield as a sole stereoisomer with a contracted sequential reaction. Finally, Bistramide **A** (**290**) was obtained in 69% overall yield after several steps. Noticeably, the longest linear sequence in this approach is 14 steps commencing from market purchasable 4-cloro-1-buthanol as starting material to the aforementioned naturally occurring compound **292** (scheme 41).[304]



a) 294, 4 Å M.S., then DDQ, CH_2Cl_2; then *p*-TsOH.H_2O, 87%

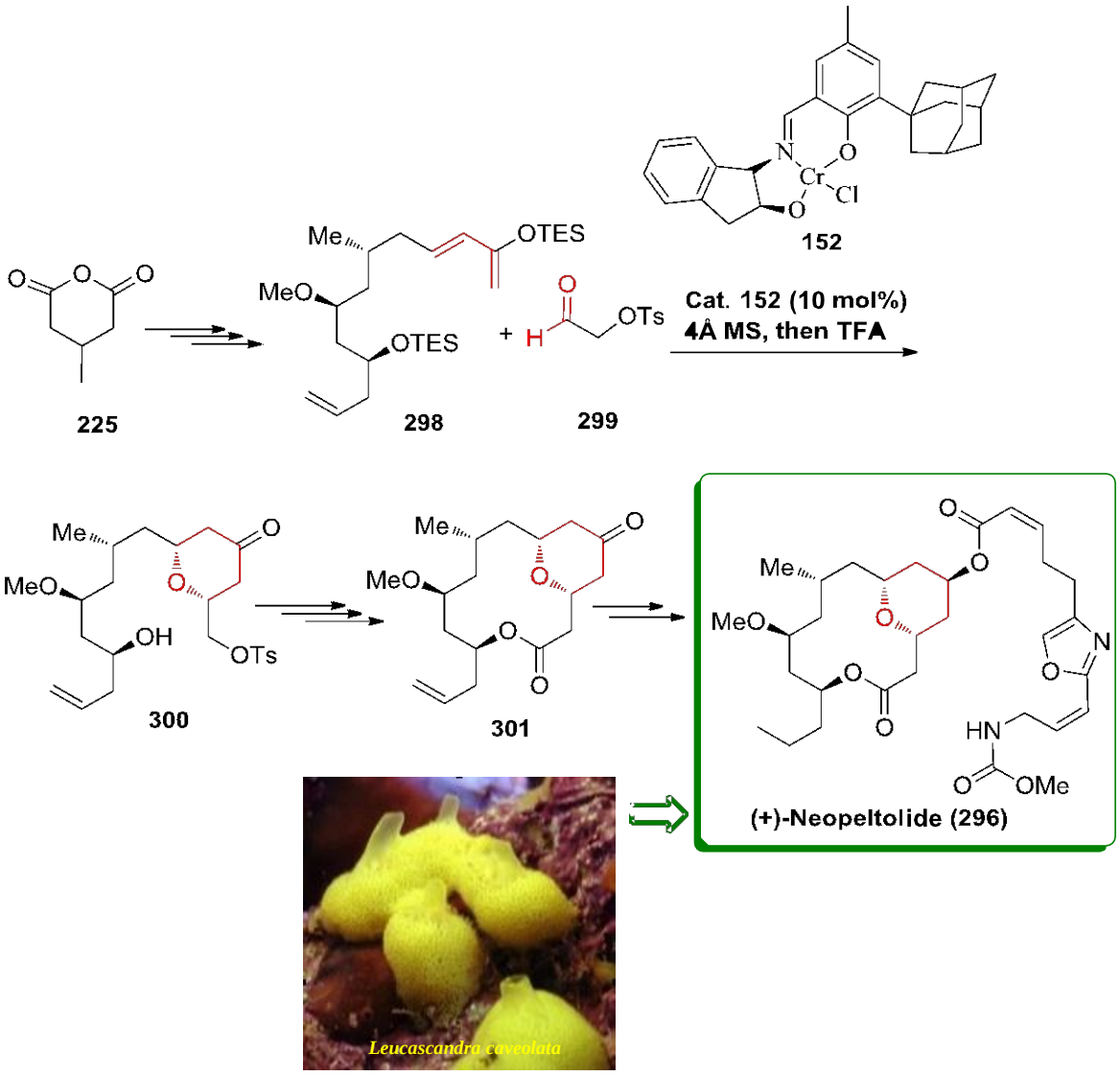


Scheme 41

An enantioselective synthesis of the anti-proliferatory agent (+)-neopeltolide has been achieved in 2.1% overall yield for 21 steps by the longest linear sequence. Remarkably, this synthetic approach was convergent and operationally scalable, using, market purchasable starting materials.

Neopeltolide (**296**) is a complex macrolide which was isolated by Wright and co-workers in 2007. It was initially collected from a deep-water sponge of the family neopeltidae from the northwest coast of Jamaica.[305] Although, this species was not identified but was categorized as a member of the genus *Daedalopelta* and a close relative of *Callipelta*. Compound **296** have been proven being a rich source of biologically potent marine metabolites.[306, 307]

The enantioselective total synthesis of (+)-neopeltolide **296** has been achieved and reported. The total synthesis of the macrolactone ring of (+)-neopeltolide (**296**) started with market purchasable 3-methylglutaric anhydride **297**, which gives the desired silyloxy diene **298** in virtually quantitative yield (scheme 42). Upon the synthesis of silyloxy diene **298** it was reacted with, several aldehydes following HDA reaction to obtain product **300**. The latter exhibited excellent diastereoselectivity upon purification using flash chromatography. Ultimately after several steps, the anti-proliferatory agent (+)-neopeltolide **296** was produced from **300**.[308]



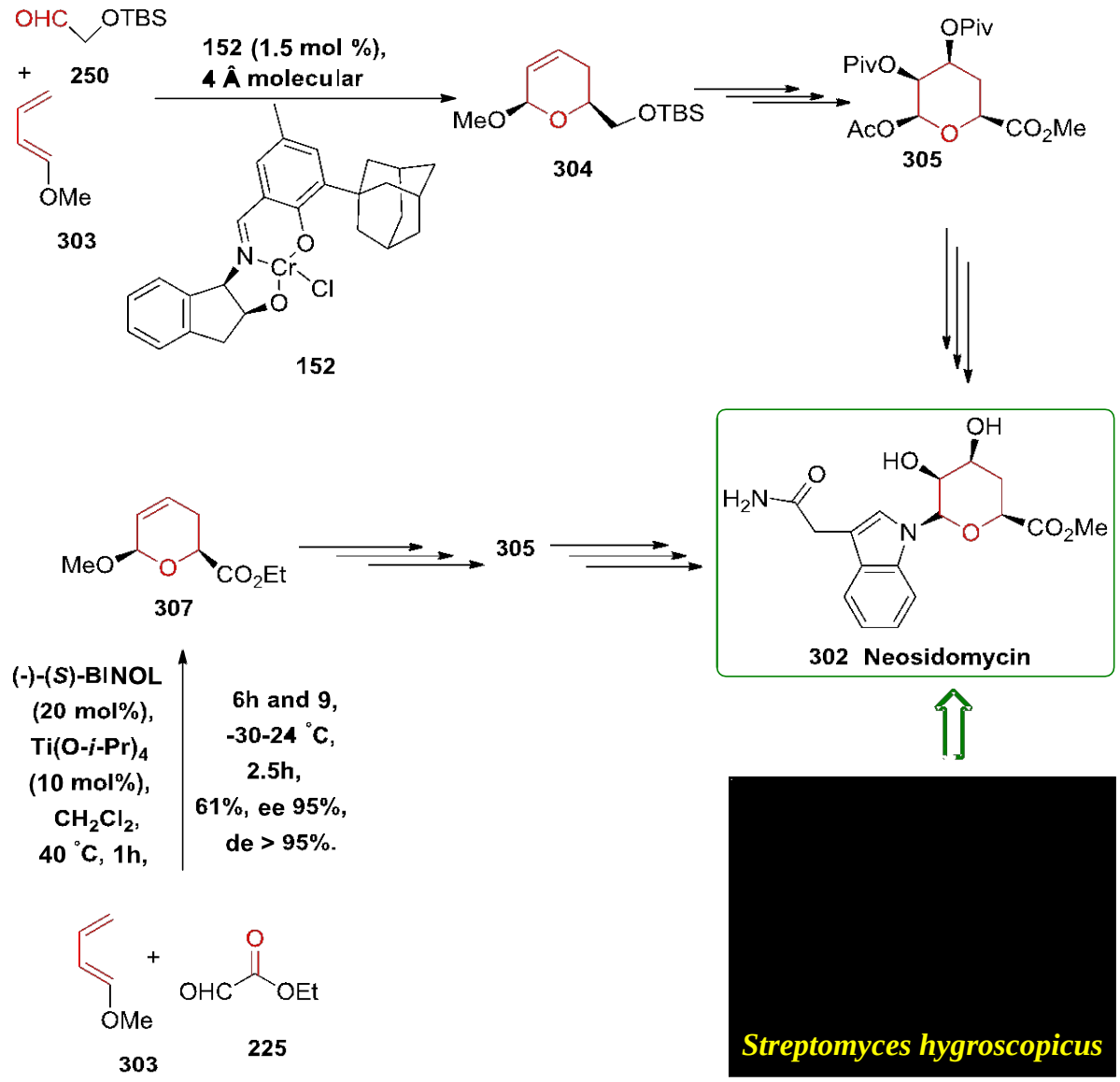
Scheme 42

In light of extension of the usefulness of this protocol for the synthesis of 4-deoxy-D-hexopyranose-containing natural products, the synthesis of neosidomycin **302** was developed. This natural product initially was isolated in 1979 from *Streptomyces hygroscopicus* by the Furuta group.[309] These molecules exhibit antibacterial or antiviral potencies. For neosidomycin **302** only one approach has been previously reported. In this procedure **302** has been synthesized as an inseparable anomeric mixture. The syntheses were started with the highly enantio- and diastereoselective HDA reaction of 1-methoxybutadiene **303** and (tert-butyldimethylsilyloxy)-acetaldehyde **250** under the 1.5 mol % of Jacobsen chiral tridentate chromium(III) catalysis

conditions **152**[289, 310] to afford **304** (Scheme43). Dihydropyran **304** (89% yield, ee >99%, de >99%) has two stereogenic center, thus setting C-1 with a β configuration and C-5 creating the D series of the newly generated carbohydrate core.

Compound **305** was prepared utilizing a de novo protocol as follows. The second-generation and the first-generation preparation of glycosyl donor **305** progressed through an identical protocol.

The HDA cycloaddtion of 1-methoxybutadiene **303** and ethyl glyoxylate **306** using a 2:1 molar ratio of (−)-(S)-1,1′-binaphthol (20 mol %) and $Ti(O\text{-}i\text{-}Pr)_4$ (10 mol %) as catalyst system gave dihydropyran **307** in good yield but in high de and ee.[311] The already made compound **305** found available upon hydroxyl group protection employing PivCl in pyridine in high yield, with subsequent acetolysis to give the corresponding product in 70% yield. The compound **305** gave neosidomycin **302** after 3 reaction steps.[312]

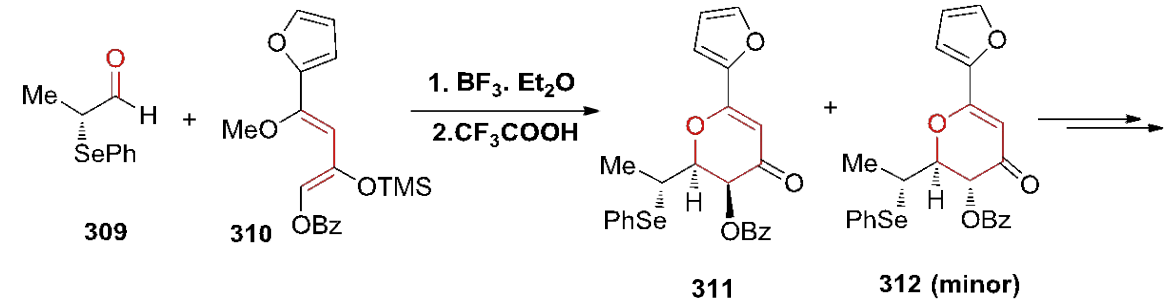


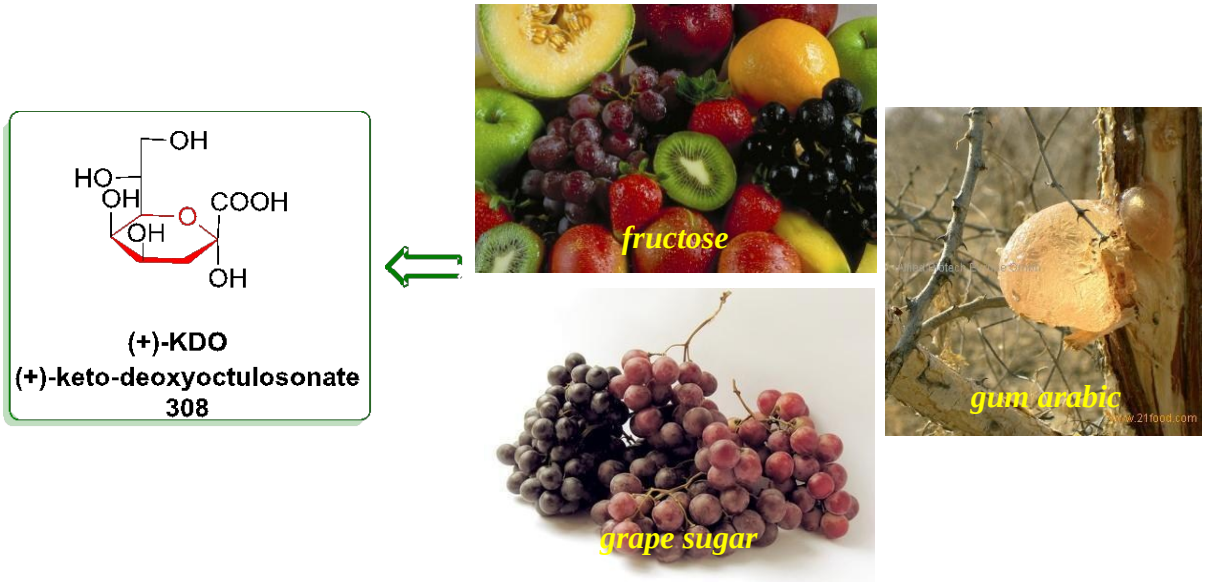
Scheme 43

The first total synthesis of (+)-keto-deoxyoctulosonate (**308**, (+)-KDO) is relied on the HDA reaction of α-selenoaldehyde **309** to the α-furylsubstituted diene **310**.[313] The reaction provides an adduct mixture which upon treatment with CF_3COOH gives a 5:1 mixture of cis/trans dihydropyrones **311** and **312**. Compound **311** was separated and used as pure form to afford the target KDO (Scheme 44).[314]

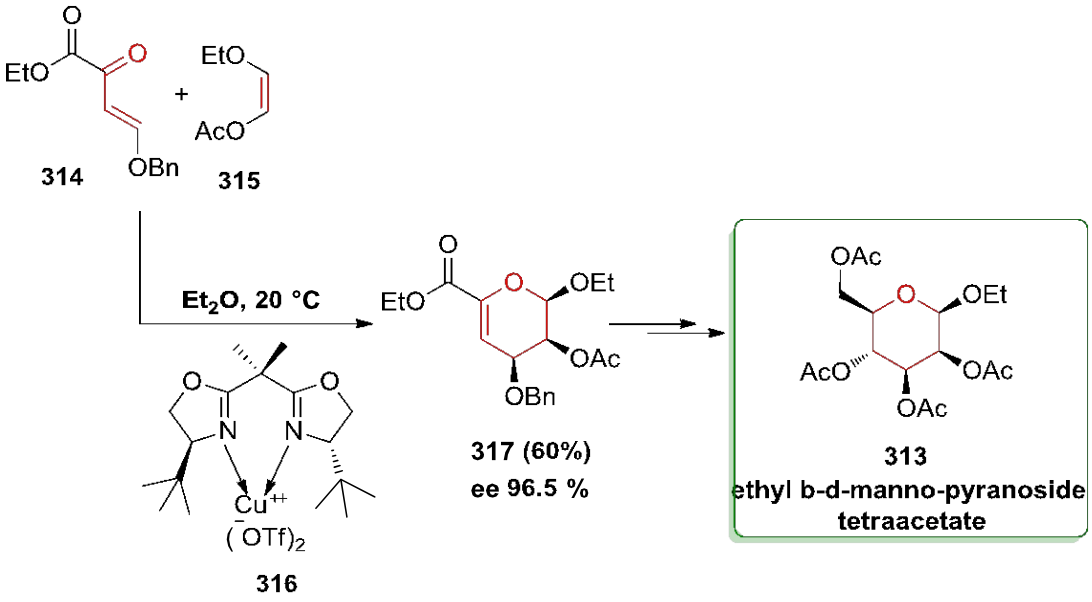
Evans[315, 316] and Jørgensen[317] have independently demonstrated that β,γ-unsaturated α-keto ester **314** reacts stereoselectively with ethyl vinyl ether **315** catalyzed by optically pure bisoxazoline copper(ii) complex **316** as a chiral catalyst. From this reaction, enantiomerically pure

dihydropyran **317** was provided via HDA cycloaddition reaction. The latter was transformed into ethyl β-D-*manno*-pyranoside tetraacetate **313** in several steps (Scheme 45).[314, 318]





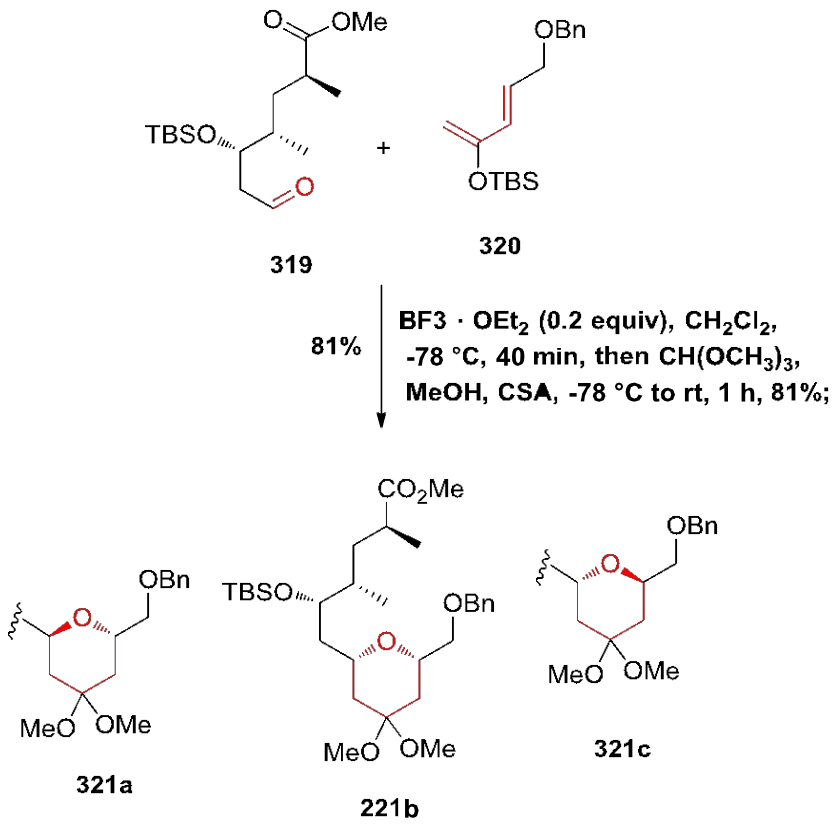
Scheme 44



Scheme 45

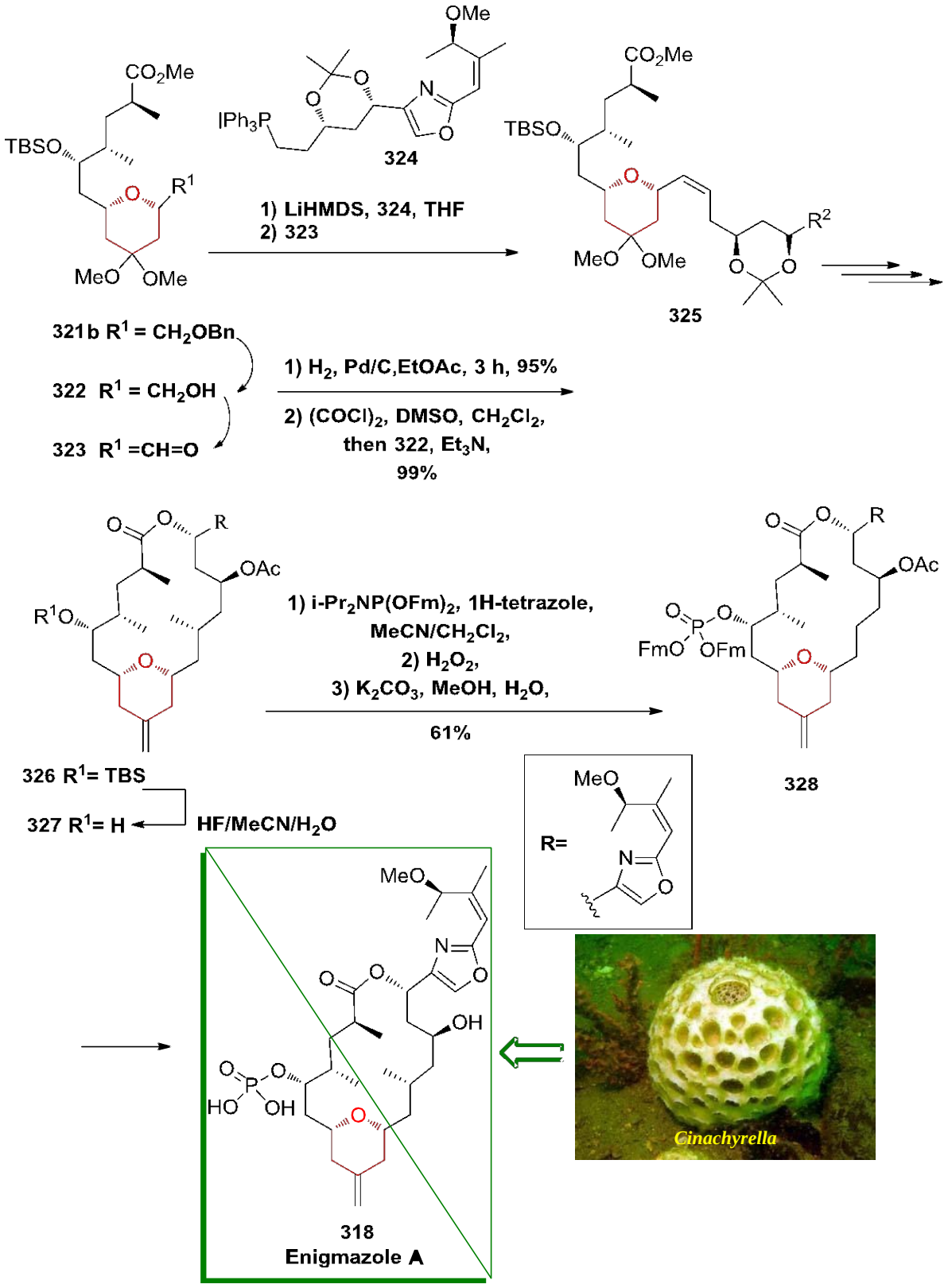
Enigmazole A (**318**) is a member of class of cytotoxic macrolides which were isolated from the sponge *Cinachyrella enigmatica* which includes compounds that selectively target aberrant c-Kit.[319, 320] The total synthesis of **318** was the completed in 22 steps. It is actually the longest linear sequence. Combination of "Eastern" and "Western" hemispheres of enigmazole A commenced with HDA cycloaddition between aldehyde **319** and diene **320** (Scheme 46). Optimization of the reaction resulted in a mixture of three of the four possible diastereomers which can be separated via flash column chromatography to give pure (**321a-c**)

Upon Hydrogenolysis of **321b**, with subsequent Swern oxidation of product **322**, afforded aldehyde **323**. Compound **326** were found surprisingly unaffected to desilylation. The best conditions afforded the desired alcohol in satisfactory average yield. The phosphate was introduced to the C5 hydroxy group of **327** as a protected phosphoramidite (i-Pr_2NP(OFm)$_2$) to provide the entirely protected natural product **328** in satisfactory yield.[321-323] Dissolving of **328** dissolved K_2CO_3 in MeOH/H_2O smoothly and cleanly slashed the C15 acetate and both 9-fluorenylmethyl groups of the phosphate ester, giving raise to enigmazole A (**318**) (scheme 47).[324]



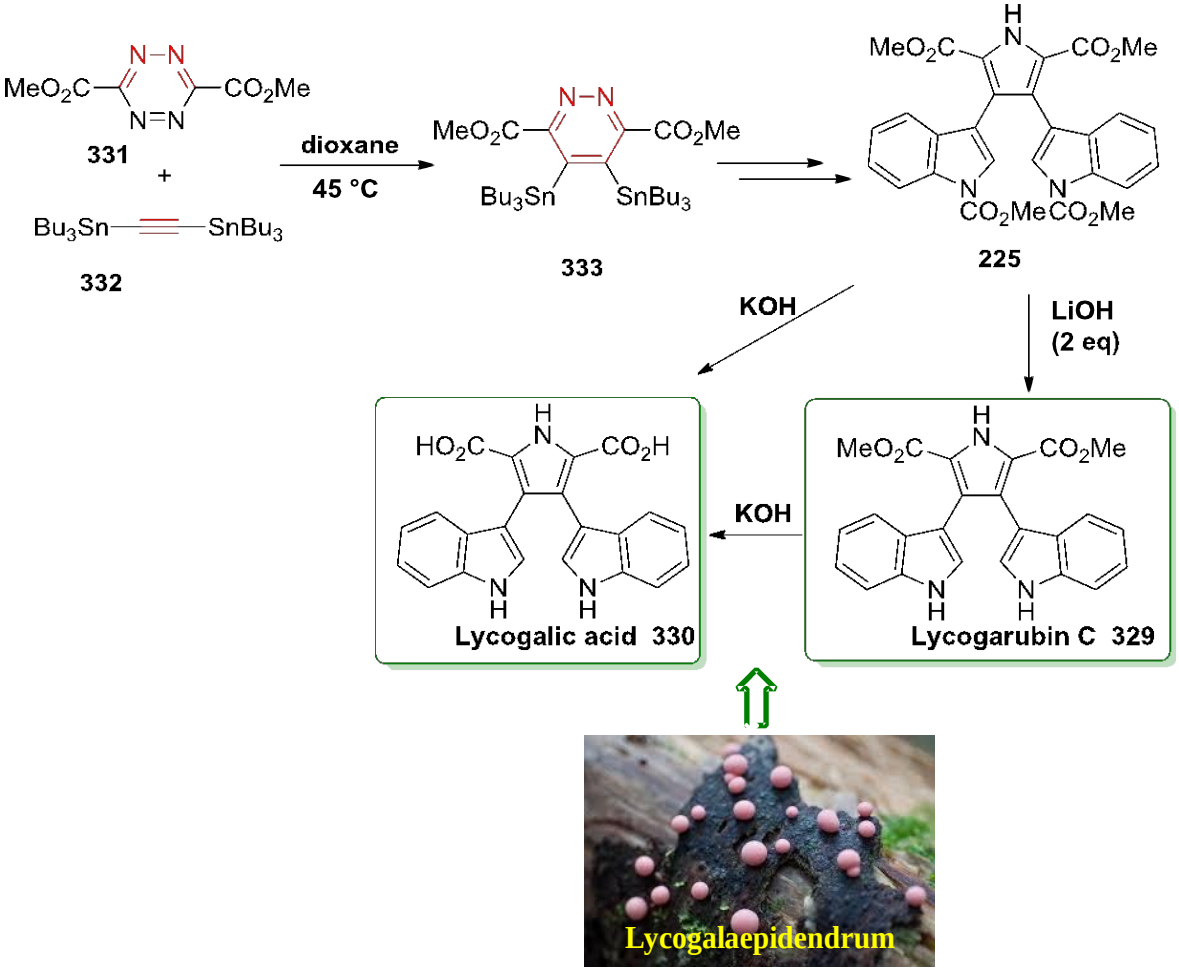
321a: 321b: 321c= 1.2: 4.2: 0.25

Scheme 46



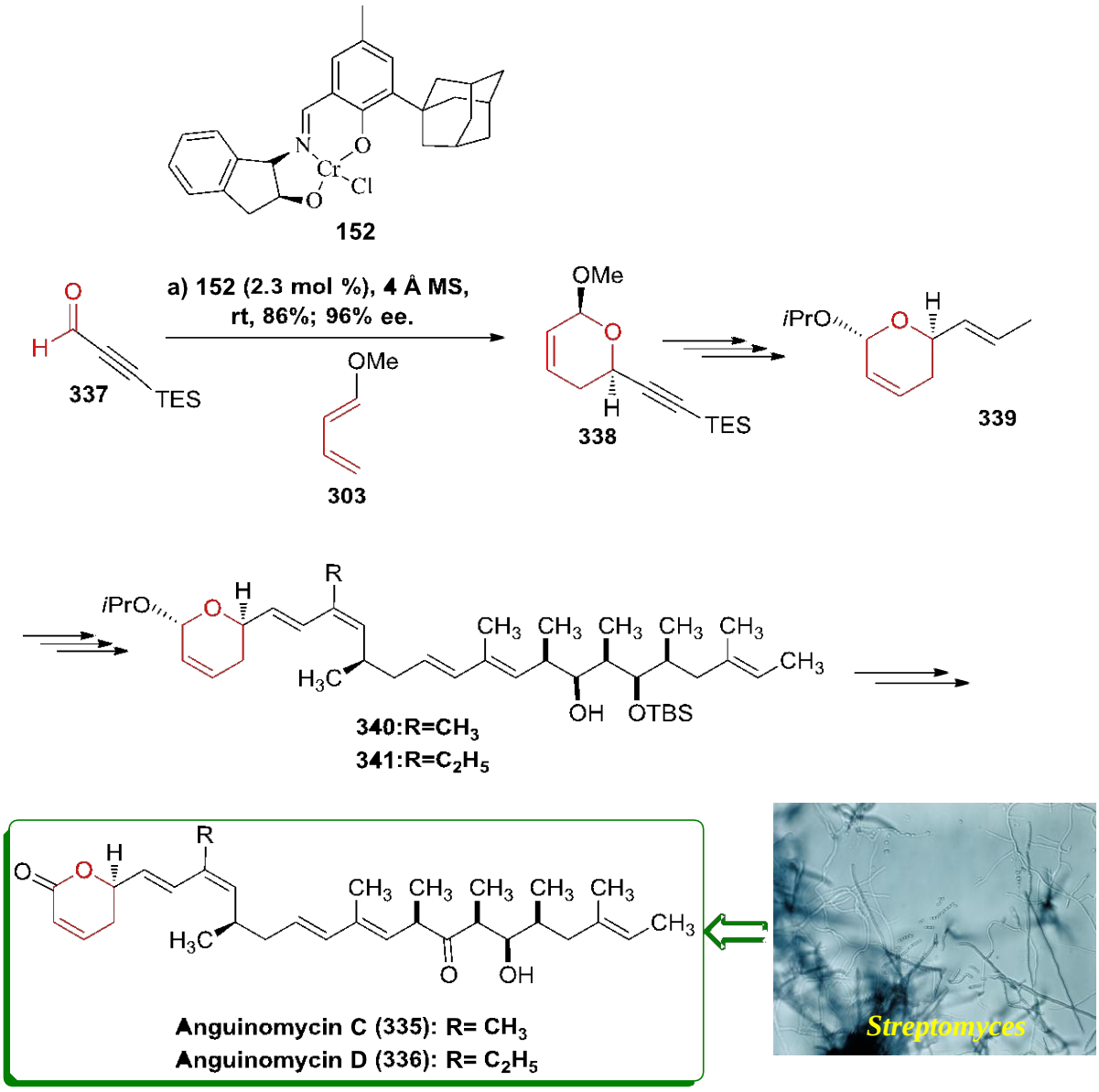
Scheme 47

Lycogarubin C (**329**) and lycogalic acid (**330**) as natural products were initially isolated in 1994 from *Lycogala epidendrum*, a slime mold and shortly after, identified independently by Steglich[325] and Akazawa and co-workers.[326] The total synthesis of **329** or **330** has been achieved and reported,[325, 327-329] In another approach, **329** and **330** were readily synthesized via use of a 1,2,4,5-tetrazine → 1,2-diazine → pyrrol, HDA cycloaddition reaction protocol, which apparently perfectly suited for their synthesis.[330, 331] The reaction of 1,2-bis(tributylstannyl)acetylene (**332**)[332-334] with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**331**) progressed cleanly in dioxane under mild thermal conditions, providing the HDA adduct **333** in excellent conversions (97%). The indole *N*-methoxylcarbonyl groups of **334** under mild conditions, were selectively, removed to afford lycogarubin C (**329**) in good to excellent conversion (65-89%), while exhaustive hydrolysis of **334** or hydrolysis of **329** provided lycogalic acid (**330**) in exceptional conversion (95%) (scheme 48).[335]



Scheme 48

Several highly cytotoxic polyketides, including the anguinomycins,[336] have initially been isolated from *Streptomyces* strains.[337] The total synthesis of anguinomycins C (**335**) and D (**336**) commenced with the providing dihydropyran **338** via a HDA cycloaddtion reaction of already known aldehyde **337**[338] and market purchasable 1-methoxy-1,3-butadiene (**305**) catalyzed by the Cr(III) catalyst (**152**) developed by Jacobsen et al[290] Interestingly this HDA reaction was performed under solventless system and in the presence of 4 Å molecular sieves.[339] The dihydropyran **338** was obtained in high chemical yield (86%), and excellent enantioselectivity (96% ee), however as a 5:1 diastereomeric mixture due to unavoidable epimerization at the anomeric center under the reaction conditions. In this case delightfully, the trans isomer **339** was obtained, and by an inversion of the configuration gave the cis product it is required in the anguinomycin structure. The reaction made progress smoothly, and the coupled product **340** featured the complete scaffold of anguinomycin C was isolated in 80% yield (Scheme 49).[340] Notably Both anguinomycins C (**335**) and D (**336**) were isolated as colorless oils.[341]

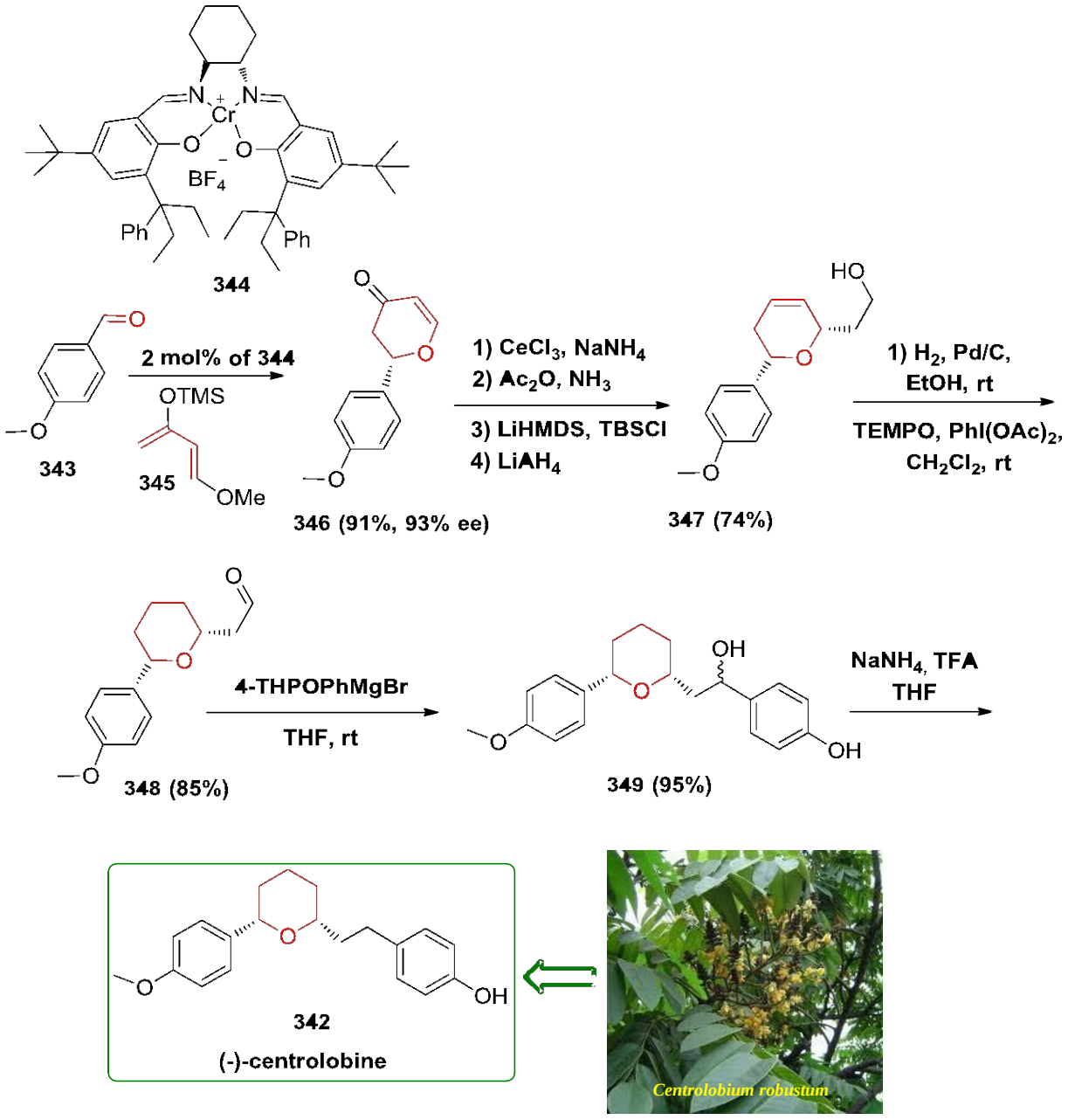


Scheme 49

(−)-Centrolobine is a naturally occurring compound, which initially isolated from the heartwood of *Centrolobium robustum*[342-344] and from the stem of *Brosinum potabile*[345] in the Amazon forest in Brazil. It shows potency towards *Leishmania amazonensis promastigotes*, a bug accompanying with leishmaniasis, which is one of chief health problem in Brazil.[344, 346] Its structure, was elucidated by the synthesis of racemic **347** which showed it contains 2,6-syn-tetrahydropyran **347**.[342, 343] Its absolute configuration was revealed by the first enantioselective total synthesis of (−)-1 in 2002.[347, 348] Stimulated with structural assignment, several research

groups have attempted, successfully achieved and reported the total synthesis of **347** in both racemic [349-351] and optically active forms.[352-355]

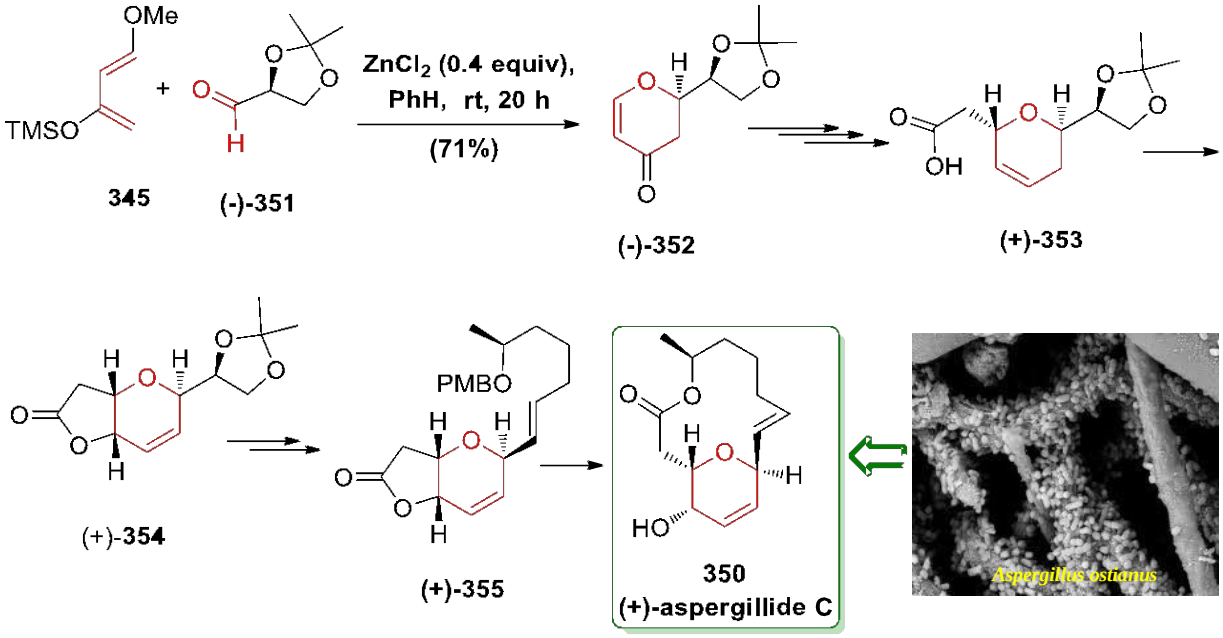
Among them an efficient protocol employed for the total synthesis of (-)-centrolobine **342** is outlined in scheme 50 is worthy being mentioned. The paramount this approach is the utilization of the readily available sterically modified salen complex **344** which acts as catalyst in HDA cycloaddition reaction of Danishefsky"s diene **345** to various aldehydes in high yields and enantioselctivities to yield the pyranones of type **346** and after that the corresponding dihydropyran.[356] In a key step of this total synthesis, dihydropyran **347**, which was obtained from HDA reaction of anisaldehyde in 67% chemical yield and 93% ee, was hydrogenated and followed by conducting other chemical reaction to be converted into **348** in high overall yield. Upon acidic workup of the reaction mixture deprotection of the phenolic hydroxy function occurred, affording the alcohol **349** in 91% yield. The hydroxy group at the benzylic position was removed via utilization of combination of $NaBH_4$ and TFA in THF,[357] to give (-)-centrolobine **342** in 73% yield.[358]



Scheme 50

Kusumi and co-workers initially in 2008, isolated the secondary metabolites, aspergillides C, from a marine-derived fungus, *Aspergillus ostianus* strain 01F313. They collected the samples from the coast of Pohnpei.[359] Significantly, aspergillides A-C exhibited cytotoxicity against mouse lymphocyticleukemia cells. An enantioselective approach to the total synthesis of (+)-aspergillide C (**350**) has been accomplished. Noticeably that overlaps at a late stage with recently

reported Kuwahara"s synthesis.[360] It was envisioned that aspergillide C could be synthesized staring from lactone (+)-**355** upon sequential saponification/protecting group adjustment/ macrolactonization. This approach for the total synthesis started with a zinc-mediated HDA cycloaddition reaction of (S)-(-)-glyceraldehyde acetonide (**351**), provided from L-(+)-arabinose,[361, 362] and the Danishefsky-Kitahara diene[363, 364] (**345**) to give dihydropyrone (-)-**352** (Scheme 51). According to prior accounts, dihydropyrone (-)-**352** was isolated as a single diastereomer as expectedly by Felkin"s model, thus securing the required configuration at C(7).[365] Upon treatment with acid, (+)-**353** to the cyclized via a procedure reported by Larock[366] to give lactone (+)-**354** in 78% yield. The final stage of the synthesis involved the hydrolysis of the lactone in (+)-**355**, protecting group adjustment, along with macrolactonization. In fact, during the course of this approach, an alternative route to (+)-**355** and its fruitful expansion to (+)-aspergillide C via such a sequence was achieved and published by Kuwahara et al.[360, 367]

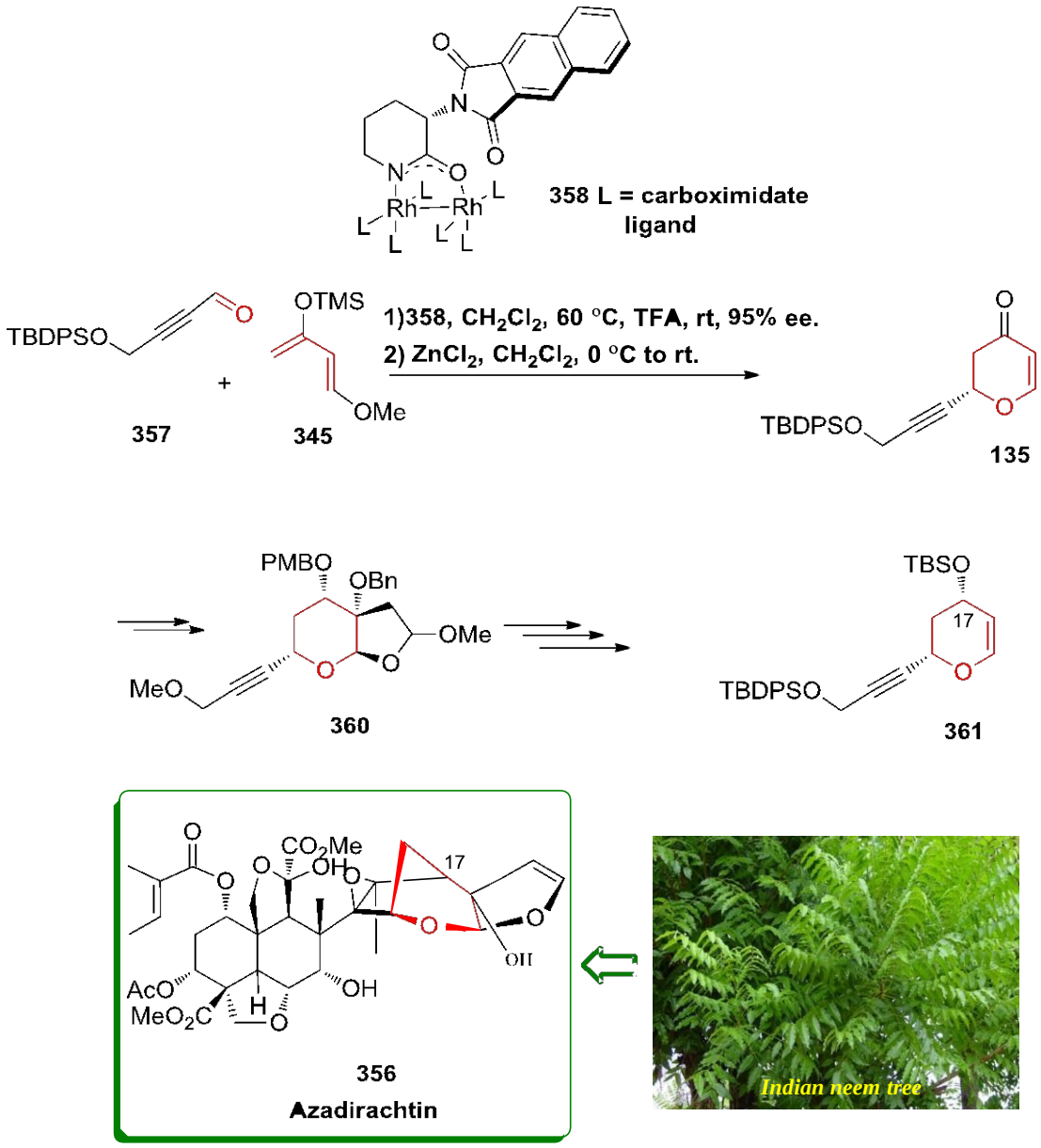


Scheme 51

Azadirachtin (**356**) is a complex natural product which was initially isolated from the *Indian neem tree* in 1968.[368] It is known as an active insect antifeedant and growth inhibitor,[369, 370] the stimulating architecture, created a great interest and challenge in its total synthesis.[371-378] Recently a first total synthesis of azadirachtin by using a strategy which evolved over many repetitions was successfully accomplished and reported.[379]

Initially the appropriate aldehyde **357** was synthesized from readily available 2-propyn-1,4-diol via HDA reaction (Scheme 52).[380] Noticeably, there are only few examples of alkynal derivatives employed as substrates in the HDA reaction,[381-384] and in addition the aldehyde **357** was found being extremely unstable. Consequently, many known suitable catalysts used in HDA reactions were inappropriate for this transformation and gave raise either to low yield or poor enantioselectivity. After several practical attempts, Hashimoto's dirhodium carboximidate catalyst **358**[382, 383] was found effective. Therefore it was specifically optimized for the HDA reaction of propargylic aldehydes. Under catalysis of **358** the desired cycloaddition, was promoted affording the target molecule in 90% ee and 77% chemical yield over the two steps. With adequate amounts of the dihydropyranone **359** in hand it was converted to the enol ether **360** after two steps reaction.

Nevertheless, the enol ether **360** presented several alternatives for the assemblage of the remaining moiety in the mesylate **361**. Consequently, this pathway offers a greatly efficient synthesis of the azadirachtin **356** coupling partner **361** after several steps reaction (scheme 52), and progressed being completed in only 17 steps which is more concise in comparison to 26 steps reported previously for the original approach.[385]



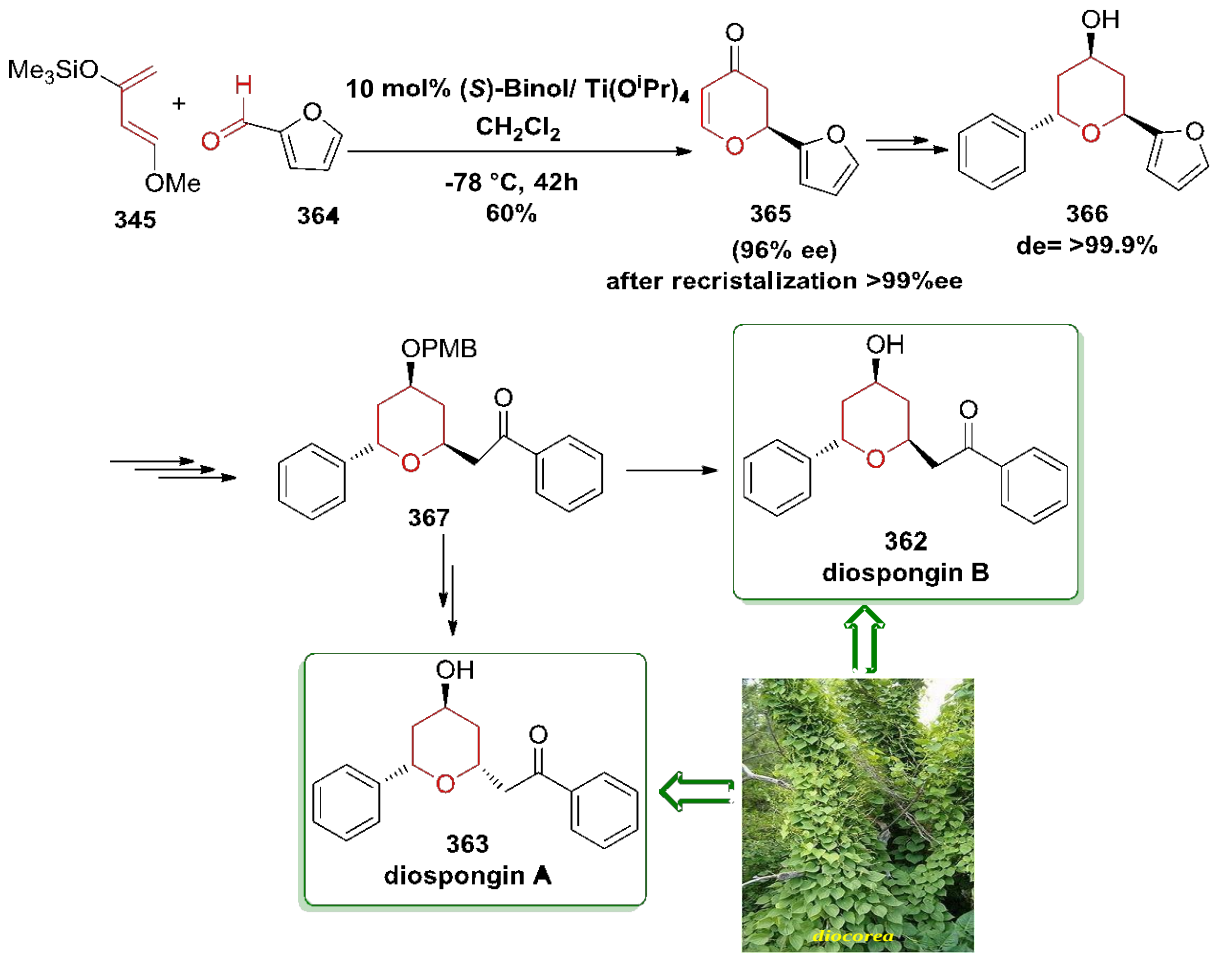
Scheme 52

Generally, the aryl-substituted tetrahydropyran core is present in several biologically important natural products having small molecules in many of.[386-388] Natural products bearing tetrahydropyran scaffold, are somehow privileged since this moiety dedicates several biological properties including potency of inhibitory activity to the molecules. One of the most important is, the interesting C-aryl glycoside natural products diospongins A (**363**) and B (**362**). They were isolated from the rhizomes of *Diocorea spongiosa* via a bioassay-guided fractionation exhibit

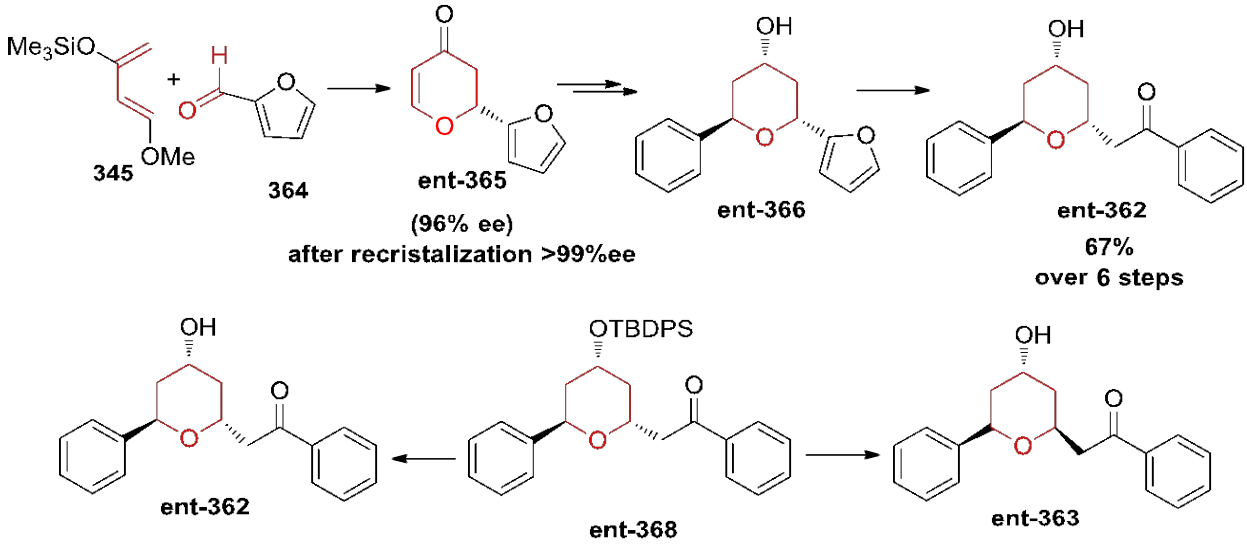
suspicious antiosteoporotic activity. Thus compounds bearing pyran moiety, are considered being a model and a lead for the discovery and design of active new antiosteoporotic agents.

Jennings et al[389] initially accomplished unambiguous total syntheses of both (-)-diospongins A (**363**) and B (**362**). These total synthesis was not only a great achievement but also confirmed the structures suggested for the structures **362** and **363** by Kadota et al.[390] Consequently, a plethora of synthetic approaches and routes has appeared in the chemical literature for the total synthesis of this family of compounds.[389, 391-393]

The catalytic asymmetric HDA reaction between Danishefsky"s diene **345** and furfuraldehyde **364** in the presence of 10 mol % of the (S)-BINOL/Ti(OiPr)$_4$ as a derived catalyst generated gave dihydropyranone **367** in 96% ee. Furthermore, single re-crystallization of **364** led to 99.9% ee with 60% chemical yield. The reaction made progress giving a mixture of alcohol **366** or ent-**366**. The (R)-BINOL/Ti(OiPr)$_4$ derived catalyst created ent-**365**, then, ent-**365** was transformed to ent-**366** using the same reagents and similar sequence. At last, **367** was subjected to DDQ in DCM/H_2O (9:1) for 1h to provide the desired compound **362** in excellent isolated yield (Scheme 53). The 2,6-trans enantiomer ent-**362** was obtained in moderate yield overall yield (over 6 steps) from ent-**366** pursuing the aforementioned conditions (Scheme 54). The C-5 hydroxyl group of diospongin B (**362**) gave product **363** in 86% yield over two reaction steps. Under similar conditions ent-**368** also led to ent-**363**.



Scheme 53

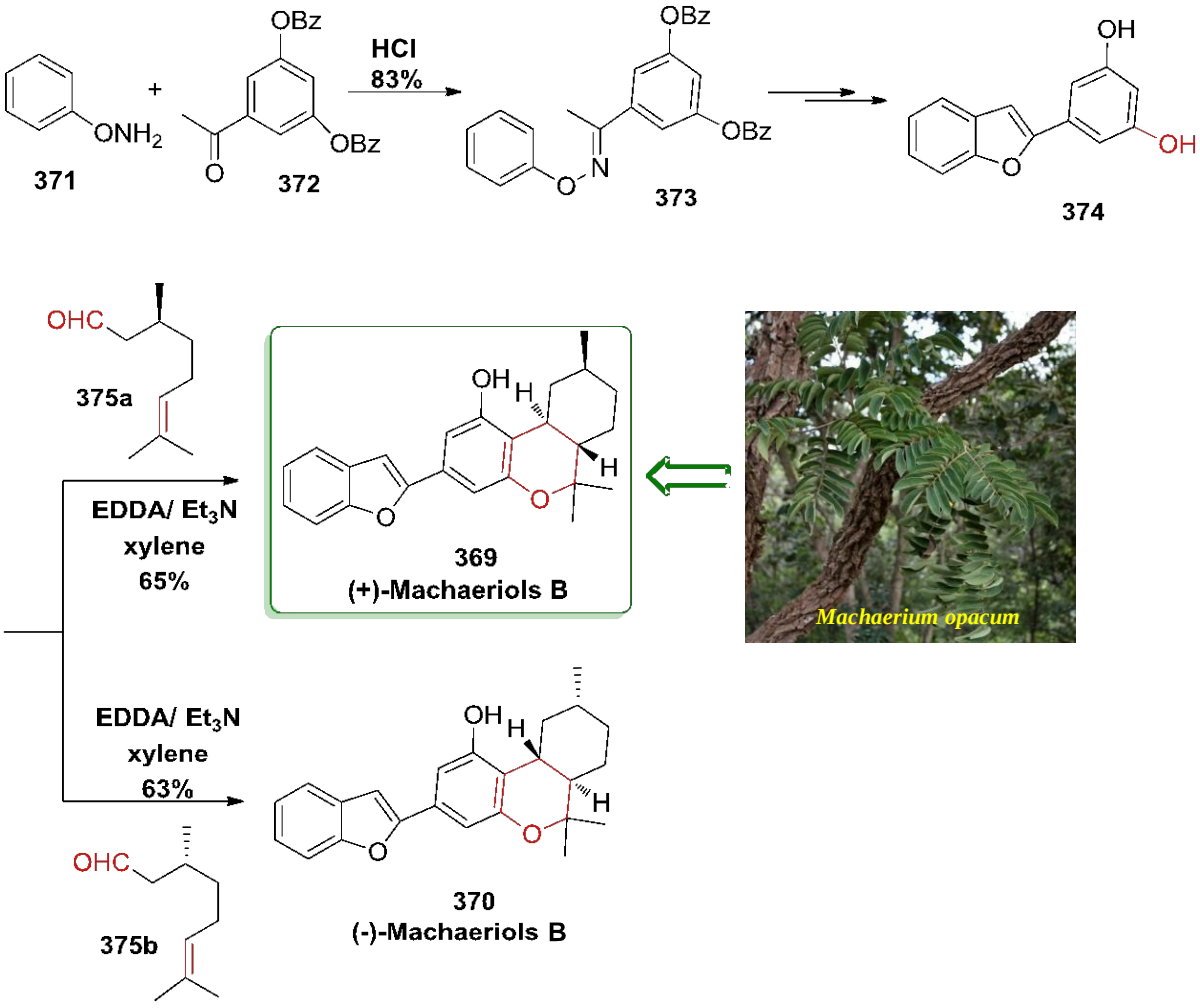


Scheme 54

(±)-Machaeriols A, B, C, and D, having the cannabinoid structure, in 2009 were isolated from the bark of the *Machaerium multiflorum* spruce found in Loreto and Peru.[394, 395] They exhibited potential in vitro antimicrobial potency.

The first total syntheses of machaeriol B (**369**) were accomplished and presented by Avery et al. Their strategy stated from phloroglucinol (¼benzene-1,3,5-triol) proceeding via a HDA cycloaddtion and Suzuki coupling reaction as the crucial steps giving the targets in high overall yields in 7 steps for both compound **369**.[396]

Scheme 55 illustrates a brief synthetic route to natural (+)-machaeriol B (**369**) and its unnatural enantiomer **370**. (+)-Machaeriol B (**369**) can be synthesized stating from stemofuran A (**374**) and (−)-(3S)-citronellal (**375a**) via a HDA cycloaddtion reaction.[397] The precursor **376** for this total synthesis of **369** and **370** was provided by a previously reported method.[398, 399] Thus, the condensation of *O*-phenylhydroxylamine (**371**) with 3,5-bis(dibenzoyloxy)acetophenone (**372**) catalyzed by conc. HCl in EtOH gave the oxime ether **373** in excellent yield.



Scheme 55

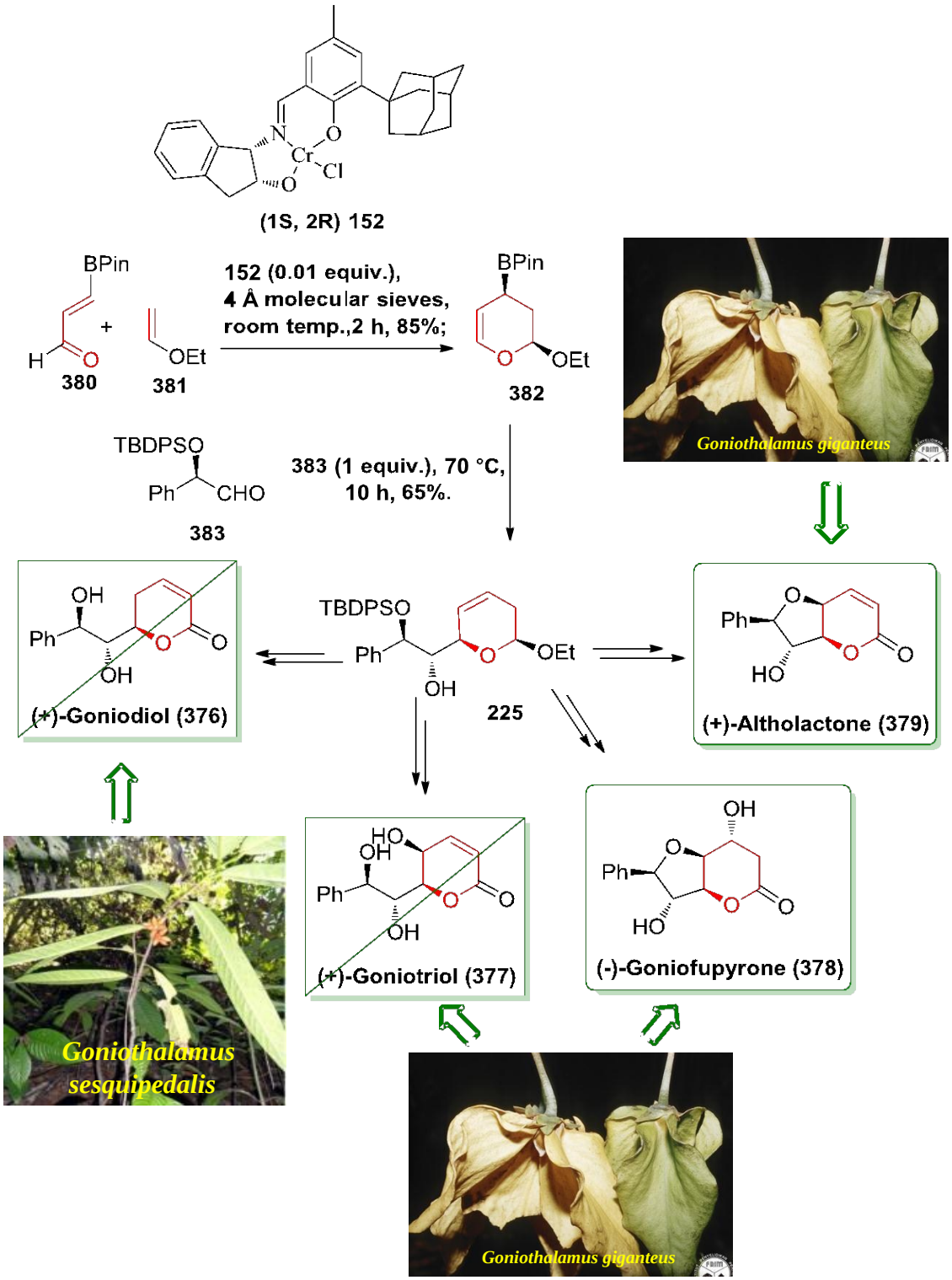
In the registered plants used in folk medicine in Asia, the *Goniothalamus* species (Annonaceae) are well documented. The phytochemical investigations of the genus *Goniothalamus* was strengthened when, in 1972, Geran and his coworkers reported the observed toxicity of that the ethanolic extract of stem bark of *Goniothalamus giganteus* to mice during a P-388 in vivo antileukemic screening.[400] Further studies of this extract by McLaughlin research group, resulted in isolation and extraction and structural elucidation of two major families of compounds showing biologically remarkable activities and properties including annonaceous acetogenins[401] and styryllactones.[402-405] Nowadays, more than 30 bioactive molecules belonging to the styryllactone family from various *Goniothalamus* species can be found in a prepared list.[406, 407]

(+)-Goniodiol (**376**) was first initially isolated from the leaves and twigs of *Goniothalamus sesquipedalis*,[408] (+)-goniotriol (**377**) a poly oxygenated styryllactone, has been, initially, isolated

from the stem bark of *Goniothalamus giganteus*,[405] and (–)-goniofupyrone (**378**), and (+)-altholactone (**379**). They have actually a common bicyclic framework. They were initially isolated from the stem bark of *Goniothalamus giganteus*[409] and from the bark of an unnamed *Polyalthia* (Annonaceae) samples, respectively.[410]

A brief, stereoselective pathway to bioactive styryllactones, namely, (+)- goniodiol (**376**),[411] (+)-goniotriol (**377**), (–)-goniofupyrone (**378**), and (+)-altholactone (**379**) by employing a cascade reaction appropriate for the synthesis of different stereoisomers along with the design of analogues has been reported.[412]

In this total synthesis, the reaction sequence started by the formation of cyclic allylboronate **382** provided from ethyl vinyl ether and boroacrolein pinacolate by employing a catalyzed enantioselective inverse-electron-demand HDA reaction. The stereoselective total synthesis of few members of the styryllactone family was accomplished efficiently via an intermediate **384**, provided by a catalyzed asymmetric inverse electron-demand sequential HDA/allylboration reaction. The conversion of **384** into α,β-unsaturated lactone resulted in the synthesis of (+)-goniodiol (**376**) in a compact number of steps. The epoxidation reaction was employed to create the remaining chiral centers on the lactone moiety of **384**, and these intermediates were subsequently expanded into (+)-goniotriol (**377**), (–)-goniofupyrone (**378**), and (+)-altholactone (**379**) (scheme 56) via either isomerization or cyclization step.[413]

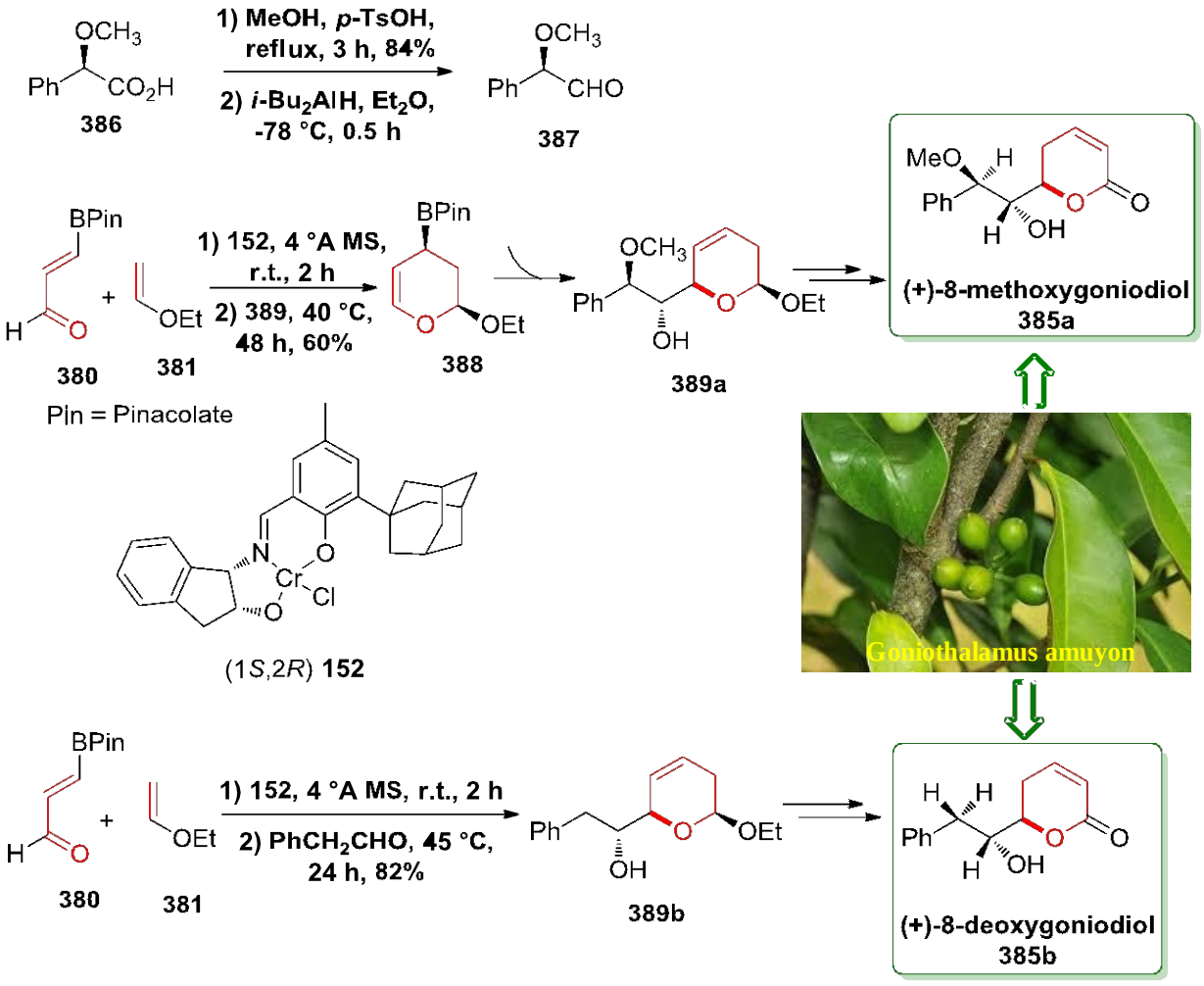


Scheme 56

Asian trees of the genus *Goniothalamus* have been found a rich source of plethora families of compounds showing significant biological activities including alkaloids,[414] styryllactones[415] and acetogenins.[416] In 2005, the isolation of new members of the natural styryllactones have been reported from *Goniothalamus amuyon*.[417, 418] The structure and absolute stereochemistry of one of these compounds, **385a**, have been found being very similar with those of (+)-goniodiol, except for the existence of a methoxy group at C-8. For this reason, the common name of 8-methoxygoniodiol was given to this compound. Despite of this structural similarity, **385a** showed a very dissimilar cytotoxicity from (+)-goniodiol, depends on the kind of human cancer cell lines.[417, 418]

The asymmetric synthesis of cyclic allylboronate **388** was accomplished starting from ethyl vinyl ether and **380**, with subsequent HDA cycloaddition reaction under catalysis of Jacobsen"s chiral Cr(III) complex **152**.[419] Compound **388** was converted to **389a** in several steps. The desired natural product was obtained upon desilylation with TBAF in 28.9% overall yield from the generated intermediate **389a**.[412] The spectral and physical data of synthetic (+)-8-methoxygoniodiol **385a** were compared with those of already reported and found being identical.[417]

The synthesis of 8-deoxygoniodiol **385b** commenced with the asymmetric catalyzed HDA/allylboration sequence using phenylacetaldehyde instead of *O*-methyl mandelic aldehyde. The cascade process was conducted in „one pot fashion" and furnished the desired pyran **389b** in high yield as single diastereoisomer in excellent ee (96%).[420] The final steps, includes isomerization of the double bond and of the removal of silyl protective group, to give the desired product **385b** (scheme 57).[412]

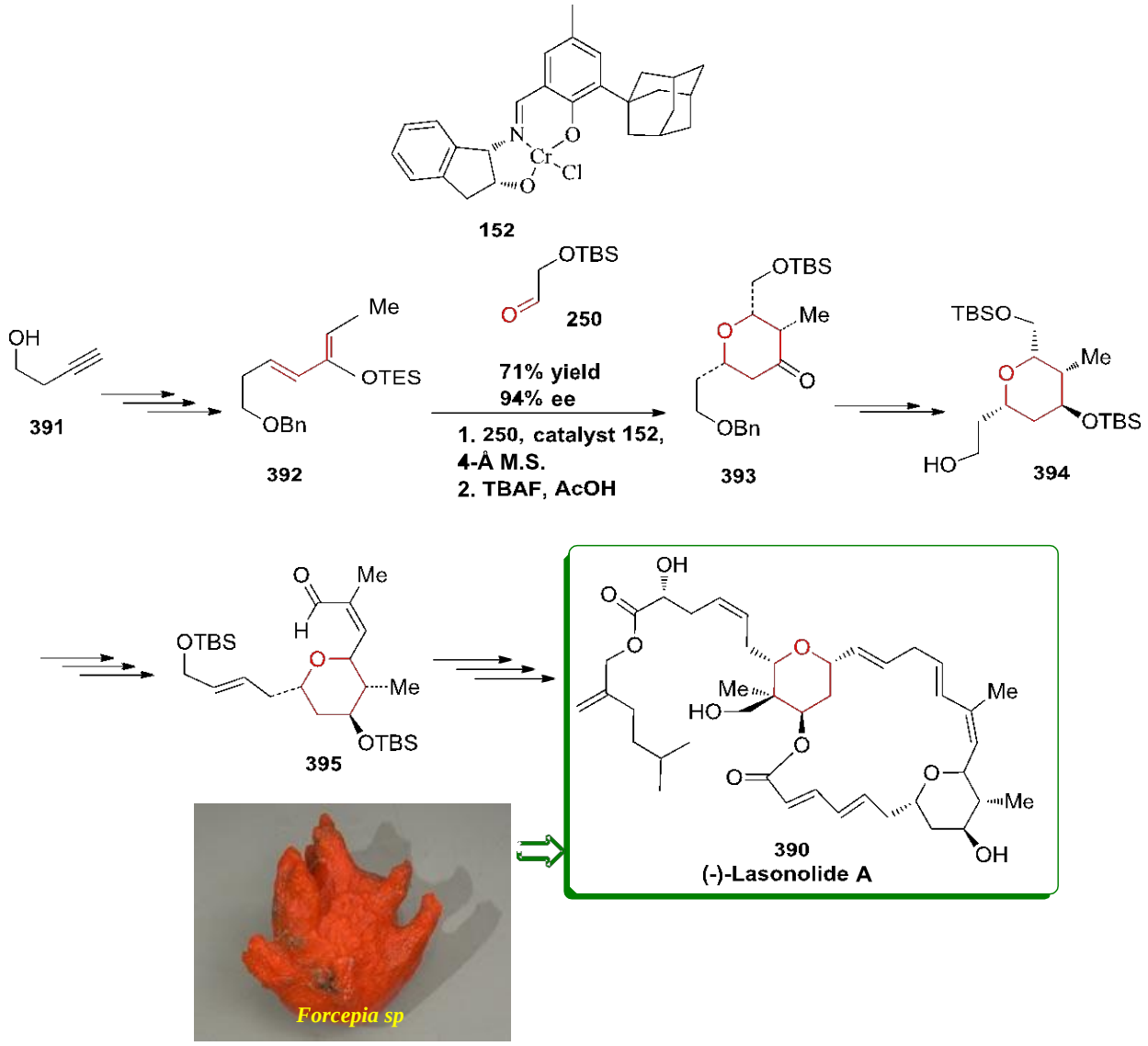


Scheme 57

In 1994, lasonolide A (**390**), a structurally exceptional 20-membered macrolide, was initially isolated from the Caribbean marine sponge *Forcepia* sp. by McConnell and his research group.[421] Lasonolide A shows a potent cytotoxic activity towards the proliferation of A549 human lung carcinoma and P388 murine leukemia cells.

In their total synthesis route to (−)-lasonolide A to Ghosh and Gong also employed a HDA cycloaddition reaction for the construction of THP ring. A convergent and enantioselective synthesis of (−)-lasonolide A HDA been previously reported.[422] The details of this synthetic achievement includes a Lewis acid catalyzed HDA cycloaddtion reaction for the construction of the lower tetrahydropyran ring as the key step along with an intramolecular 1,3-dipolar cycloaddition reaction to install the upper tetrahydropyran ring.

The construction of the bottom tetrahydropyran ring commenced with the synthesis of nucleophilic diene **392** (Scheme 5). The alcohol **391** was protected with BnBr and NaH to provide the benzyl ether in virtually quantitative yield. The enone was prepared as an appropriate Diels–Alder precursor dienol silyl ether **392** via treatment with Et_3N and TESOTf. The chiral tridentate Schiff base chromium- (III) complex (1S,2R)-**152** developed previously by Jacobsen et al[289, 310] was employed as the catalyst (10 mol%) in the stereoselective HDA cycloaddtion reaction between diene **392** and (*tert*-butyldimethylsilyloxy)acetaldehyde (**250**). The resultant, dihydropyran silyl enol ether was then treated with TBAF/AcOH in the same reaction vessel for the removal the TES group resulting in the corresponding ketone **393** in satisfactory yield and excellent ee (94%). Tetrahydropyran **394** provided by the HDA cycloaddtion reaction was now available in hand being used for the synthesis of **395** after several steps, manipulating functional group transformation (Scheme 58). Ultimately, conventional TBS removal using HF·Py in the presence of excess amount of pyridine completed the total synthesis of (−)-lasonolide A (**390**).[423]

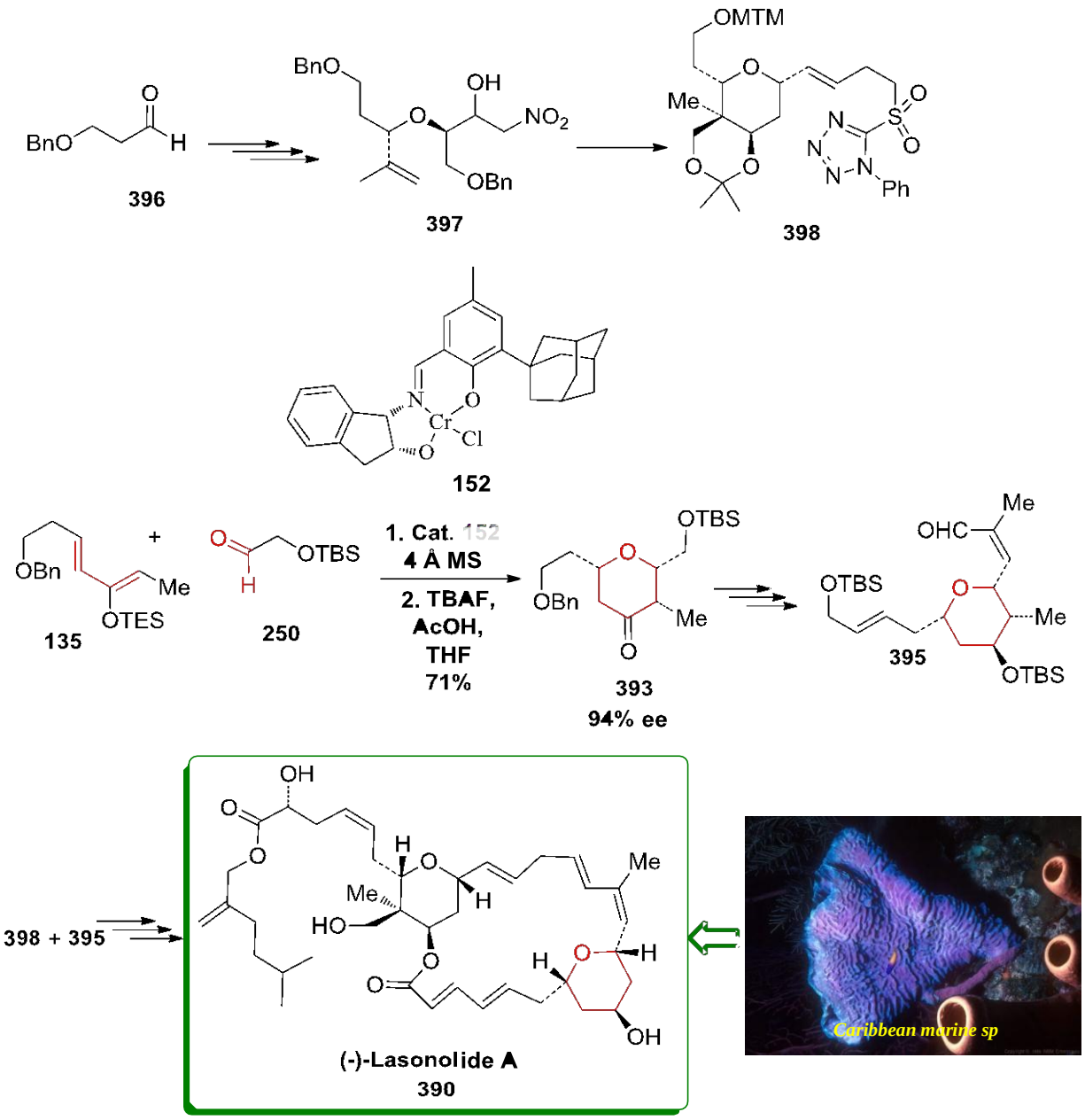


Scheme 58

Marine natural products are important source for obtain structurally diverse molecules with interesting biological and physiological activities. Several such compounds exhibit antitumor activity; however, the insufficiency of natural richness frequently limits or even prevents their subsequent biological investigation.[424] Lasonolide A (**390**), a 20-membered macrolide, was initially isolated from the Caribbean marine sponge, *Forcepia* sp., in 1994 by McConnell and his research group.[421] The primarily structural elucidation and stereochemical determination of lasonolide A was well established by NMR spectra analysis. However its structure and absolute configuration were later revised and modified via total synthesis[425] and Lasonolide A‟s structural

features combined with its active antitumor activities attracted substantial synthetic chemist interest as a target. So far, three total syntheses[425-427] and a number of synthetic investigations on both tetrahydropyran rings 6 have been accomplished and disclosed. An efficient and enantioselective has the total synthesis of (−)-lasonolide A (**390**). Has been successfully achieved and reported.

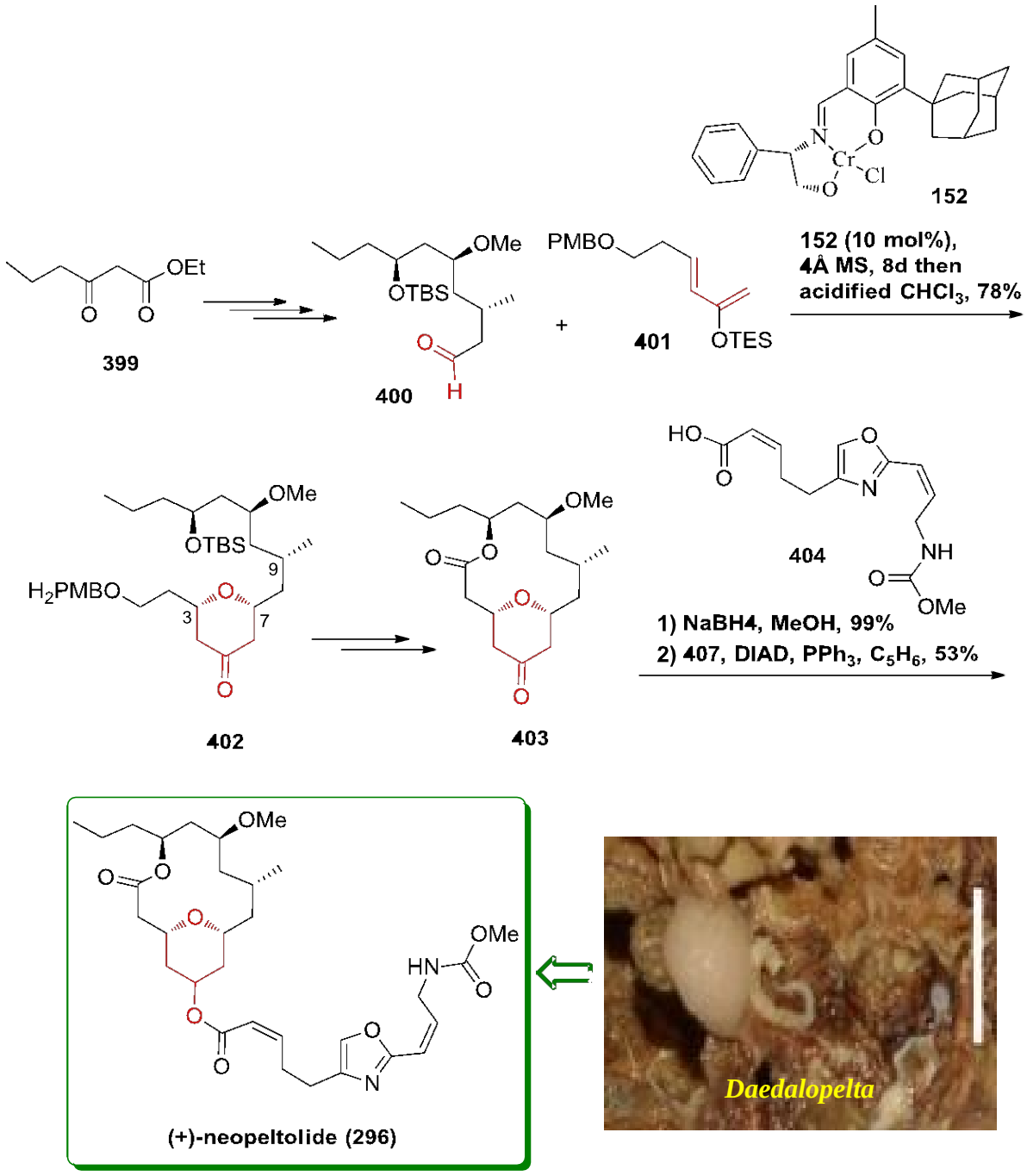
The synthesis of ring A commenced with the already known aldehyde **396**[428] as illustrated in Scheme 59. Initially Alcohol **397** was protected using benzoyl peroxide and Me_2S furnishing MTM ether **398** in high yield.[429] The synthesis of the lower tetrahydropyran ring B of lasonolide A is also depicted in Scheme 59. In a key step of this total synthesis, the chiral tridentate Schiff base chromium(III) complex (1S,2R)-**152** developed and reported previously by Jacobsen[419] was employed as catalyst (10 mol %) in the asymmetric HDA reaction between diene **392**[430] and aldehyde **250**.[431] The obtained dihydropyran silyl enol ether upon treatment with TBAF/AcOH in a one pot fashion caused the removal of the TES group to afford the corresponding ketone **393** in satisfactory chemical yield but excellent ee (94%) to provide aldehyde **395** in high chemical yield in several steps. Finally conventional TBS-deprotection with HF·Py in the presence of excess pyridine gave (-)-lasonolide A.[432] The spectra data of synthetic lasonolide A (**390**) were compared with those previously reported for natural product and found being identical.[421]



Scheme 59

Marine macrolides showing potent cytotoxic activities is found to be promising anticancer agents, if the supply issue can be committed.[433] Neopeltolide (**296**, Scheme 60) is a bioactive macrolide which was in 2007 initially two species of the sponge *daedalopelta* were collected [305] from a deep-water Caribbean sponge of the class Neopeltidae by Wright and co-workers.[305] Initial investigations disclosed high antiproliferative potency towards several cancer cell lines, as well as the ability of inhibition of the growth of the fungal pathogen *Candida albicans*.

A relatively brief but efficient total synthesis of the potent antiproliferative macrolide (+)-neopeltolide (**296**) has been accomplished in 18 steps as a longest linear sequence, and 5.8% overall yield. This approach involves a Jacobsen catalyzed HDA cycloaddition reaction as the crucial step. The synthesis of the needed aldehyde **400** started with a Noyori stereoselective hydrogenation[434] of the β-keto ester **399** employing the (S)-BINAP–Ru(II) catalyst to afford the desired (13S)-alcohol.[435-437] While the aldehyde **400** was available in hand, the formation of the tetrahydropyran ring of neopeltolide initially was contemplated (Scheme 60). Therefore, conduction a Jacobsen catalyzed asymmetric HDA cycloaddtion reaction of **400** and the easily accessible 2-siloxydiene **401**,[438] promoted by the chiral tridentate chromium as catalyst **152**[439] (10 mol%), was attempted which was successfully, upon mild acidic workup, afforded the desired cis-tetrahydropyranones **402**. Interestingly the reaction proceeded with absolute control over the introduction of the C3 and C7 stereogenic centers. At this stage, the major isomer **402** (60%) was easily separated from its C9 epimer. All that continued for the final result was reduction of the ketone **403** to the equatorial alcohol **404** using $NaBH_4$ in MeOH, with subsequent Mitsunobu esterification reaction with the side chain acid,[438] as used by other groups,[435, 436, 440] giving (+)-neopeltolide (**296**) in satisfactory yield.[441]



Scheme 60

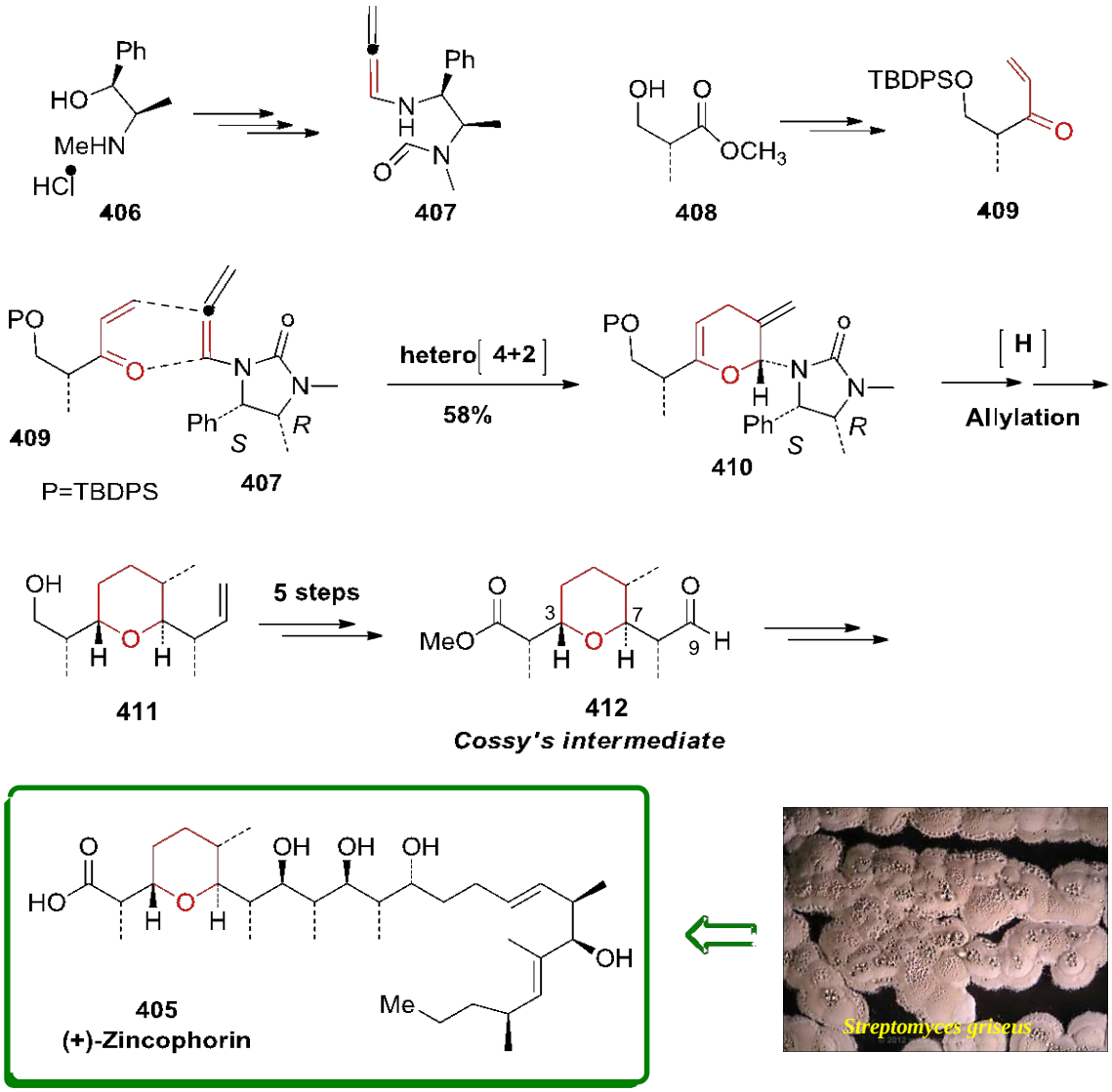
In 1984, two new monocarboxylic acid ionophores, griseocholin and antibiotic M144255, were initially isolated from cultured strains of *Streptomyces griseus*.[442, 443]

Polyoxygenated ionophore-containing naturally occurring products show high potency as anti-infectious via proton-cation exchange courses across biological membranes. (+)-Zincophorin

possesses show strong in vivo activity against Gram-positive bacteria and *Clostridium coelchii*. In addition its ammonium and sodium salts exhibit high anti-coccidal potency towards *Eimeria tenella* in chicken embryos. Moreover its methyl ester was reported in a patent as exhibiting high inhibitory potencies towaeds influenza WSN/virus with decreased toxicity for the host cells.[444]

Over the last two decades, (+)-zincophorin has attracted tremendous attentions and stirred up array of synthetic attempts including Danishefsky"s first total synthesis together with two recent sophisticated total syntheses successfully achieved and reported by Cossy and Miyashita.[445] A part from those successful endeavors a formal total syntheses of (+)-zincophorin based on seizure of Miyashita"s advanced intermediate **(**if **50= 411)** has been developed. The key feature in this approach based on previously reported asymmetric inverse electron demand HDA cycloaddition of chiral allenamides (Scheme 61).[446-452] In this line the synthesis of Cossy"s C1-C9 subunit of (+)-zincophorin relied on the aforementioned approach was attempted. Notably, in this strategy was an unusual urea-directed Stork-Crabtree hydrogenation was observed.

Total synthesis of chiral allenamide **407** started from (+)-ephedrine hydrochloride salt **406** and urea. Chiral enone **409** was provided from the market purchasable chiral hydroxy ester **408** as illustrated in Scheme 61. Having chiral allenamides **407** available in hand, the key inverse demand HDA reaction was performed. Having in mind with the fact that the stereochemical result could be controlled via either the suitable chiral auxiliary attached to the allenamide or the chiral enone, leading potentially to matched and/or mismatched consequences. It has been found that by conduction cycloaddition protocol in CH_3CN as the solvent under pressure in the sealed tube, upon heating at 85 °C, reactions of **407** with **409** proceeded easily and smoothly to afford pyrans **410** in satisfactory yield, as single isomers. For completion of the synthesis of the C1-C9 fragment as subunit, the crotylated pyran **411** was transformed to aldehyde **412** to afford (+)-Zincophorin in reasonable yield over three steps.[453]



Scheme 61

Diarylheptanoid natural products comprising a tetrahydropyran ring, such as centrolobine,[344, 345] de-*O*-methylcentrolobine,[344, 454] calyxins[455] and diospongins,[456] showed wide scope of biological potencies. For these features, thus, these compounds have attracted great attentions among the medicinal and synthetic organic chemistry chemists.[457-459]

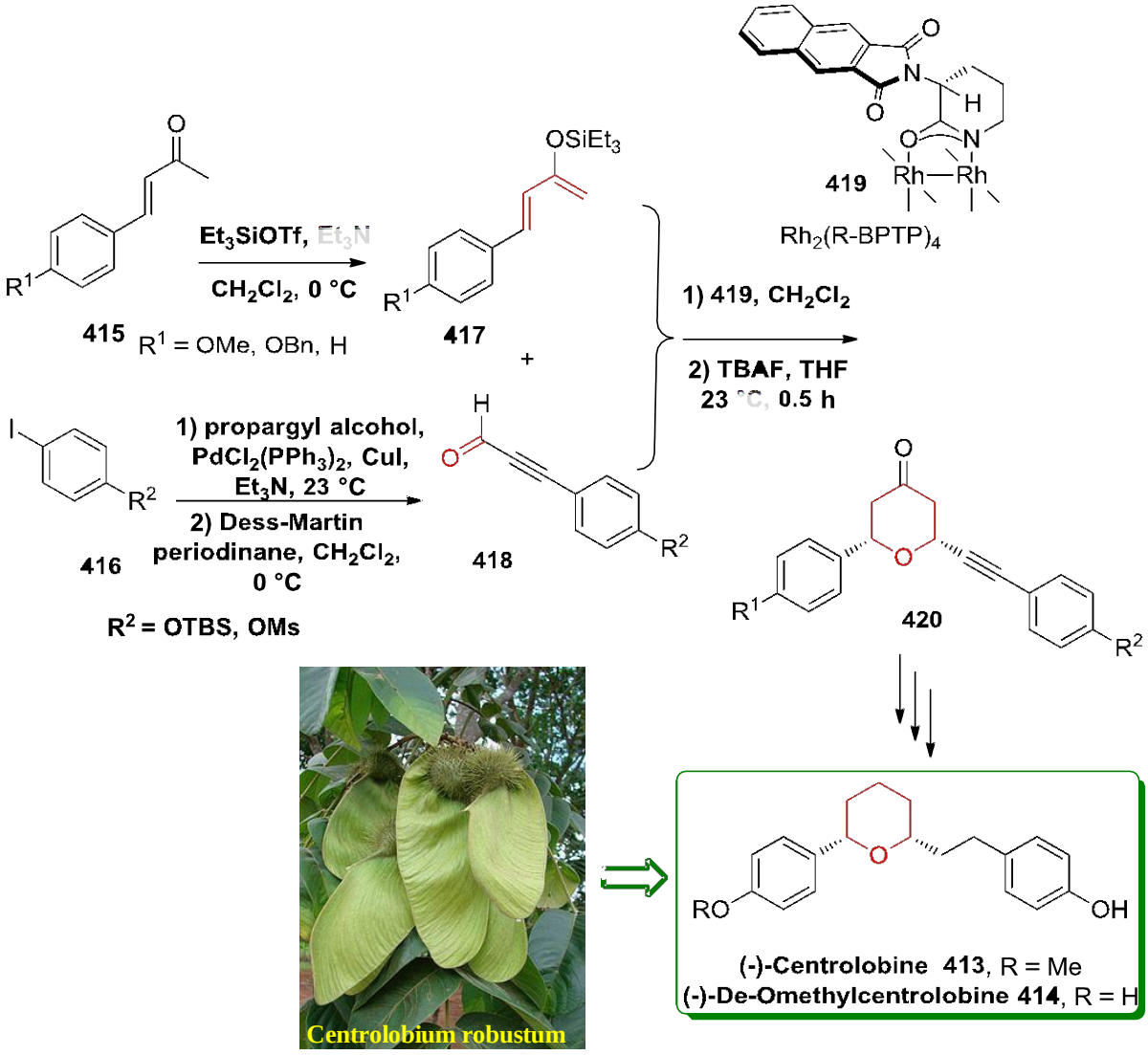
(−)-Centrolobine (**413**) is an antibiotic which initially isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* in the Amazon rain forest in Brazil.[344, 345] (−)-De-Omethylcentrolobine (**414**), isolated from the same heartwood of C.

robustum, exhibits reasonable antileishmanial potency.[344] In 2002 Solladie and his research group attempted the first asymmetric.

Total synthesis of (−)-centrolobine (**413**) and successfully achieved. They have also determined and confirmed the absolute configuration of **413**.[460] Since then, a plethora of research group have attempted to develop their strategy leading to the total synthesis of **413** in both racemic[461] and optically active forms.[462] Remarkably in neither of these attempts, the HDA reaction has not still been employed to the diarylheptanoid tetrahydropyran system.[463] Dirhodium(II) tetrakis-[(S)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh_2-(S-BPTPI)$_4$ **419** has been used as a highly effective Lewis acid catalyst in the endo- and enantioselective HDA cycloaddtion reactions of a wide and different range of aldehydes with Danishefsky-type dienes as well as with monooxygenated dienes. By using this superior and efficient catalyst the expected corresponding products were obtained in up to 99% ee and turnover numbers as high as 48,000.[464, 465]

In a developed the total synthesis, the dienes **417** were initially provided by the reaction of easily accessible α,β-unsaturated ketones **415**[466, 467]. Then phenylpropargyl aldehydes **418**, contain tert-butyldimethylsilyloxy and methanesulfonyloxy groups at the para-position on the benzene ring, were synthesized via the Sonogashira coupling[468] of propargyl alcohol with two iodophenols **416**[469, 470]

Catalytic asymmetric syntheses of (−)-centrolobine and (−)-de-*O*-methylcentrolobine have been successfully accomplished, combining a HDA reaction of 4-aryl-2-silyloxy-1,3-butadienes **417** and phenylpropargyl aldehyde derivatives **418** as a decisive step (scheme 62). This HDA reaction was catalyzed by dirhodium(II)tetrakis[(R)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh_2(R-BPTPI)$_4$ **419** as an efficient chiral Lewis acid catalyst to furnish entirely cis-2,6-disubstituted tetrahydropyran-4-ones **420** in excellent ee.(93%)

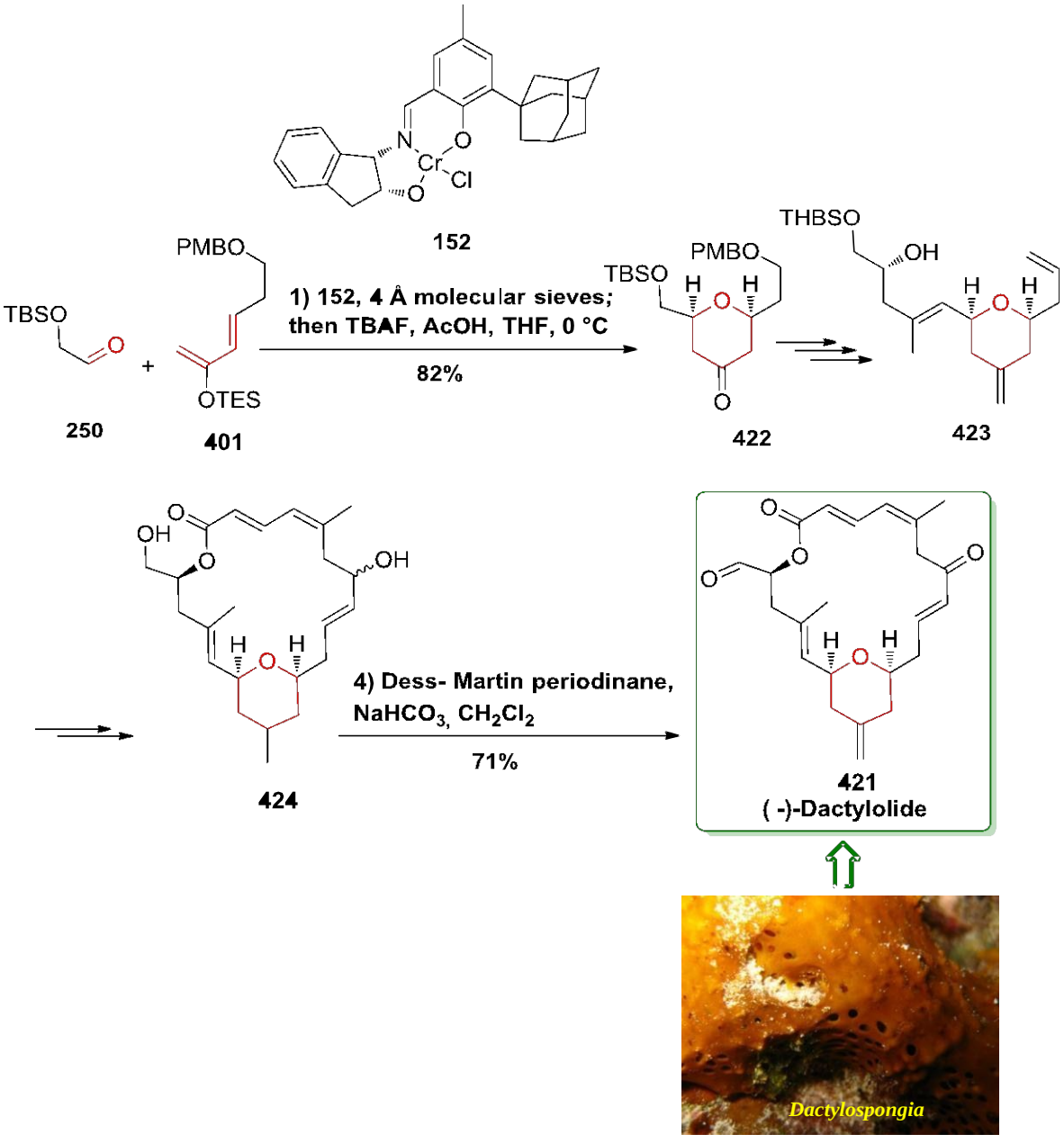


Scheme 62

The asymmetric total synthesis of (-)-dactylolide has been achieved and reported. The absolute configuration of the tetrahydropyran was determined by catalyzed asymmetric Jacobsen HDA cycloaddition reaction. Initially in 2001, Riccio and his research group[471] isolated dactylolide **421** from a marine sponge belongs to the genus *Dactylospongia* found and collected the coast of Vanuatu. It showed cytotoxicity toward L1210 and SK-OV-3 tumor cell lines, with a range of 40%- 63% inhibition.[471] The absolute configuration was determined by Smith et al[472] in the first total synthesis of (+)-dactylolide **421**. Notably, after this first communication, four other

approaches for total synthesis by research groups of Hoye, Jennings, Floreancig, and Keck till date have been reported for the total synthesis of dactylolide.[473-476]

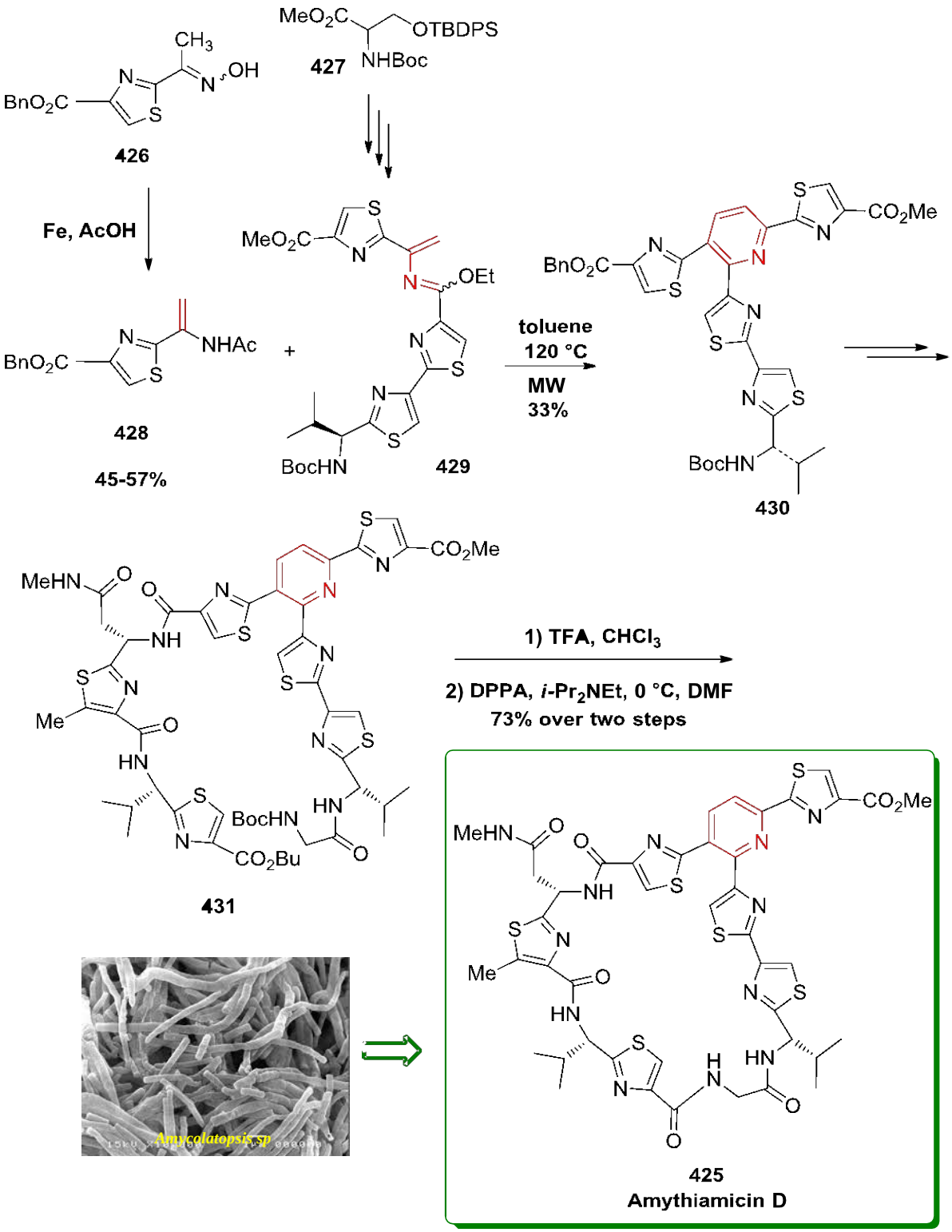
The synthesis of tetrahydropyran **423** with the combination of triethylsilyl enol ether **401** and aldehyde **250** catalyzed by Jacobsen"s chiral tridentate chromium(III) catalyst **152** (Scheme 63).[438, 439] Cautious workup of the resulting silyl enol ether gave the *cis*-tetrahydropyranone **422** in high chemical yield and excellent ee (99%) *via* an endo-selective HDA cycloaddition approach, providing of compound **422** on a multigram scale. The last step in the total synthesis of (-)-dactylolide involved the conventional oxidation of diols **424**.[477]



Scheme 63

The thiopeptide (or thiostrepton) antibiotics are a class of sulfur containing greatly modified cyclic peptides with remarkable biological activities, including reported potency against methicillin-resistant *Staphylococcus aureus* (MRSA),[478] and malaria. One reported total synthesis of the thiopeptide naturally occurring product amythiamicin D, is based on a biosynthesis-inspired HDA cyloaddition pathway leading to the pyridine core of the antibiotic as a vital step. The amythiamicins (A-D) are among the most outstanding thiopeptide antibiotics, and initially were isolated from a strain of *Amycolatopsis* sp. MI481-42F4. Notably, structures are determined by combination of degradative protocol and spectroscopic techniques [478, 479] , which is worthy to mention. They are among the very few thiopeptides that do not have a dehydroalanine residue,[480] the details of the first total synthesis of the thiopeptide antibiotic amythiamicin D **425** is described. Basically the pathway to synthesis **425** is similar to a route that, Nicolaou group synthesized thiostrepton, utilizing a biomimetic strategy to construct the 2,3,6-trisubstituted pyridine core of the naturally occurring product.[481]

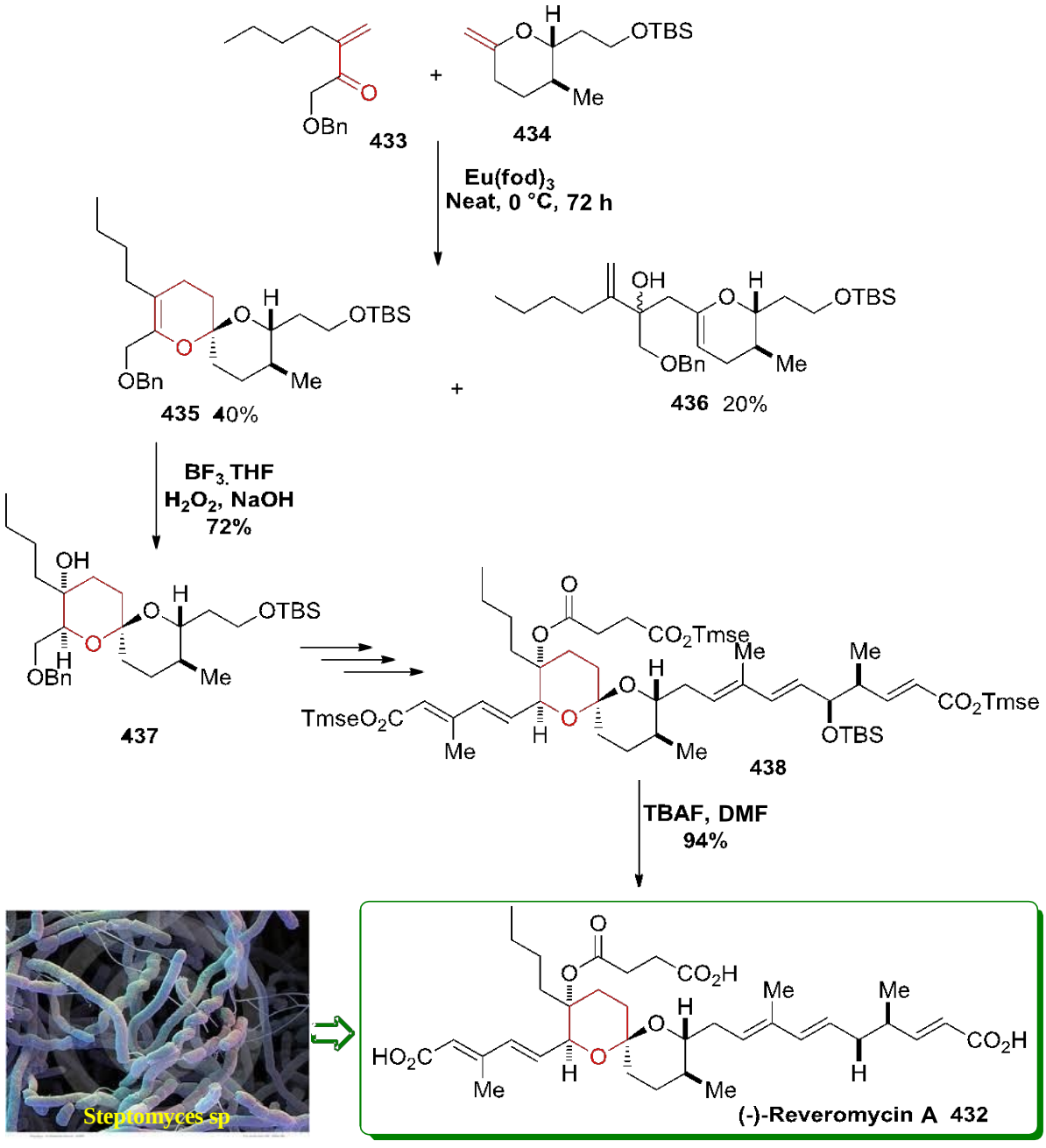
Dienophile **428** were synthesized via reduction of the corresponding oximes **426** employing iron and acetic anhydride-acetic acid in refluxing toluene.[482] Silyl derivative **427** was transformed into **429** after several steps manipulating functional group transformation. In this way 2-azadiene component **429** containing the remaining three thiazole rings was provided. Now the synthetic path way HDA grasped the important HDA reaction. Upon non-conventional heating of the azadiene **429** with enamide dienophile **428** under microwave irradiation in toluene at 120 °C afforded the required 2,3,6-tris(thiazolyl)pyridine **430**, albeit in a moderate chemical yield. As a matter of fact obtained pyridine **430** is actually the core of the natural product since it is necessary to control and establish its stereochemical dignity, and this is again accomplished by generation of Mosher amides. This led in macrolactamization in a satisfactory yield stating from **431** to afford amythiamicin D **425** (Scheme 64).[483]



Scheme 64

The reveromycins A (**432**) is member of a class of compounds which were initially isolated from the soil actinomycete *Steptomyces* sp.[484, 485] Reveromycin A (**432**) has been found to be active inhibitor of the mitogenic activity of epidermal growth factor in a mouse keratinocyte. Besides, compound **432** shows antiproliferative potency towards human tumor cell Lines. Until now, only one total synthesis of **432** has been successfully achieved and reported,[486] Besides several strategies to the 6,6-spiroketal core have been reported.[487-489] In 2000 the total synthesis of (-)-reveromycin A (**432**) employing a HDA protocol to build up the stimulating spiroketal motif of this molecule.[489]

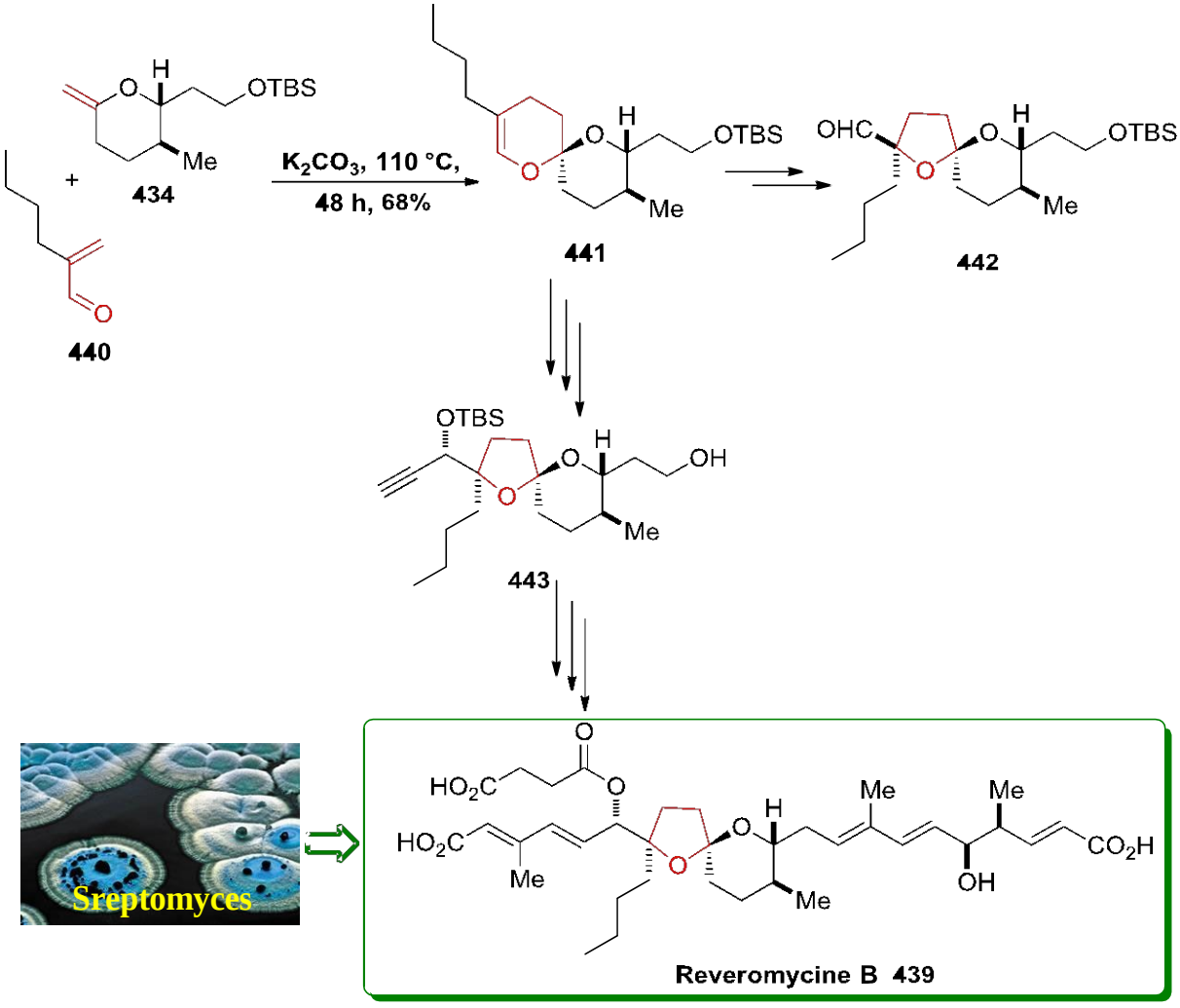
The HDA reaction between **433** and **434** was treated with 15 mol % $Eu(fod)_3$ as catalyst, promoted by $ZnCl_2$ in THF at 0 °C. Although the reaction provided the desired spiroketal **435** as a single diastereoisomer in a higher yield than that obtained employing K_2CO_3,[489] the by-product **436**, obtained from an ene reaction, was also insulated as a mixture of diastereoisomers. Hydroboration of spiroketal **435** with subsequent oxidation completed in good yield to provide the tertiary alcohol **437** as the single isomer. The fully protected reveromycin A, precursor **438**, was exposed to TBAF in DMF affording reveromycin A (**432**) in high yield (scheme 65). The synthetic compound was purified via reverse-phase chromatography and its physical and spectroscopic data (NMR, IR, UV, HRMS) was found to be in agreement in full aspects with those to the natural product.[490]



Scheme 65

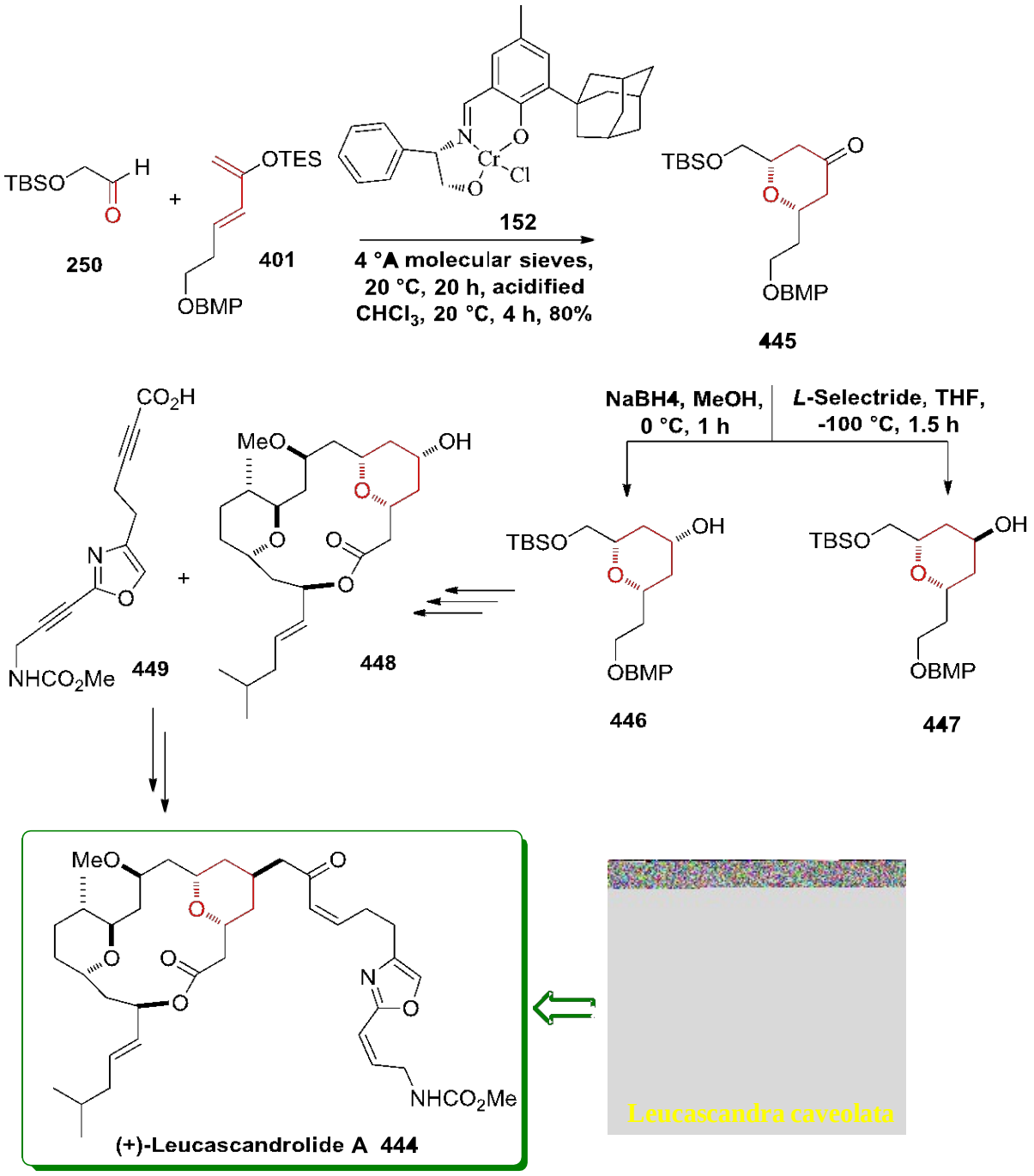
Spiroketals or spiroacetals are sub-structures that ensue in a wide variety of naturally occurring compounds from several and different sources such as, plants, fungi, marine organisms, insects and microbes[491] Reveromycins A, B (**439**), C, and D are specimens of natural products bearing 5,6- and 6,6-spiroketal moieties. They have been isolated from a soil actinomycete belonging to the *Sreptomyces* genus.[492-494] Reveromycin B (**439**) has been found to act as epidermal growth

factor inhibitor. Its total synthesis has been accomplished and reported in 25 linear steps staring from chiral methylene pyran **434**. The key step in this approach is an inverse electron demand HDA reaction between dienophile **434** and diene **440** for construction of the 6,6-spiroketal **441**. The latter upon oxidation using dimethyldioxirane followed by acid catalyzed rearrangement provided the 5,6-spiroketal aldehyde **442**. A sequential reaction including lithium acetylide addition/oxidation/reduction, using protective group manipulation afforded the reveromycin B spiroketal core **443**. Other crucial steps in this strategy leading to the target molecule **439** are a Stille coupling, succinoylation, selective deprotection, oxidation, and Wittig condensation to form the final bond. Finally reveromycin B (**439**) is obtained in pure form and satisfactory overall yield (scheme 66).[495]



Scheme 66

A highly stereoselective total synthesis of leucascandrolide A (**444**) has been achieved and reported. leucascandrolide A is a cytotoxic 18-membered macrolide which was isolated in 1996 from the New Caledonian calcareous sponge *Leucascandra caveolata* by Pietra and his research group.[496] The total synthesis begins with a Jacobsen asymmetric HDA reaction to construct the 2,6-cis tetrahydropyran ring. Leucascandrolide A has drawn enormous attention and several research groups focused on its total synthesis,[27, 497-500] The first total synthesis was accomplished and reported by Leighton et al.[497] In 2003, a successful strategy to (+)-leucascandrolide A has also been achieved,[27] In this synthetic attempt Jacobsen HDA reaction[439] plays a key role in constructing of the right-hand tetrahydropyran ring of **444** in a decisive step. The total synthesis starts from easily accessible 2-silyloxydiene **401** The latter could be provided by silyl enol ether generation from the corresponding enone.[27] Reaction of a neat mixture of diene **401** and aldehyde **250** catalyzed with the chiral tridentate chromium-(III) catalyst **152** followed by mild acidic work-up which hydrolyses the initially generated [4+2]-cycloadduct, afforded the required 2,6-cis-tetrahydropyran **445** in high yield. The latter could be subsequently converted to both alcohols **446** and **447** under different reaction conditions. Initially, isomer **446** was chosen to be used in the in the synthetic route in order to assess and evaluate the chemistry in ahead. It was delightfully observed that the reaction of the side-chain acid **449** and macrocycle **448**, in the presence of excess DEAD and PPh_3, smoothly proceeded, leading to the formation of expected coupled product. At last, upon smooth double Lindlar hydrogenation of the two triple bonds, (+)-leucascandrolide A (scheme 67), was obtained in 92% yield.[438] The physical and spectroscopic data for this synthetic material were compared with those reported previously by Pietra[496] and Leighton[497] and found being identical in aspects.

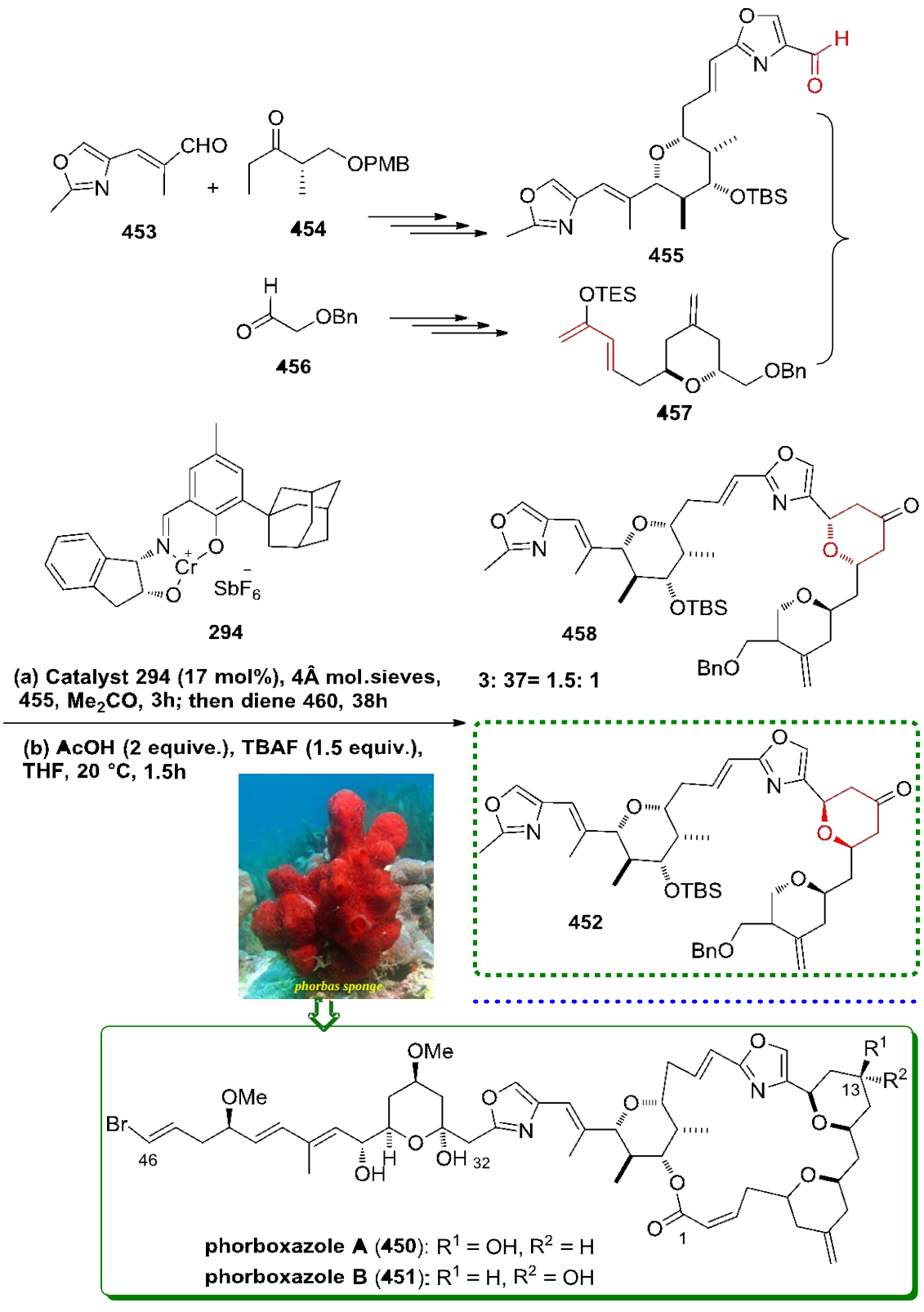


Scheme 67

Phorboxazoles A (**450**, Scheme 68) and B (**451**) were initially isolated[501, 502] from the sponge *Phorbas* sp. found in western coast of Australia and Indian Ocean. Due to the remarkable structural complexity of these marine macrolides, combined with their high biological potency and properties, the phorboxazoles have stirred up appreciable synthetic interest, resulted in

sphosticated total syntheses reported by Forsyth,[503] Evans[504] and Smith,[505, 506] along with of wide variety of structural fragments by professional chemists, worldwide.[507-509]

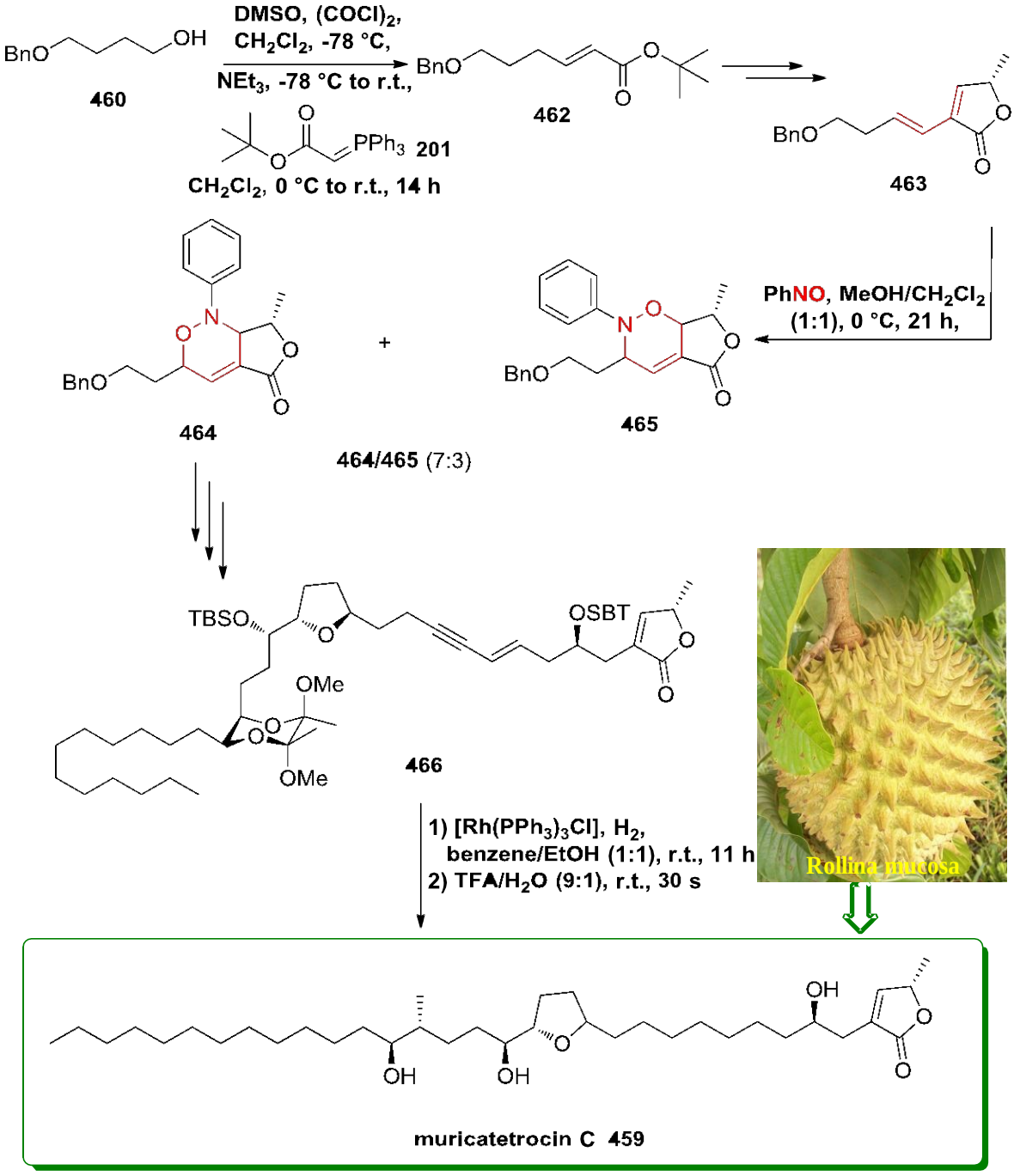
The tetrahydropyranone **452**, containing a pentacyclic C4–C32 fragment of the phorboxazoles, was prepared by a complex HDA cycloaddtion coupling taken place between the 2-siloxydiene **457** and the oxazole aldehyde **453**, catalyzed by the chiral tridentate Cr(III) **294**. In this way ketones **452** and **458** as diastereomers were obtained, in a ratio of 1.5:1. The chief product **452** attributes to the full pentacyclic C4–C32 fragment of the phorboxazoles. The C15–C32 subunit **455** were provided via aldol reaction between ketone **454** and aldehyde **453**. On the other hand the diene **457** having an *exo*-methylene was provided in the several steps and 50% overall yield.[510]



Scheme 68

In 1996, muricatetrocin C (**459**) was isolated by McLaughlin et al from the leaves of *Rollina mucosa*, a tropical fruit tree grown in the West Indies and some part of Central America. It shows antitumor potency.[511]

The synthesis began with 1,4-butanediol, which was monoprotected to give the primary benzyl ether **460**, then a tandem Swern−Wittig reaction afforded the α,β-unsaturated tertbutyl ester **463** in excellent yield (Scheme 69). With **463** now readily available, the key HDA reaction was investigated. It was found that overnight stirring of a methanol/dichloromethane (1:1) solution of **463** with nitrosobenzene at 0 °C afforded a mixture of regioisomers (**464**/**465** 7:3), favoring the desired adduct **464**, in overall 89% yield. Pleasingly, inspection of the crude ^{1}H NMR showed that the major regioisomer **464** had been formed with a diastereoisomeric ratio of greater than 20:1−thus the observed diastereoselection appeared to be limited only by the original geometry of the external olefin in the diene precursor. According to this precedent, reduction of **466** with hydrogen in ethanol/benzene in the presence of Wilkinson's catalyst gave, after eleven hours, fully protected **459** in good (76%) yield with no reduction of the butenolide portion.[512, 513]

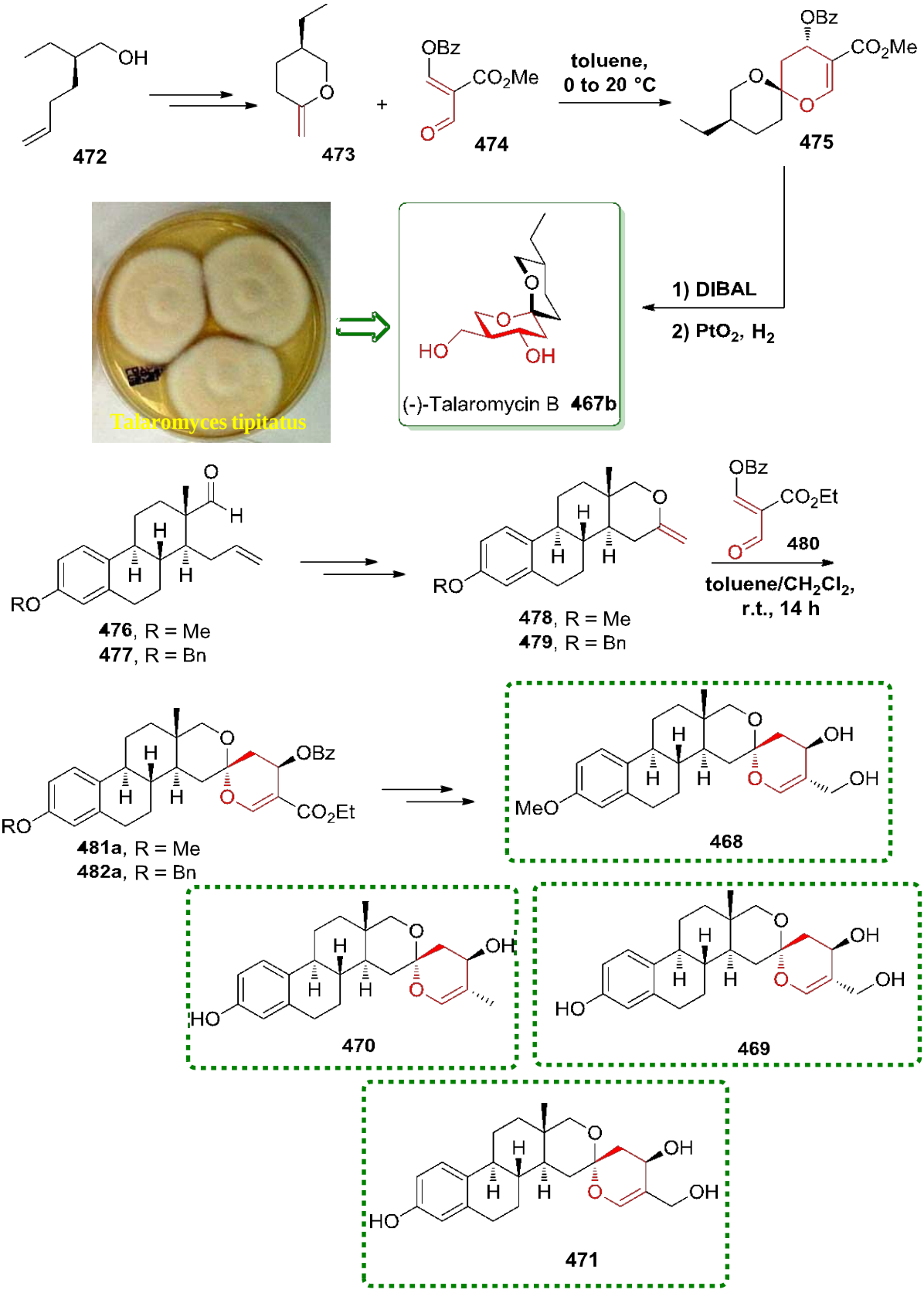


Scheme 69

The talaromycins A and B are toxic metabolites that were isolated from the fungus *Talaromyces tipitatus*[514, 515] in 1982 by Lynn and co-workers. It has already been found that the chemotherapeutic potency of cytostatics toward estrone hormone-receptive tumors could be increased via the formation of linkage between them and estrone.[515-517] Thus, any attempt to

combine estrone with mycotoxins for designing a new class of cytotoxic compounds are desirable. The asymmetric total synthesis of the established highly biologically active spirocyclic mycotoxin (-)-talaromycin B (**467b**) has been achieved and reported.[518] This approach was chiefly relied on an HDA cycloaddition reaction[519] of methyl *O*-benzoyldiformylacetate (**474**)[520] as a 1-oxa-1,3-butadiene derivative with the exocyclic enol ether **473**. The latter in turn can be obtained from **472** by iodoetherification followed by elimination (Scheme 70).[521]

In this line the total synthesis of hybrid natural mycotoxin talaromycin **467b** employing the same approach have been achieved and reported. This protocol this commenced from the D-secoestrones **476** and **477**.[522] Upon HDA cycloaddtion reaction, steroidal exocyclic enol ethers **478** to **479**, the secoestrones **476** and **477** were obtained which by sequential reduction/iodoetherification/elimination, with ethyl *O*-benzoyldiformylacetate (**480**) resulted in the spiroacetals **481** and **482** as a mixture of four diastereomers respectively. Reduction of the chief diastereomers **481a** and **482a** using DIBAH followed by hydrogenation led to the novel natural product hybrids **468**, **469**, **470**, and **471**, which show the structural features similar to those of the mycotoxin talaromycin **467b**.[523]



Scheme 70

Curiosity in polyketide coumarins was flashed by the discovery of the strong anthelmintic[524] and molluscicidal[525] properties of ethuliacoumarin A (**483**). It is one of the constituent of the Egyptian medicinal plant *Ethulia conyzoides L.*[526] The relative analogues **484-486** were also isolated,[527] some exhibited biological properties similar to **483** (figure 3).[525] Ethuliacoumarins (**483-485**) can be obtained in substantial amounts by isolation[528]. However their source in plant kingdom is not readily accessible, nor is the natural analogues are numerous to withstand a remarkable natural products chemistry effort.

In an attempt to total synthesis of natural product **485**, initially an swift path way was designed to the acetal **490**, involving its remodeling to the vinyl-substituted lactol **491** and the ultimate transformation of the later into (±)-preethulia coumarin (**485**),[527] Compound **485** is the least oxygenated of ethulia coumarins member. The strategy to install the acetal **490** involved the development of a three-component sequential cascade Knoevenagel/HDA reaction[236, 283] between 4-hydroxy-5-methylcoumarin (**487**), diacetyl (= 2,3-butandione, **488**) and a vinyl ether **489**. As a model to have access to ethulia coumarins from the hemiacetal **492**, its transformation into (±)-preethulia coumarin (**485**)[527] was contemplated and successfully accomplished. Practically, norprenylation of the hemiacetal via reaction with 2-methyl-1-propenyllithium under sonication afforded a ca 2:1 pair of diastereomeric alcohols **493**, which subjected to Mitsunobu intramolecular etherification to afford **485** in 55% yield (scheme 71). This compound showed identical spectroscopic properties identical data except the optical rotation to those of natural preethulia coumarin (**485**).[529]

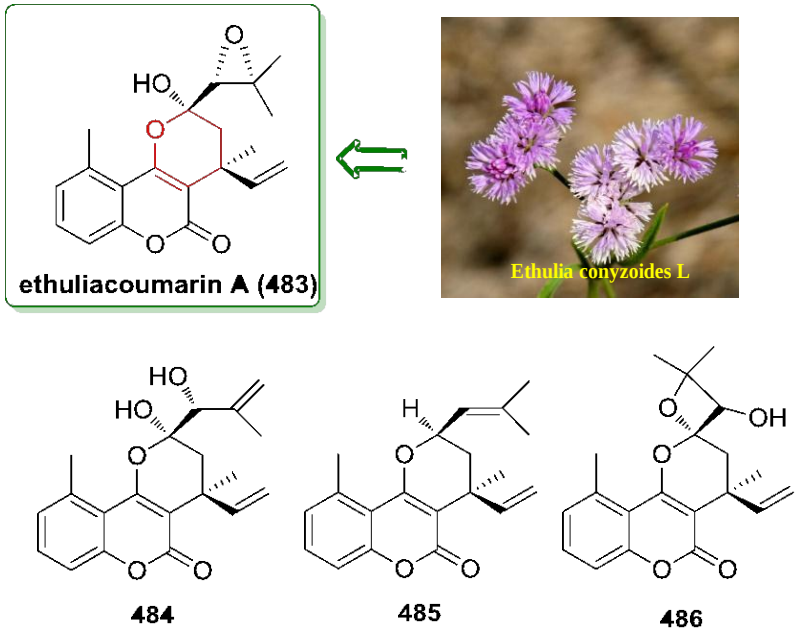
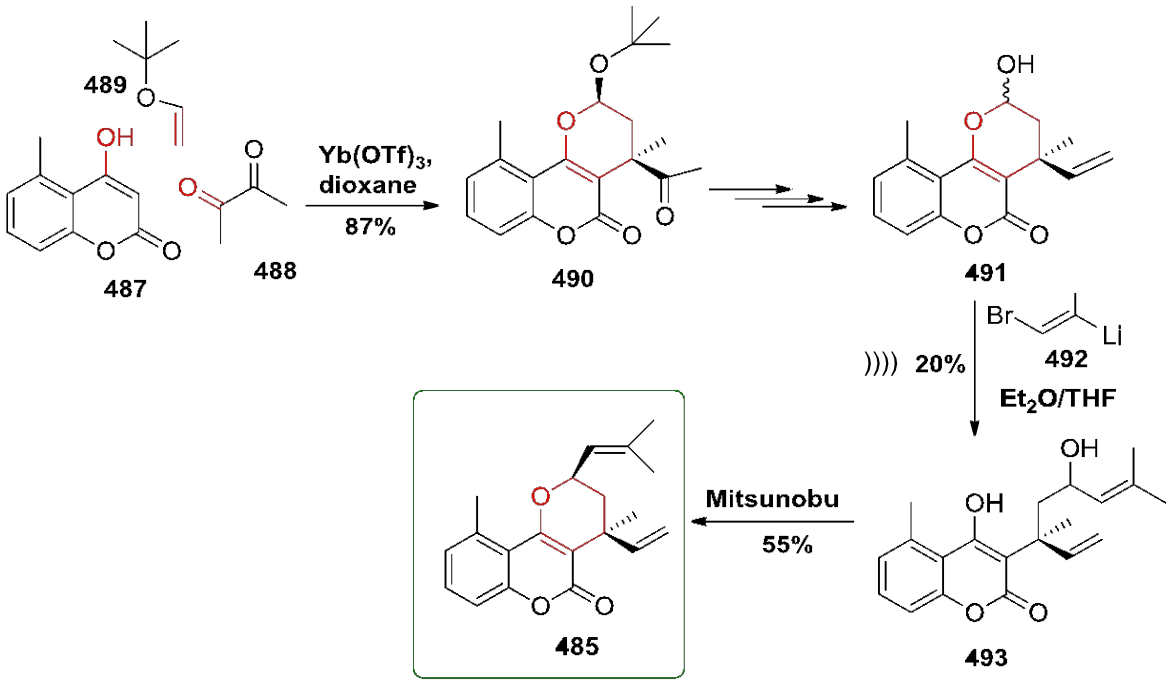


Figure 3



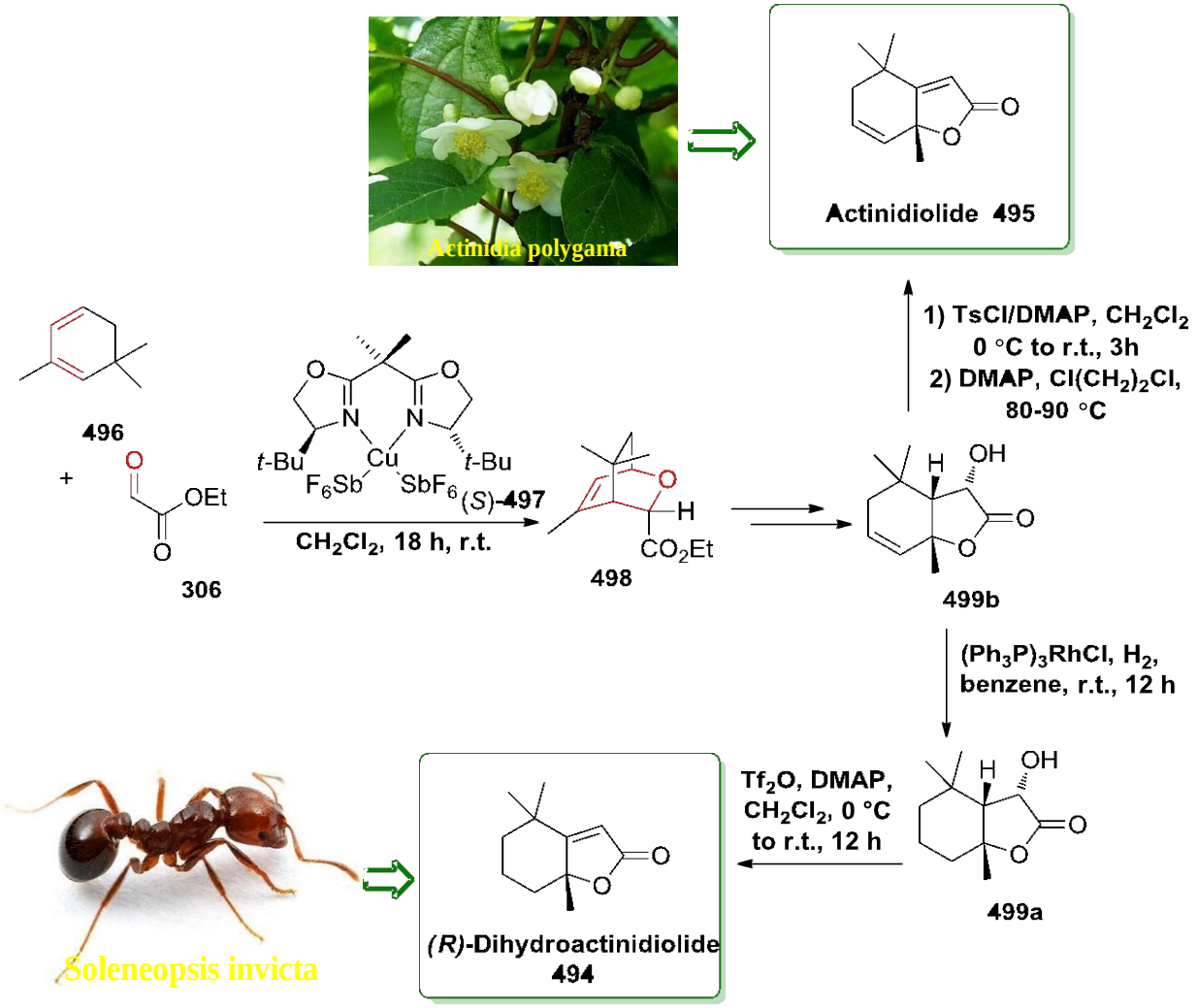
Scheme 71

(*R*)-Dihydroactinidiolide (**494**) has been found as one of the three components of the pheromone involved in queen recognition of the workers of the red fire ant, namely *Soleneopsis invicta*.[530] Due to importance of pheromones in controlling insects its, total synthesis has attracted much

attentions. Thus a plethora of different syntheses of dihydroactinidiolide have been attempted, achieved and reported, all of them, resulted in isolation of racemat.[531, 532] However a few asymmetric synthesis is also available.[533, 534] The asymmetric total syntheses of (*R*)-dihydroactinidiolide (**494**) is relied on the use of chiral starting materials and multistep reactions, or compounds which, at a definite step of the reaction route, are separated as the pure enantiomers, frequently resulting in low overall yields of **494**. A close structurally related compound to (*R*)-dihydroactinidiolide (**494**) is (*R*)-actinidiolide (**495**). Both **494** and **495** were initially isolated as cat attractants from leaves from *Actinidia polygama*.[531] Therefore since then they also been recognized as flavor components in many plant sources such as tobacco[535] and tea.[535]

The total synthesis of (*R*)- dihydroactinidiolide (**494**) and (*R*)-actinidiolide (**495**) with excellent enantiomeric excess (ee) and in high overall chemical yield by asymmetric catalytic (HDA) has been achieved. In addition and delightfully, a common intermediate generated in this approach for the total synthesis of **494** and **495** were found being useful for the synthesis of a series of related compounds (scheme 72). This strategy for the total synthesis of **494** and **495** is made possible by development to perform a highly selective and enantioselective HDA reactions of conjugated dienes with glyoxylates mediated by Cu(II)-bisoxazoline complexes **497**.[536-538]

The pathway to total synthesis of (*R*)-dihydroactinidiolide (**494**) and (*R*)-actinidiolide (**495**) from 2,6,6-trimethyl-1,3-cyclohexadiene (**496**) and ethyl glyoxylate (**306**) is depicted in Scheme 72. (R)-Dihydroactinidiolide (**494**) and (R)-actinidiolide (**495**) can be synthesized from **499b**. The bicyclic lactone **499b** was provided from **498** upon treatment of base followed by acid.[536, 537] Compound **498** was provided by an asymmetric catalytic HDA reaction of 2,6,6-trimethyl-1,3-cyclohexadiene (**496**) with ethyl glyoxylate (**306**). Therefore the key step in the total synthesis of **494** and **495** via this strategy is thus the HDA reaction, which is pleasantly proceeded with high regio- and endo-diastereoselectivity, and in excellent ee (scheme 72). The catalytic effectiveness of several Cu(II)-bisoxazoline complexes in this HDA reaction was evaluated and 2,2′-isopropylidenebis[(4S)-4-tert-butyl-2-oxazoline] $Cu(SbF_6)_2$ ((S)-**497**) was found to be as the catalyst of choice. Compound **499b** was converted to the desired natural product in several steps.[539]

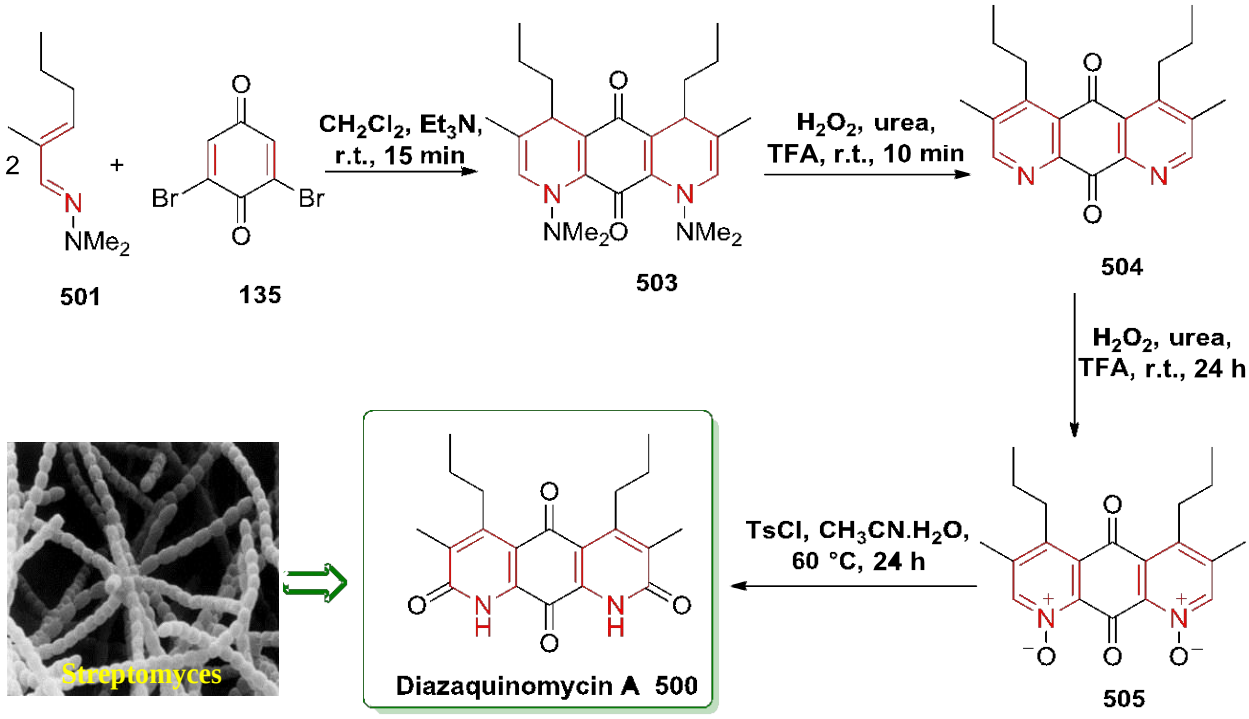


Scheme 72

Diazaquinomycin A (**500**) has been found to be a naturally occurring antibacterial agent. It was initially isolated by Omura and his coworkers[540] from a *Streptomyces* strain. Further investigation by the same group[541] attributed its antibiotic potency to inhibition of thymidilate syntase. Till now, there is only one total synthesis reported for diazaquinomycin,(A) **500** involving a double Knorr cyclization as the key step.[542]

Due to the symmetry of the target ring system, in this approach, a double HDA cycloaddition reaction was envisaged. The first one involved the HDA cycloaddtion of 1-dimethylamino-l-azadienes[543] and a benzoquinone derivative which resulted in a short approach to a 1,8-diaza-anthraquinone system, which would then be expanded to provide the double lactam. Consequently, reaction of 2-metyl-2-hexenal dimethylhydrazones **501**[544] with 2,6-dibromobenzoquinone **502** promoted by triethylamine via trapping the liberated hydrobromic

acid gave compound **503**. Notably all attempts for aromatization of compound **503** with simultaneous double elimination of dimethylamine under previously reported conditions[545, 546] failed. Ultimately, the doubly N-oxide **505** with perearbamide in trifluoroacetic acid followed by rearrangement to the double lactam via treatment with tosyl chloride in CH_3CN-H_2O gave diazaquinomycin A **500**, which found being identical to the natural product in all points of view (Scheme 73).[547]



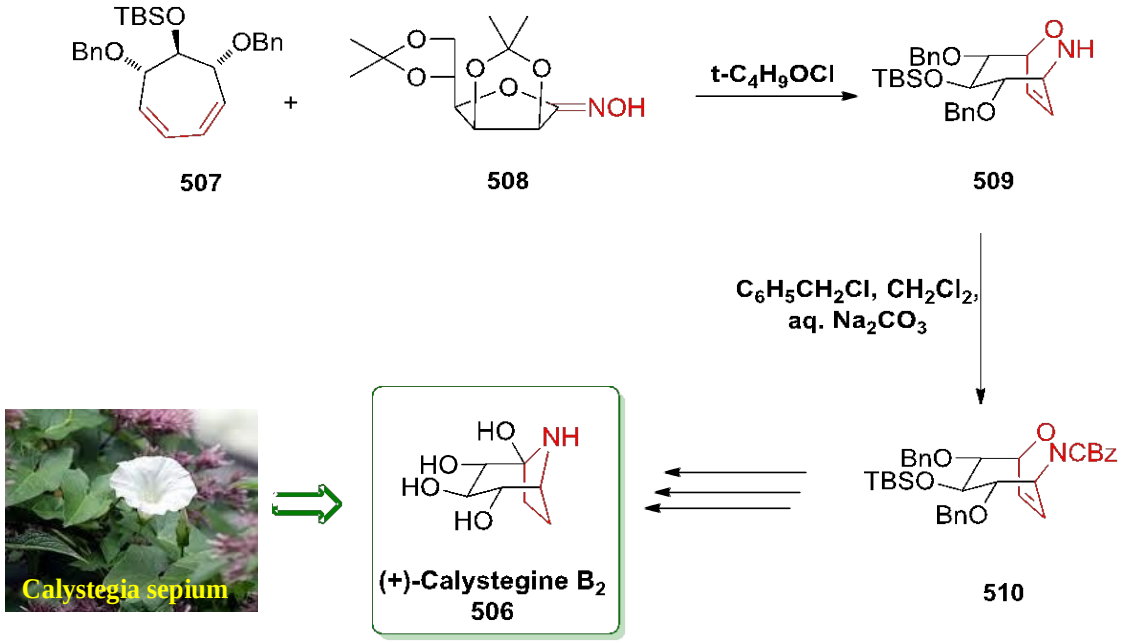
Scheme 73

The most plentiful calystegines, A_3, B_1, and B_2 (**506**), occur in *C. sepium*.[548] Nitroso compounds are known to act as an ideal dienophiles especially in HDA cycloadditions to provide bicyclo-dihydroxazines.[549] Calystegines are chiral polyhydroxylated nortropanic substances. The absolute configuration of natural calystegine B_2 has been determined as (1R,2S,3R,4S,5R).[550] Generally, the chirality can be introduced in various ways. One of the most global way is to induce chirality during the HDA cycloaddition reaction, involving a chiral nitroso substrate.

This synthesis of natural calystegine B_2 has been remarkably improved, decreasing the steps and providing to obtain a satisfactory (13%) overall yield.[551]

In this protocol for the total synthesis of natural calystegine B_2, the trisubstituted cycloheptadiene **508**, is an appropriate precursor.[552] then, the produced free dihydroxazine **509** was protected as

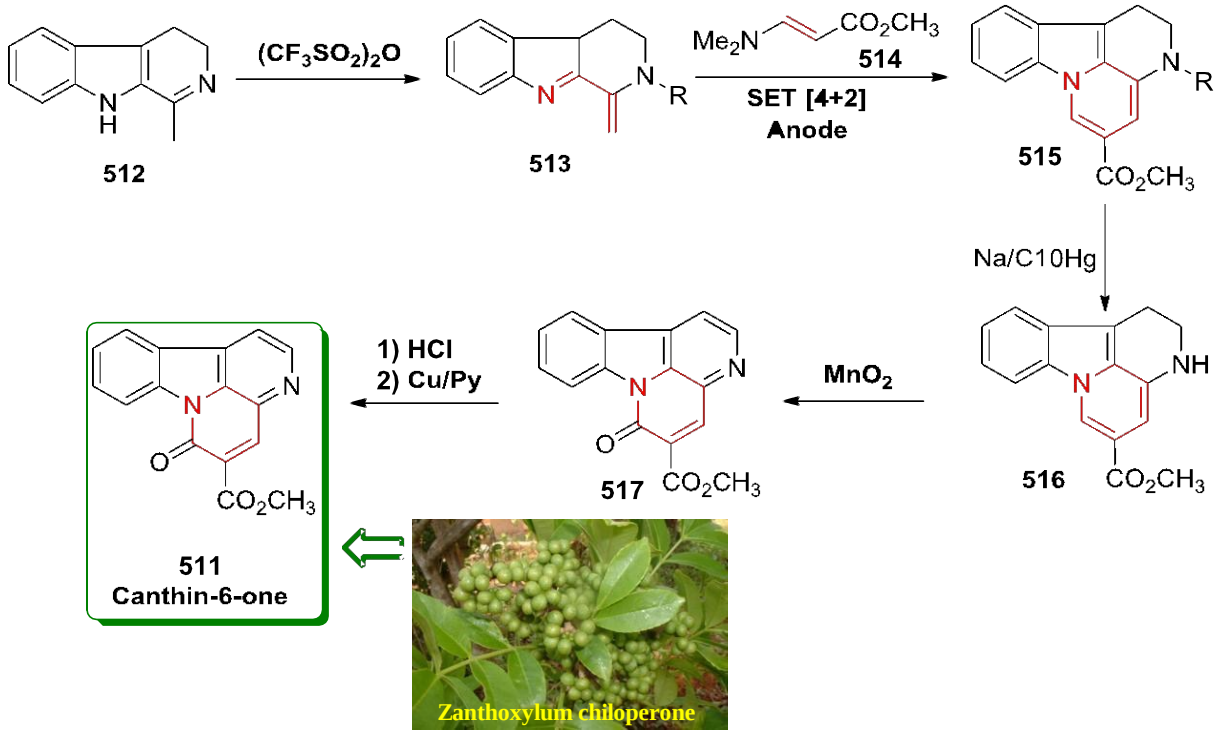
its benzylcarbamate derivative (**510**) and the subsequent steps according to the procedure as in the literature gave B_2 (Scheme 74).[550, 552]



Scheme 74

Canthin-6-one (**511**), was first isolated from *Zanthoxylum chiloperone*. It exhibited a wide scope of antifungal and leishmanicidal activities.[553] To date, several approaches for the total synthesis of canthin-6-one (**511**) have been accomplished and reported.[554-558] Among them, perhaps the following pathway (Schemc 75) is exceptionally concise (six synthetic steps) and in addition gives a satisfactory overall yield (18%) because to the high yielding key step. In addition, it is one of the rare electron transfer induced total syntheses of a naturally occurring compounds.[559] The acceptor, substituted 2-vinylindoles in the cycloaddition is provided from readily available harmalane **512**,[560] and acyl halides or anhydrides.[561] In present approach the trifyl substituted harmalanc derivative **513**, was provided from harmalane **512**. Interestingly, HDA cycloaddition reaction between **513** and methyl E-3-(N,N-dimethylamino)-acrylate (**514**) as the dienophile was conducted electrochemically at a potential of 400 mV in CH_3CN/CH_2Cl_2 at ambient temperature in accordance with previously reported general procedure.[562] A ratio of 5:1 between the diene **513** and the dienophile **514** provided the best yield (87%) of the corresponding adduct **515**. Noticeably, it is one of the highest yields ever reported for this kind of cycloaddition reaction. In addition, 84% of the residual diene **513** can be recovered upon chromatography. Compound **517** is also an intermediate for the synthesis of canthin-6-one **511** reported by Mitscher et al.[555] The

latter could be transformed into the natural product **511** in 50% yield during acidic ester hydrolysis and decarboxylation promoted by Cu/pyridine.[563]

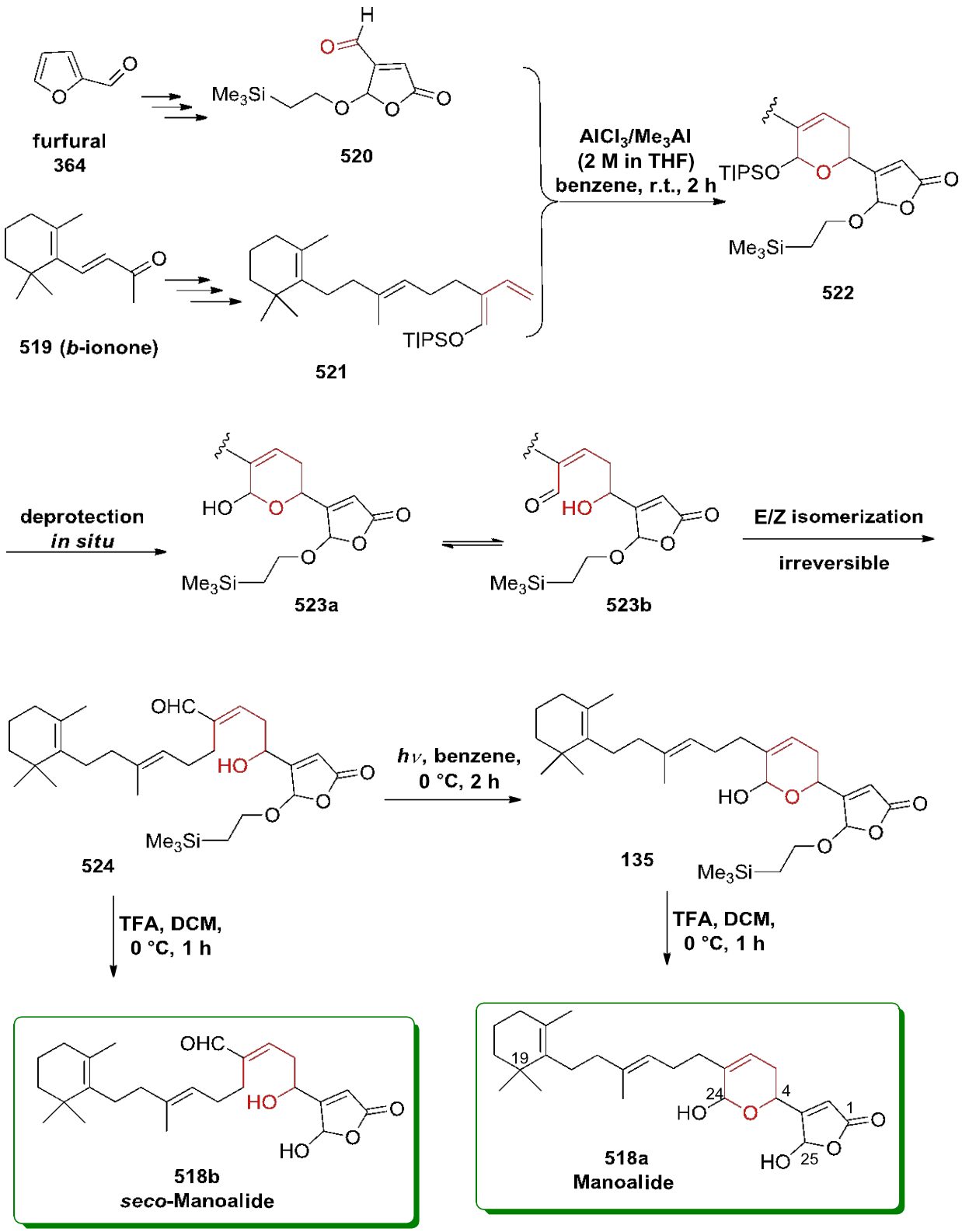


Scheme 75

In 1989, the extracts of the soil microorganism *Streptoverticillium verticillus* were proved to have an unusual pentasubstituted cyclopentane namely, mannostatin A.[564, 565] Manoalide has previously been prepared by Katsumura and Isoe,[566, 567] Garst,[568] Kocienski[569, 570] and their respective colleagues. All these reported strategies have one thing in common. That is, the sensitive γ-hydroxybutenolide moiety was created in the last step, via HDA cycloaddtion reaction of singlet oxygen to a 2-trialkylsilylfuran derivative. Accordingly, a new protocol employing, a 3-formylated butenolide, **520** has been reported. In this approach the latter was subjected to a Lewis acid-catalyzed HDA reaction. In this regard several silyloxydienes were employed in the key cycloaddition reaction.

Furfural provides the desired 4-formyl-5-[2-(trimethylsilyl)eth-1-oxy]furan-2(5H)-one **520** as key intermediate. The required 20 carbon western silyloxydiene **521** was synthesized in 5 steps, starting from commercially avialable β-ionone **519**. Reaction of silyloxydiene **521** and aldehyde **522** under the optimized conditions concluded, from the model reaction (Scheme 76), gave raise into the HDA cycloadduct, which was desilylated in situ (silica gel, H_2O) at carbon C-24

affording monoprotected *seco*-manoalide (**524**). Deprotection, of the latter using trifluoroacetic acid gave manoalide (**518b**) (Scheme 4). As an alternative to the common photoisomerization of **518b** into **518a**, compound **524** was cyclized to monoprotected manoalide **525**.[571]



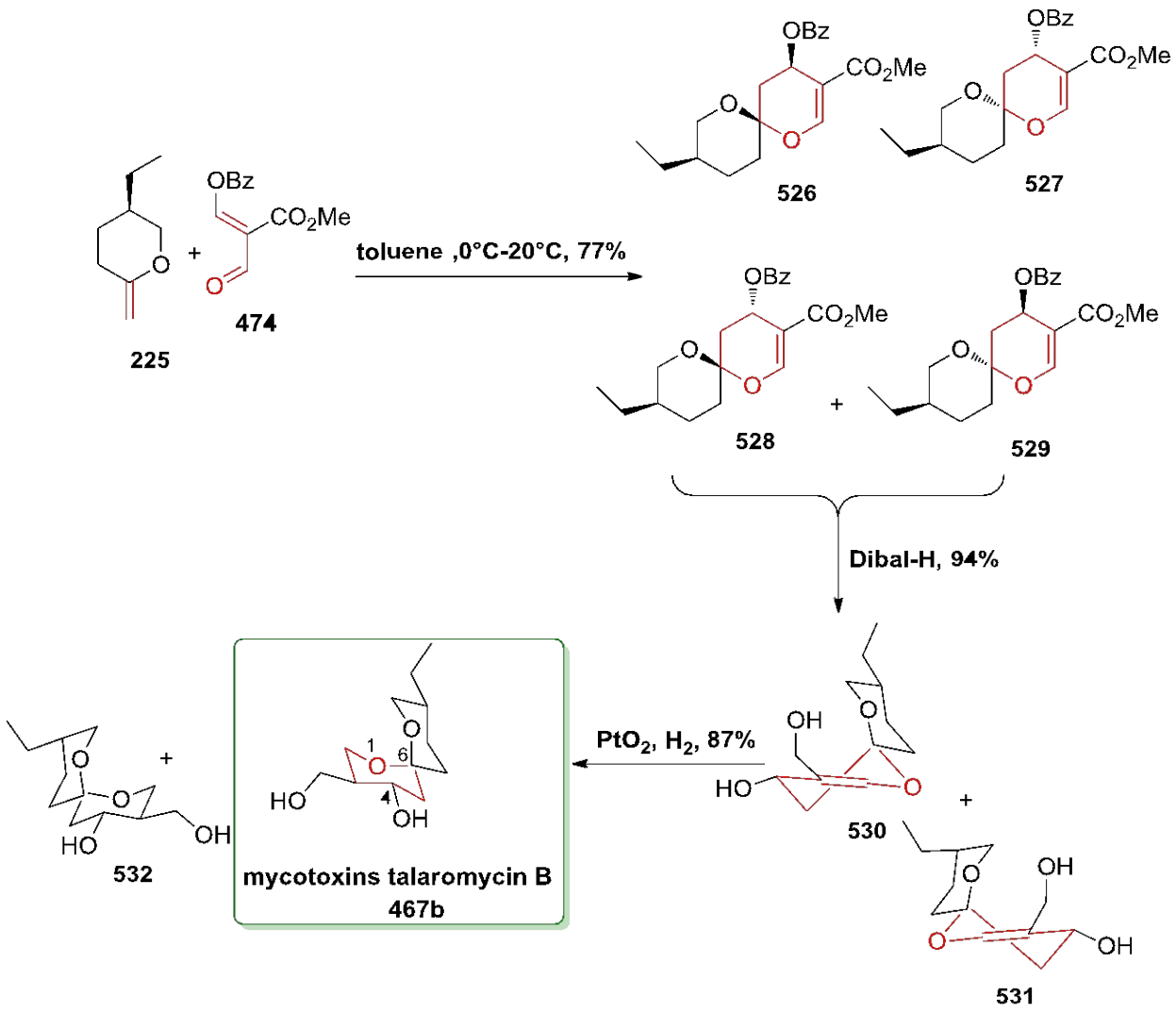
Scheme 76

In 1982 Lynn et al isolated and identified the highly toxic mycotoxins talaromycin A (**467a**) and B **(467b)** as the first spiro- acetals of the fungus *Talaromyces stipitatus*.[515] This interesting structural feature takes place in several natural product, such as, polyether antibiotics, pheromones, milbemycins, and avermectins. They exhibit a wide range of biological potencies.[572]

Thus, the synthetic strategies to spiroacetals have been extensively studied.[573] A concise and enantioselective synthesis of (-)-talaromycin B **(467b)** through nine steps has been achieved and afforded the desired natural product in an overall yield of 5%.[514] In this protocol the key step in the synthesis is a HDA reaction of exocyclic vinyl ether **473** and methyl *O*-benzoyldiformylacetate **(474)**. The oxa-1,3-butadiene **474**, was readily prepared by formylation of methyl 3,3-dimethoxypropionate via benzoylation. It is a versatile substrate for HDA reactions. In addition analogous compounds, **474** was used in the synthesis of 3,4-dihydropyrans, as shown in scheme 77).[574]

Vinyl ether **473** should be instantly subjected to the HDA reaction, which cleanly and smoothly reacted with O in a ratio of 3:1.5:2:1 with the overall yield of 77% (scheme 77). Delightfully, the major isomer **528** have the correct (4S,6R) configuration at the two newly generated chiral centers. Thus, flash chromatography of the cycloadducts provided a mixture of the trans adducts **528** and **529** along with a mixture of the cis adducts **526** and **527**. At last, hydrogenation of the double bond in **530** and **531** gave (-)-talaromycin B (**467b**) along with a small amount of the diastereomer **531**. This hydrogenation was highly stereo selective, taking place only from the bottom side of **530** and **531** to provide exclusively **467b** from **530** and moreover, **532** were obtained from **531**.

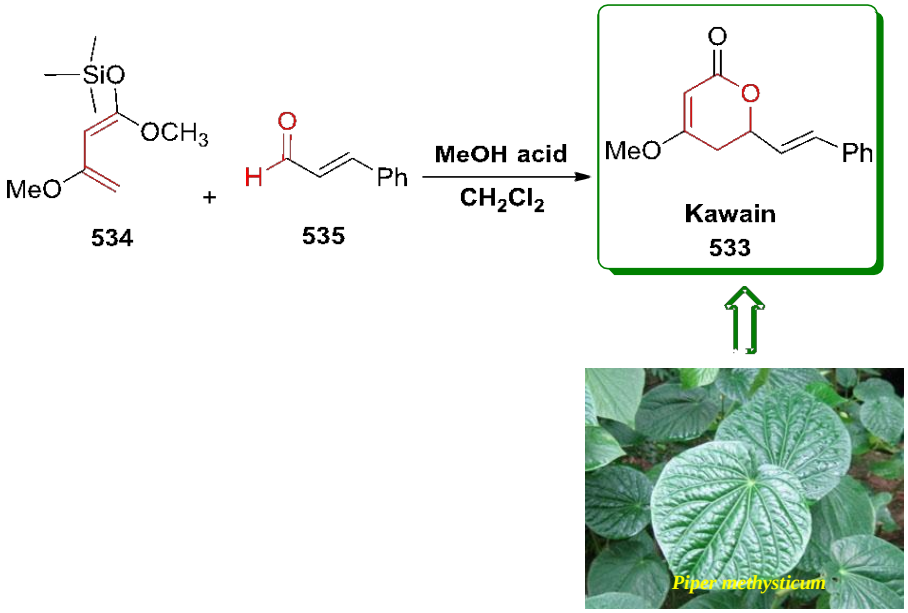
Figure 4



Scheme 77

Kawain **533**, is α-pyrones among others isolated from the kava plant, *Piper methysticum*. substances isolated from this plant have exhibited several biological properties.[575]

The HDA cycloaddition reaction between dienes, 1,3-dimethoxy-1-trimethylsilyloxybutadiene **534** and aldehydes, cinnamaldehyde **535** in dichloromethane under N_2, atmosphere catalyzed by $Eu(fod)_3$ or $Yb(fod)_3$ offers a facile and effective synthesis of (+) kawain **533**[576, 577] in 75% and 84% yield respectively. When Ag(fod) is used as an effective catalyst a unique condensation reaction takes place in which two acyclic diastereomers were obtained in 72% yield (scheme 78).[578]



Scheme 78

(−)-Pyrimidoblamic acid, **537,** and its related peptide naturally occurring derivative, P-3A, **538**, are known as key subunit for the classical synthesis of modified or simplified bleomycin analogs. The bleomycin (**536**, figure 5) is known as a group of basic glycopeptides that were initially isolated by Umezawa[579] as copper complexes from cultures of *Streptomyces verticillus*.[580] The total synthesis of (−)-pyrimidoblamic acid were and accomplished and reported by Umezawa,[581] Hecht,[582] and by other research groups.[583, 584]

It is proposed that the pyrimidine core of (−)-pyrimidoblamic acid is constructed via an inverse electron demand D-A reaction between the highly functionalized amidine **544** and 1,2,3-triazine **541a** (Scheme 79). Moreover, the same amidine **544** via cycloaddition with 1,2,3-triazine **541b** can produce the pyrimidine core present in **P-3A.** The required N-aminopyrazole **540a** for oxidative ring expansion to the 1,2,3- triazine **541a** was provided from **539a**. On the other hand, the required N-aminopyrazole **540b** employed to obtain 1,2,3-triazine **541b** was provided from pyrazole **539b**. Amidine **544** was provided from market purchasable N-(triphenylmethyl)-L-asparagine (**542**) and aldehyde **543**. [4 + 2] Cycloaddition reaction of 1,2,3-triazine **541a** with amidine **544** afforded the desired pyrimidine **545.** Under the optimized conditions, the reaction of **544** and **541a,** gives **545** as single diastereomer in 54% chemical yield. With this efficient pathway for the synthesis of **545** in hand, (−)-pyrimidoblamic acid **537** was prepared in virtually quantitative yield which was found identical by comparison of its physical and spectral data with

those of authentic sample (Scheme 79). Accordingly, the cycloaddition reaction between **544** and **541b** gave **P-3A** (**538**) in 89% yield after several steps reactions.[585]

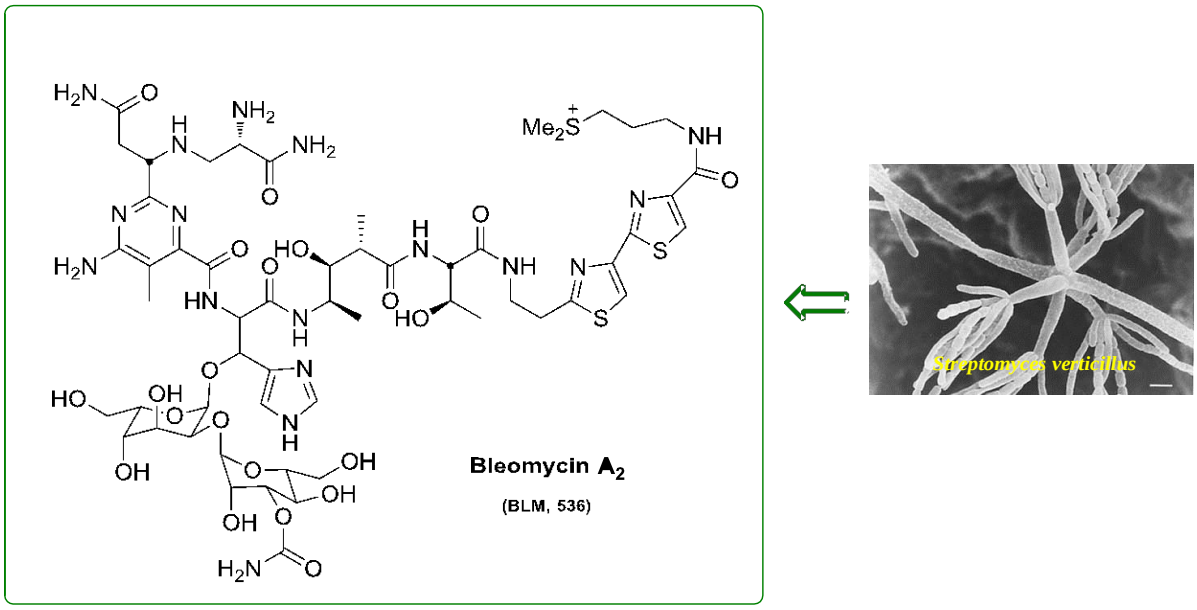
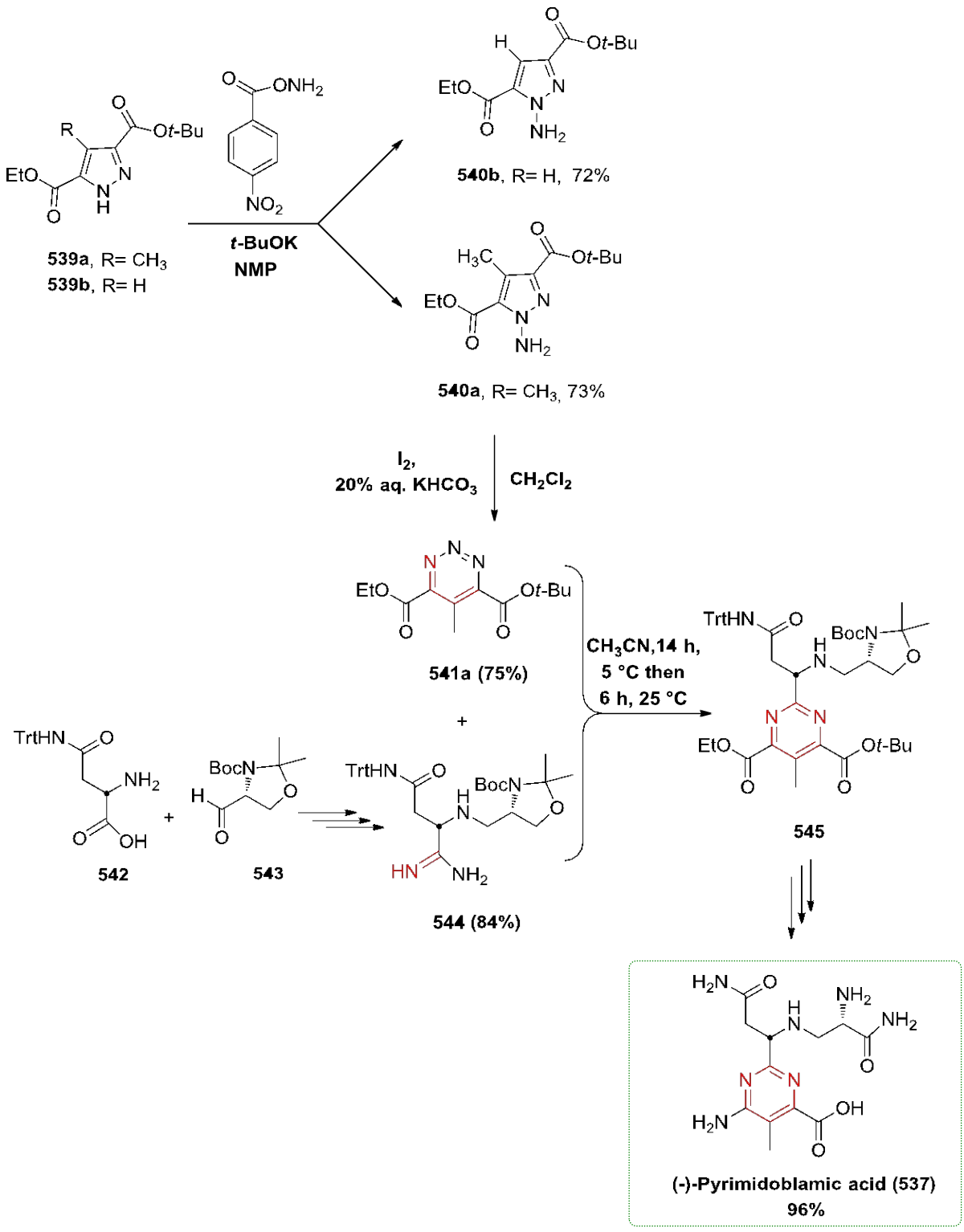
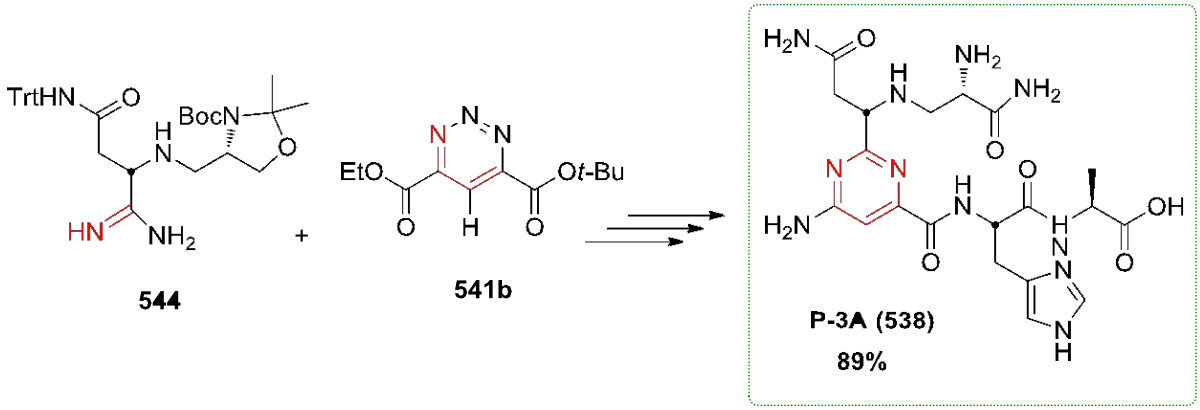


Figure 5



Scheme 79



Scheme 80

The ergot alkaloids initially isolated from the fungus *Claviceps purpurea*, containing a large group of biologically active indole alkaloids.[586] Among this class of naturally occurring products, the notorious lysergic acid (LSD)[587] is the most widely renowned member. However its several semi-synthetic derivatives are used as medicine in the treatment of wide range of neurological diseases.

An efficient total synthesis of dihydrolysergic acid (**546**) and dihydrolysergol (**547**) have been achieved and revealed. This strategy used an inverse electron demand D-A reaction of the tricyclic ketone **548** derived enamine **549** with 5-carbomethoxy-1,2,3-triazine (**550**) for the late-stage synthesis of the tetracyclic scaffold of the ergot alkaloid core structure (scheme 80). As a matter of fact, in the synthesis of tricyclic ketone **548** a key step is intramolecular Pd(0)-catalyzed Larock indole annulation of a N-acetyl 2-bromoaniline derivative which is substituted with a pendant alkyne for the assemblage of the tricyclic fused indole, already known being present in ergot alkaloids. This approach consciously designed to permit the late-stage cycloaddition reaction of the electron-rich dienophile **549** with additional reactive heterocyclic azadienes for the divergent synthesis of several corresponding heterocyclic D-ring derivatives which were not easily accessible via conventional strategies, including alternatives such as substituted pyridines, pyrimidines, pyridazines and pyrroles.[588]

3. Summary

In conclusion , six-membered aza- and oxa-heterocycles as frameworks are frequently present in in naturally occurring products, including drugs endowed with a gathering of biologicalactivities. HDA and IMHDA reactions provide efficient and convenient access to these scaffolds. HDA reactions of aza- or oxa-substituted dienes or dienophiles are powerful approach to synthesize a wide variety of heterocyclic system, in a regio- and stereoselective fashions, especially to assemble them as a moiety in the structures of natural products. However, the strategic incorporation of a HDA reaction in the synthesis of complex molecules, for instance, natural products, sometimes may be complicated, on the one hand, often multistep and tedious synthesis of the required precursors, and selectivity problems may frequently be encountered. In general, the development of asymmetric, reactions remains highly challenging, and commonly stoichiometric amounts of chiral precursors are required to obtain appreciate levels of stereoselectivity.

Using of organo- catalysts or Lewis acid catalysts under mild reaction conditions, high atom economy, and tolerance of non-interacting functional groups makes the HAD or IMHDA, a reaction of choice for construction of complex molecules and natural products as key step (steps) in total synthesis of naturally occurring compounds. IMHDAs are particularly have been found useful for this purpose, due to their economical and stereocontrolled nature. These reactions permit the generation of two or more rings in a single operation, circumventing sequential chemical transformations.

4. Acknowledgment

The authors gratefully acknowledge the partial financial support from the Research Council of Alzahra University.

5. References

1 O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, 1928, **460**, 98-122.

2 T. L. Gresham and T. R. Steadman, *J. Am. Chem. Soc.*, 1949, **71**, 737-738.

3 K. A. Jørgensen, *Eur. J. Org. Chem.*, 2004, **2004**, 2093-2102.

4 R. R. Schmidt, *Acc. Chem. Res.*, 1986, **19**, 250-259.

5 E. R. Larson and S. Danishefsky, *J. Am. Chem. Soc.*, 1983, **105**, 6715-6716.

6 H. Waldmann, *Synthesis.*, 1994, 535-551.

7 S. Danishefsky, J. F. Kerwin Jr and S. Kobayashi, *J. Am. Chem. Soc.*, 1982, **104**, 358-360.

8 L. F. Tietze and G. Kettschau, in *Top. Curr. Chem.*, Springer, 1997, pp. 1-120.

9 J. Cossy, M. Brimble and M. Cordes, *Synthesis of Saturated Oxygenated Heterocycles I*, Springer, 2014.

10 S. M. Weinreb and R. R. Staib, *Tetrahedron.*, 1982, **38**, 3087-3128.

11 D. T. Amos, A. R. Renslo and R. L. Danheiser, *J. Am. Chem. Soc.*, 2003, **125**, 4970-4971.

12 D. C. Bland, B. C. Raudenbush and S. M. Weinreb, *Org. Lett.*, 2000, **2**, 4007-4009.

13 T.-L. Ho, L.-R. Kung and R.-J. Chein, *J. Org. Chem.*, 2000, **65**, 5774-5779.

14 E. J. Thomas, *Acc. Chem. Res.*, 1991, **24**, 229-235.

15 M. Jayagobi and R. Raghunathan, *Tetrahedron: Asymmetry.*, 2010, **21**, 2726-2732.

16 K. N. Houk, Y. Li and J. D. Evanseck, *Angew. Chem. Int. Ed.*, 1992, **31**, 682-708.

17 M. Hamzehloueian, S. Yeganegi, Y. Sarrafi, K. Alimohammadi and M. Sadatshahabi, *J. Serb. Chem. Soc.*, 2014, **79**, 911-924.

18 A. G. Fallis, *Acc. Chem. Res.*, 1999, **32**, 464-474.

19 J. R. Bull, R. Gordon and R. Hunter, *J. Chem. Soc., Perkin Trans. 1*. 2000, 3129-3139.

20 V. Eschenbrenner-Lux, K. Kumar and H. Waldmann, *Angew. Chem. Int. Ed.*, 2014, **53**, 11146-11157.

21 B. S. Bodnar and M. J. Miller, *Angew. Chem. Int. Ed.*, 2011, **50**, 5630-5647.

22 D. L. Boger and S. M. Weinreb, *Hetero Diels-Alder methodology in organic synthesis*, Elsevier, 2012.

23 A. E. Hurtley, M. A. Cismesia, M. A. Ischay and T. P. Yoon, *Tetrahedron.*, 2011, **67**, 4442-4448.

24 C. F. Thompson, T. F. Jamison and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2000, **122**, 10482-10483.

25 P. Liu and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 10772-10773.

26 I. Paterson, C. De Savi and M. Tudge, *Org. Lett.*, 2001, **3**, 3149-3152.

27 I. Paterson and M. Tudge, *Angew. Chem. Int. Ed.*, 2003, **42**, 343-347.

28 E. A. Voight, H. Seradj, P. A. Roethle and S. D. Burke, *Org. Lett.*, 2004, **6**, 4045-4048.

29 L. F. Tietze, N. Rackelmann and I. Müller, *Chem. Eur. J.*, 2004, **10**, 2722-2731.

30 U. Majumder, J. M. Cox, H. W. Johnson and J. D. Rainier, *Chem. -Eur. J.*, 2006, **12**, 1736-1746.

31 S. Bonazzi, S. Güttinger, I. Zemp, U. Kutay and K. Gademann, *Angew. Chem. Int. Ed.*, 2007, **46**, 8707-8710.

32 A. K. Dilger, V. Gopalsamuthiram and S. D. Burke, *J. Am. Chem. Soc.*, 2007, **129**, 16273-16277.

33 M. M. Heravi and S. Asadi, *Tetrahedron: Asymmetry.*, 2012, **23**, 1431-1465.

34 M. M. Heravi and V. Zadsirjan, *Tetrahedron: Asymmetry.*, 2014, **25**, 1061-1090.

35 M. M. Heravi and V. Zadsirjan, *Tetrahedron: Asymmetry.*, 2013, **24**, 1149-1188.

36 S. Khaghaninejad and M. M. Heravi, *ChemInform.*, 2014, **45**.

37 M. M. Heravi and T. Alishiri, *Adv. Heterocycl. Chem.*, 2014, **113**, 1.

38 M. M. Heravi, S. Khaghaninejad and M. Mostofi, *Adv. Heterocycl. Chem.*, 2015, **112**, 1.

39 M. M. Heravi, S. Khaghaninejad and N. Nazari, *Adv. Heterocycl. Chem.*, 2015, **112**, 183.

40 M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem.*, 2014, **113**, 143-244.

41 M. M. Heravi, S. Sadjadi, H. A. Oskooie, R. H. Shoar and F. F. Bamoharram, *Catal. Commun.*, 2008, **9**, 470-474.

42 M. M. Heravi and V. F. Vavsari, *Adv. Heterocycl. Chem*. 2015.

43 M. M. Heravi, S. Sadjadi, N. M. Haj, H. A. Oskooie and F. F. Bamoharram, *Catal. Commun.*, 2009, **10**, 1643-1646.

44 M. M. Heravi and B. Talaei, *Adv. Heterocycl. Chem*. 2015.

45 M. M. Heravi, S. Asadi and B. M. Lashkariani, *Mol. Diversity.*, 2013, **17**, 389-407.

46 M. M Heravi, P. Hajiabbasi and H. Hamidi, *Curr. Org. Chem.*, 2014, **18**, 489-511.

47 M. M. Heravi and P. Hajiabbasi, *Mol. Diversity*. 2014, **18**, 411-439.

48 M. M. Heravi, T. B. Lashaki and N. Poorahmad, *Tetrahedron: Asymmetry.*, 2015, **26**, 405-495.

49 M. M Heravi, V. Zadsirjan and K. Kamjou, *Curr. Org. Chem.*, 2015, **19**, 813-868.

50 M. M Heravi, T. Ahmadi, A. Fazeli and N. Milani Kalkhorani, *Curr. Org. Synth.*, 2015, **12**, 328-357.

51 M. M. Heravi, E. Hashemi and N. Nazari, *Mol. Diversity.*, 2014, **18**, 441-472.

52 M. M. Heravi, E. Hashemi and F. Azimian, *Tetrahedron.*, 2014, **70**, 7-21.

53 M. M Heravi, V. Zadsirjan and Z. Bozorgpour Savadjani, *Curr. Org. Chem.*, 2014, **18**, 2857-2891.

54 M. M Heravi, A. Bakhtiari and Z. Faghihi, *Curr. Org. Synth.*, 2014, **11**, 787-823.

55 M. M Heravi, H. Hamidi and V. Zadsirjan, *Curr. Org. Synth.*, 2014, **11**, 647-675.

56 M. M Heravi, S. Asadi and F. Azarakhshi, *Curr. Org. Synth.*, 2014, **11**, 701-731.

57 M. M Heravi, E. Hashemi and N. Ghobadi, *Curr. Org. Chem.*, 2013, **17**, 2192-2224.

58 M. M. Heravi and P. Hajiabbasi, *Monatsh. Chem. Chem. Mon.*, 2012, **143**, 1575-1592.

59 M. M. Heravi and E. Hashemi, *Tetrahedron.*, 2012, **68**, 9145-9178.

60 M. M. Heravi and V. F. Vavsari, *RSC Advances.*, 2015, **5**, 50890-50912.

61 L. Acebey, M. Sauvain, S. Beck, C. Moulis, A. Gimenez and V. Jullian, *Org. Lett.*, 2007, **9**, 4693-4696.

62 L. Acebey, V. Jullian, D. Sereno, S. Chevalley, Y. Estevez, C. Moulis, S. Beck, A. Valentin, A. Gimenez and M. Sauvain, *Planta Med.*, 2010, **76**, 365-368.

63 A. P. Trentin, A. Santos, A. Guedes, M. G. Pizzolatti, R. A. Yunes and J. B. Calixto, *Planta Med.*, 1999, **65**, 517-521.

64 F. Bohlmann, C. Zdero, R. M. King and H. Robinson, *Phytochemistry.*, 1980, **19**, 689-691.

65 A. D. Patil, A. J. Freyer, R. Reichwein, B. Carte, L. B. Killmer, L. Faucette, R. K. Johnson and D. J. Faulkner, *Tetrahedron Lett.*, 1997, **38**, 363-364.

66 C. Yuan, B. Du, L. Yang and B. Liu, *J. Am. Chem. Soc.*, 2013, **135**, 9291-9294.

67 M. J. Begley, L. Crombie, R. W. King, D. A. Slack and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*. 1977, 2393-2402.

68 L. Crombie and R. Ponsford, *Chem. Commun. (London)*. 1968, 894-895.

69 C. E. Turner, M. A. Elsohly and E. G. Boeren, *J. Nat. Prod.*, 1980, **43**, 169-234.

70 C.-B. Cui, S.-Y. Yan, B. Cai and X.-S. Yao, *J. Asian Nat. Prod. Res.*, 2002, **4**, 233-241.

71 S.-Z. Hua, X.-B. Wang, J.-G. Luo, J.-S. Wang and L.-Y. Kong, *Tetrahedron Lett.*, 2008, **49**, 5658-5661.

72 X. Wang and Y. R. Lee, *Tetrahedron.*, 2009, **65**, 10125-10133.

73 B. J. Burreson, P. J. Scheuer, J. Finer and J. Clardy, *J. Am. Chem. Soc.*, 1975, **97**, 4763-4764.

74 M. R. Hagadone, B. J. Burreson, P. J. Scheuer, J. S. Finer and J. Clardy, *Helv. Chim. Acta*., 1979, **62**, 2484-2494.

75 P. Karuso, A. Poiner and P. J. Scheuer, *J. Org. Chem.*, 1989, **54**, 2095-2097.

76 N. Fusetani, H. J. Wolstenholme, S. Matsunaga and H. Hirota, *Tetrahedron Lett.*, 1991, **32**, 7291-7294.

77 K. A. Miller, S. Tsukamoto and R. M. Williams, *Nat Chem.*, 2009, **1**, 63-68.

78 J. Clough, S. Chen, E. M. Gordon, C. Hackbarth, S. Lam, J. Trias, R. J. White, G. Candiani, S. Donadio and G. Romanò, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3409-3414.

79 P. Tavecchia, P. Gentili, M. Kurz, C. Sottani, R. Bonfichi, E. Selva, S. Lociuro, E. Restelli and R. Ciabatti, *Tetrahedron.*, 1995, **51**, 4867-4890.

80 G. Heckmann and T. Bach, *Angew. Chem. Int. Ed.*, 2005, **44**, 1199-1201.

81 G. Heckmann and T. Bach, *Angew. Chem.*, 2005, **117**, 1223-1226.

82 O. Delgado, G. Heckmann, H. M. Müller and T. Bach, *J. Org. Chem.*, 2006, **71**, 4599-4608.

83 T. Suzuki, A. Nagasaki and K. Okumura, *Heterocycles.*, 2001, **55**, 835-840.

84 K. Okumura, H. Saito, C.-g. Shin, K. Umemura and J. Yoshimura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 1863-1870.

85 K. Nicolaou, M. Nevalainen, B. S. Safina, M. Zak and S. Bulat, *Angew. Chem. Int. Ed.*, 2002, **41**, 1941-1945.

86 K. Nicolaou, B. S. Safina, M. Zak, S. H. Lee, M. Nevalainen, M. Bella, A. A. Estrada, C. Funke, F. J. Zécri and S. Bulat, *J. Am. Chem. Soc.*, 2005, **127**, 11159-11175.

87 P. Baumhof, R. Mazitschek and A. Giannis, *Angew. Chem.*, 2001, **113**, 3784-3786.

88 P. Baumhof, R. Mazitschek and A. Giannis, *Angew. Chem. Int. Ed.*, 2001, **40**, 3672-3674.

89 K. Nicolaou, B. Zou, D. H. Dethe, D. B. Li and D. Y. K. Chen, *Angew. Chem.*, 2006, **118**, 7950-7956.

90 K. e. C. Nicolaou, D. H. Dethe, G. Y. Leung, B. Zou and D. Y. K. Chen, *Chem. Asian. J.*, 2008, **3**, 413-429.

91 A. J. Blackman, C. Li, D. C. Hockless, B. W. Skelton and A. H. White, *Tetrahedron.*, 1993, **49**, 8645-8656.

92 C. Li and A. Blackman, *Aust. J. Chem.*, 1994, **47**, 1355-1361.

93 C. Li and A. Blackman, *Aust. J. Chem.*, 1995, **48**, 955-965.

94 S. N. Huckin and L. Weiler, *J. Am. Chem. Soc.*, 1974, **96**, 1082-1087.

95 W. Chao, J. H. Waldman and S. M. Weinreb, *Org. Lett.*, 2003, **5**, 2915-2918.

96 W. Chao and S. M. Weinreb, *Org. Lett.*, 2003, **5**, 2505-2507.

97 W. Chao, Y. R. Mahajan and S. M. Weinreb, *Tetrahedron Lett.*, 2006, **47**, 3815-3818.

98 G. Rall, T. Smalberger, H. De Waal and R. Arndt, *Tetrahedron Lett.*, 1967, **8**, 3465-3469.

99 H. Rapoport and H. D. Baldridge, *J. Am. Chem. Soc.*, 1951, **73**, 343-346.

100 T. R. Govindachari, B. R. Pai and N. S. Narasimhan, *J. Chem. Soc. (Resumed).*, 1954, 1847-1849.

101 G. Strunz and J. Findlay, 26 Academic Press, Orlando, 1985.

102 D. Ma and N. Ma, *Tetrahedron Lett.*, 2003, **44**, 3963-3965.

103 K. K. Kumar and A. Datta, *Tetrahedron.*, 1999, **55**, 13899-13906.

104 R. Singh and S. K. Ghosh, *Tetrahedron Lett.*, 2002, **43**, 7711-7715.

105 E. Brown and A. Bourgouin, *Tetrahedron.*, 1975, **31**, 1047-1051.

106 E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1974, **96**, 5614-5616.

107 E. J. Corey, K. C. Nicolaou and L. S. Melvin, *J. Am. Chem. Soc.*, 1975, **97**, 654-655.

108 T. Ozawa, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 2001, **66**, 3338-3347.

109 H. Abe, S. Aoyagi and C. Kibayashi, *J. Am. Chem. Soc.*, 2000, **122**, 4583-4592.

110 S. Aoyagi, R. Tanaka, M. Naruse and C. Kibayashi, *J. Org. Chem.*, 1998, **63**, 8397-8406.

111 M. Naruse, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 1994, **35**, 595-598.

112 T. Sato, S. Aoyagi and C. Kibayashi, *Org. Lett.*, 2003, **5**, 3839-3842.

113 B. Steffan, *Tetrahedron.*, 1991, **47**, 8729-8732.

114 J. Kubanek, D. E. Williams, E. D. de Silva, T. Allen and R. J. Andersen, *Tetrahedron Lett.*, 1995, **36**, 6189-6192.

115 N. Toyooka, M. Okumura and H. Takahata, *J. Org. Chem.*, 1999, **64**, 2182-2183.
116 T. Ozawa, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 2001, **66**, 3338-3347.
117 J. Bosch, J. Bonjoch and M. Amat, *Alkaloids: Chem. Pharmacol.*, 1996, **48**, 75-189.
118 J. Bonjoch and D. Solé, *Chem. Rev.*, 2000, **100**, 3455-3482.
119 S. E. Barron and P. S. Guth, *Trends Pharmacol. Sci.*, 1987, **8**, 204-206.
120 P. J. C. Pelletier, J. B. , *Ann. Chim. Phys.*, **1818**, **8**, 323.
121 R. Robinson, *Experientia*., 1946, **2**, 28.
122 H. Openshaw and R. Robinson, *Nature*., 1946, **157**, 438.
123 R. B. Woodward, W. J. Brehm and A. L. Nelson, , *J. Am. Chem. Soc*., 1947, **69**, 2250.
124 R. Woodward and W. J. Brehm, *J. Am. Chem. Soc.*, 1948, **70**, 2107-2115.
125 S. D. Knight, L. E. Overman and G. Pairaudeau, *J. Am. Chem. Soc.*, 1993, **115**, 9293-9294.
126 S. D. Knight, L. E. Overman and G. Pairaudeau, *J. Am. Chem. Soc.*, 1995, **117**, 5776-5788.
127 T. A. Henry and T. M. Sharp, *J. Chem. Soc. (Resumed)*., 1927, 1950-1959.
128 M. F. Millson, R. Robinson and A. F. Thomas, *Experientia*., 1953, **9**, 89-91.
129 R. B. Woodward, M. P. Cava, W. Ollis, A. Hunger, H. Daeniker and K. Schenker, *Tetrahedron*. ,1963, **19**, 247-288.
130 S. F. Martin, J. E. Hunter, B. Benage, L. S. Geraci and M. Mortimore, *J. Am. Chem. Soc.*, 1991, **113**, 6161-6171.
131 M. Ito, C. W. Clark, M. Mortimore, J. B. Goh and S. F. Martin, *J. Am. Chem. Soc.*, 2001, **123**, 8003-8010.
132 K. M. Werner, J. M. de los Santos, S. M. Weinreb and M. Shang, *J. Org. Chem.*, 1999, **64**, 4865-4873.
133 W. H. Pearson and Y. Ren, *J. Org. Chem.*, 1999, **64**, 688-689.
134 L. Ollero, G. Mentink, F. P. Rutjes, W. N. Speckamp and H. Hiemstra, *Org. Lett.*, 1999, **1**, 1331-1334.
135 E. Corey and D. L. Boger, *Tetrahedron Lett.*, 1978, **19**, 2461-2464.
136 S.-I. Murahashi, S. Sasao, E. Saito and T. Naota, *Tetrahedron*., 1993, **49**, 8805-8826.
137 S. Murahashi, S. Sasao, E. Saito and T. Naota, *J. Org. Chem.*, 1992, **57**, 2521-2523.
138 D. L. Comins and A. Dehghani, *Tetrahedron Lett.*, 1991, **32**, 5697-5700.
139 R. P. Polniaszek and L. W. Dillard, *J. Org. Chem.*, 1992, **57**, 4103-4110.
140 A. Brandi, F. M. Cordero, A. Goti and A. Guarna, *Tetrahedron Lett.*, 1992, **33**, 6697-6700.
141 A. Meyers and G. Milot, *J. Am. Chem. Soc.*, 1993, **115**, 6652-6660.
142 J. W. Daly, T. Tokuyama, G. Habermehl, I. L. Karle and B. Witkop, *Justus Liebigs Ann. Chem.*, 1969, **729**, 198-204.

143 T. Tokuyama, T. Tsujita, A. Shimada, H. Garraffo, T. Spande and J. Daly, *Tetrahedron*. 1991, **47**, 5401-5414.

144 J. W. Daly and T. F. Spande, *Alkaloids: Chem. Bio. Perspect.*, 1986, **4**, 1-274.

145 M. Naruse, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 1994, **35**, 9213-9216.

146 V. Ahluwalia, N. Sharma, B. Mittal and S. Gupta, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1988, **27**, 238-241.

147 S. F. H. Zaidi, I. Yoshida, F. Butt, M. A. Yusuf, K. Usmanghani, M. Kadowaki and T. Sugiyama, *Biol. Pharm. Bull.*, 2009, **32**, 631-636.

148 J. Bukuru, T. N. Van, L. Van Puyvelde, W. He and N. De Kimpe, *Tetrahedron*. 2003, **59**, 5905-5908.

149 R. Mechoulam and Y. Gaoni, *Fortschr Chem Org Naturst.*, 1967, pp. 175-213.

150 X. Wang and Y. R. Lee, *Tetrahedron*. 2011, **67**, 9179-9184.

151 N. Tanaka, T. Kubota, H. Ishiyama, Y. Kashiwada, Y. Takaishi, J. Ito, Y. Mikami, M. Shiro and J. Kobayashi, *Heterocycles.*, 2009, **79**, 917-924.

152 A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry and T. K. Hemscheidt, *J. Org. Chem*. 2001, **66**, 8717-8721.

153 A. Numata, C. Takahashi, Y. Ito, T. Takada, K. Kawai, Y. Usami, E. Matsumura, M. Imachi, T. Ito and T. Hasegawa, *Tetrahedron Lett.*, 1993, **34**, 2355-2358.

154 J. A. May, R. K. Zeidan and B. M. Stoltz, *Tetrahedron Lett.*, 2003, **44**, 1203-1205.

155 A. S. Ratnayake, W. Y. Yoshida, S. L. Mooberry and T. K. Hemscheidt, *J. Org. Chem.*, 2003, **68**, 1640-1640.

156 K. Wojciechowski, *Eur. J. Org. Chem.*, 2001, **2001**, 3587-3605.

157 S. L. Crawley and R. L. Funk, *Org. Lett.*, 2003, **5**, 3169-3171.

158 J. L. G. Ruano, C. Pedregal and J. H. Rodriguez, *Tetrahedron.*, 1989, **45**, 203-214.

159 K. Nishiyama, H. Kubo, T. Sato, K. Higashiyama and S. Ohmiya, *Heterocycles.*, 1998, **6**, 1103-1106.

160 K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. Vassilikogiannakis, *Angew. Chem. Int. Ed.*, 2002, **41**, 1668-1698.

161 K. Natsuki, T. Shindo and M. Toyota, *Heterocycles.*, 2012, **84**, 1301-1304.

162 Z.-Z. Ma, Y. Hano, T. Nomura and Y.-J. Chen, *Heterocycles.*, 1997, 541-546.

163 T. R. Govindachari, K. R. Ravindranath and N. Viswanathan, *J. Chem. Soc., Perkin Trans. 1.*, 1974, 1215-1217.

164 T. Kametani, H. Takeda, H. Nemoto and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1.*, 1975, 1825-1828.

165 M. Toyota, C. Komori and M. Ihara, *J. Org. Chem.*, 2000, **65**, 7110-7113.

166 M. R. TePaske, J. B. Gloer, D. T. Wicklow and P. F. Dowd, *Tetrahedron Lett.*, 1991, **32**, 5687-5690.

167 B. B. Snider and Q. Lu, *J. Org. Chem.*, 1994, **59**, 8065-8070.

168 J. A. Findlay, J. Krepinsky, F. Y. Shum and W. H. J. Tam, *Can. J. Chem.*, 1976, **54**, 270-274.

169 B. B. Snider and Q. Lu, *J. Org. Chem.*, 1996, **61**, 2839-2844.

170 J. Liu, X.-F. He, G.-H. Wang, E. F. Merino, S.-P. Yang, R.-X. Zhu, L.-S. Gan, H. Zhang, M. B. Cassera and H.-Y. Wang, *J. Org. Chem.*, 2013, **79**, 599-607.

171 J.-P. Yin, M. Gu, Y. Li and F.-J. Nan, *J. Org. Chem.*, 2014, **79**, 6294-6301.

172 Z. J. Wu, X. K. Xu, Y. H. Shen, J. Su, J. M. Tian, S. Liang, H. L. Li, R. H. Liu and W. D. Zhang, *Org. Lett*., 2008, **10**, 2397-2400.

173 A. G. Doyle and E. N. Jacobsen, *Chem. Rev*., 2007, **107**, 5713-5743.

174 A. K. Unni, N. Takenaka, H. Yamamoto and V. H. Rawal, *J. Am. Chem. Soc*., 2005, **127**, 1336-1337.

175 A. N. Thadani, A. R. Stankovic and V. H. Rawal, *Proc. Natl. Acad. Sci. U.S.A*., 2004, **101**, 5846-5850.

176 Y. Huang, A. K. Unni, A. N. Thadani and V. H. Rawal, *Nature*., 2003, **424**, 146.

177 Y. Huang and V. H. Rawal, *J. Am. Chem. Soc*., 2002, **124**, 9662-9663.

178 C. Li, X. Yu and X. Lei, *Org. Lett.*, 2010, **12**, 4284-4287.

179 M. Volgraf, J. P. Lumb, H. C. Brastianos, G. Carr, M. K. Chung, M. Munzel, A. G. Mauk, R. J. Andersen and D. Trauner, *Nat. Chem. Biol*., 2008, **4**, 535-537.

180 W. L. Wang, T. J. Zhu, H. W. Tao, Z. Y. Lu, Y. C. Fang, Q. Q. Gu and W. M. Zhu, *Chem. Biodivers.*, 2007, **4**, 2913-2919.

181 K. C. Nicolaou, S. A. Snyder, T. Montagnon and G. E. Vassilikogiannakis, *Angew. Chem.*, 2002, **114**, 1742-1773.

182 W. E. Bauta, D. P. Lovett, W. R. Cantrell, Jr. and B. D. Burke, *J. Org. Chem*., 2003, **68**, 5967-5973.

183 S. Inoue, J. Murata, N. Takamatsu, H. Nagano and Y. Kishi, *Yakugaku zasshi*., 1977, **97**, 576-581.

184 C. A. Kuttruff, H. Zipse and D. Trauner, *Angew. Chem. Int. Ed.*, 2011, **50**, 1402-1405.

185 D. J. Hart and N. A. Magomedov, *J. Am. Chem. Soc.*, 2001, **123**, 5892-5899.

186 A. S. Kende, J. Fan and Z. Chen, *Org. Lett.*, 2003, **5**, 3205-3208.

187 Z. Chen, J. Fan and A. S. Kende, *J. Org. Chem.*, 2004, **69**, 79-85.

188 M. R. Ariza, T. O. Larsen, B. O. Petersen, J. Ø. Duus, C. Christophersen and A. F. Barrero, *J. Nat. Prod.*, 2001, **64**, 1590-1592.

189 D. J. Hart and G. Oba, *Tetrahedron Lett.*, 2007, **48**, 7069-7071.

190 T. Kuriyama, E. Kakemoto, N. Takahashi, K.-i. Imamura, K. Oyama, E. Suzuki, K. Harimaya, T. Yaguchi and Y. Ozoe, *J. Agric. Food. Chem.*, 2004, **52**, 3884-3887.

191 T. Watanabe, M. Arisawa, K. Narusuye, M. S. Alam, K. Yamamoto, M. Mitomi, Y. Ozoe and A. Nishida, *Bioorg. Med. Chem.*, 2009, **17**, 94-110.

192 Y. Shimizu, *Academic Press: New York*. **1978**, **I**, Chapter 1.

193 Y.-Y. Lin, M. Risk, S. M. Ray, D. Van Engen, J. Clardy, J. Golik, J. C. James and K. Nakanishi, *J. Am. Chem. Soc.*, 1981, **103**, 6773-6775.

194 M. S. Lee, D. J. Repeta, K. Nakanishi and M. G. Zagorski, *J. Am. Chem. Soc.*, 1986, **108**, 7855-7856.

195 A. J. Bourdelais, H. M. Jacocks, J. L. Wright, P. M. Bigwarfe, Jr. and D. G. Baden, *J. Nat. Prod.*, 2005, **68**, 2-6.

196 H. Fuwa, M. Ebine and M. Sasaki, *J. Am. Chem. Soc.*, 2006, **128**, 9648-9650.

197 M. Satake, A. J. Bourdelais, R. M. Van Wagoner, D. G. Baden and J. L. Wright, *Org. Lett.*, 2008, **10**, 3465-3468.

198 T. Kuranaga, T. Shirai, D. G. Baden, J. L. Wright, M. Satake and K. Tachibana, *Org. Lett.*, 2009, **11**, 217-220.

199 O. O. Fadeyi and C. W. Lindsley, *Org. Lett.*, 2009, **11**, 943-946.

200 A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem.*, 1999, **111**, 2549-2552.

201 P. Liu and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2001, **123**, 10772-10773.

202 J. F. Fournier, S. Mathieu and A. B. Charette, *J. Am. Chem. Soc.*, 2005, **127**, 13140-13141.

203 A. K. Ghosh and J. Li, *Org. Lett.*, 2009, **11**, 4164-4167.

204 A. Itoh, Y. Ikuta, Y. Baba, T. Tanahashi and N. Nagakura, *Phytochemistry*. 1999, **52**, 1169-1176.

205 O. Hesse, *Justus Liebigs Ann. Chem.*, 1914, **405**, 1-57.

206 M. T. Gonzalez-Garza, S. A. Matlin, B. D. Mata-Cardenas and S. Said-Fernandez, J. *Pharm. Pharmacol.*, 1993, **45**, 144-145.

207 Y. F. Liou, I. H. Hall and K. H. Lee, *J. Pharm. Sci.*, 1982, **71**, 745-749.

208 A. Itoh, Y. Ikuta, T. Tanahashi and N. Nagakura, *J. Nat. Prod.*, 2000, **63**, 723-725.

209 A. Ito, Y. H. Lee, H. B. Chai, M. P. Gupta, N. R. Farnsworth, G. A. Cordell, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 1999, **62**, 1346-1348.

210 I. Marin, J. P. Abad, D. Urena and R. Amils, *Biochemistry.*, 1995, **34**, 16519-16523.

211 G. T. Tan, J. M. Pezzuto, A. D. Kinghorn and S. H. Hughes, *J. Nat. Prod.*, 1991, **54**, 143-154.

212 L. F. Tietze, N. Rackelmann and I. Muller, *Chemistry.*, 2004, **10**, 2722-2731.

213 J. Azizian, A. A. Mohammadi, F. Ardakani, A. R. Karimi and M. R. Mohammadizadeh, *Heterocycles.*, 2004, **63**, 791-795.

214 D. Osborne and P. J. Stevenson, *Tetrahedron Lett.*, 2002, **43**, 5469-5470.

215 A. Cagir, S. H. Jones, B. M. Eisenhauer, R. Gao and S. M. Hecht, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2051-2054.

216 S. B. Mhaske and N. P. Argade, *J. Org. Chem.*, 2004, **69**, 4563-4566.

217 C. O. Usifoh and G. K. Scriba, *Arch Pharm.*, 2000, **333**, 261-266.

218 H. Twin and R. A. Batey, *Org. Lett.*, 2004, **6**, 4913-4916.

219 A. Plubrukarn and B. S. Davidson, *J. Org. Chem.*, 1998, **63**, 1657-1659.

220 E. Delfourne, C. Roubin and J. Bastide, *J. Org. Chem.*, 2000, **65**, 5476-5479.

221 Y. R. Torres, T. S. Bugni, R. G. S. Berlinck, C. M. Ireland, A. Magalhães, A. G. Ferreira and R. Moreira da Rocha, *J. Org. Chem.*, 2002, **67**, 5429-5432.

222 L. Legentil, J. Bastide and E. Delfourne, *Tetrahedron Lett.*, 2003, **44**, 2473-2475.

223 A. H. Gentry and K. Cook, *j. ethnopharmacol.*, 1984, **11**, 337-343.

224 K. M. Witherup, R. W. Ransom, A. C. Graham, A. M. Bernard, M. J. Salvatore, W. C. Lumma, P. S. Anderson, S. M. Pitzenberger and S. L. Varga, *J. Am. Chem. Soc.*, 1995, **117**, 6682-6685.

225 D. A. Powell and R. A. Batey, *Org. Lett.*, 2002, **4**, 2913-2916.

226 J. Beutler and A. Brubaker, *Drugs Future.*, 1987, **12**, 957-976.

227 S. Saito, K. Kotera, N. Shigematsu, A. Ide, N. Sugimoto, Z. Horii, M. Hanaoka, Y. Yamawaki and Y. Tamura, *Tetrahedron.*, 1963, **19**, 2085-2099.

228 J. Parello, *Bull. Soc. Chim. Fr.*, 1968, **3**, 1117-1129.

229 T. Lindsay, *J. Chem. Soc., Perkin Trans. 1.*, 1991, 1863-1869.

230 G. Han, M. G. LaPorte, J. J. Folmer, K. M. Werner and S. M. Weinreb, *J. Org. Chem.*, 2000, **65**, 6293-6306.

231 G. Laus, D. Brössner and K. Keplinger, *Phytochemistry.*, 1997, **45**, 855-860.

232 E. Winterfeldt, *Fortschr Chem Org Naturst.*, 1974, pp. 469-520.

233 M. Lounasmaa, J. Miettinen, P. Hanhinen and R. Jokela, *Tetrahedron Lett.*, 1997, **38**, 1455-1458.

234 E. Wenkert, Y. D. Vankar and J. S. Yadav, *J. Am. Chem. Soc.*, 1980, **102**, 7971-7972.

235 N. Aimi, E. Yamanaka, J. Endo, S. Sakai and J. Haginiwa, *Tetrahedron.*, 1973, **29**, 2015-2021.

236 L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304-322.

237 M. D'Ambrosio, A. Guerriero, C. Debitus, O. Ribes, J. Pusset, S. Leroy and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 1993, 1305-1306.

238 M. D'Ambrosio, A. Guerriero, F. Pietra, M. Ripamonti, C. Debitus and J. Waikedre, *Helv. Chim. Acta*. 1996, **79**, 727-735.

239 A. Guerriero, M. D'Ambrosio, G. Chiasera and F. Pietra, *Helv. Chim. Acta*. 1994, **77**, 1895-1902.

240 D. Stien, G. T. Anderson, C. E. Chase, Y.-h. Koh and S. M. Weinreb, *J. Am. Chem. Soc.*, 1999, **121**, 9574-9579.

241 J. W. Daly, *J. Nat. Prod.*, 1998, **61**, 162-172.

242 T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. Yeh, L. Pannell and J. W. Daly, *J. Am. Chem. Soc.*, 1992, **114**, 3475-3478.

243 S. R. Fletcher, R. Baker, M. S. Chambers, S. C. Hobbs and P. J. Mitchell, *J. Chem. Soc., Chem. Commun.*, 1993, 1216-1218.

244 S. R. Fletcher, R. Baker, M. S. Chambers, R. H. Herbert, S. C. Hobbs, S. R. Thomas, H. M. Verrier, A. P. Watt and R. G. Ball, *J. Org. Chem.*, 1994, **59**, 1771-1778.

245 Z. Chen and M. L. Trudell, *Chem. Rev.*, 1996, **96**, 1179-1194.

246 G. Pandey, T. D. Bagul and A. K. Sahoo, *J. Org. Chem.*, 1998, **63**, 760-768.

247 N. S. Sirisoma and C. R. Johnson, *Tetrahedron Lett.*, 1998, **39**, 2059-2062.

248 H. Kosugi and M. Kato, *Chem. Commun.*, 1997, 1857-1858.

249 B. M. Trost and G. R. Cook, *Tetrahedron Lett.*, 1996, **37**, 7485-7488.

250 A. Hernandez, M. Marcos and H. Rapoport, *J. Org. Chem.*, 1995, **60**, 2683-2691.

251 D. L. Clive and V. S. Yeh, *Tetrahedron Lett.*, 1998, **39**, 4789-4792.

252 S. Aoyagi, R. Tanaka, M. Naruse and C. Kibayashi, *J. Org. Chem.*, 1998, **63**, 8397-8406.

253 M. Yotsu-Yamashita, R. L. Haddock and T. Yasumoto, *J. Am. Chem. Soc.*, 1993, **115**, 1147-1148.

254 M. Yotsu-Yamashita, T. Yasumoto, S. Yamada, F. F. Bajarias, M. A. Formeloza, M. L. Romero and Y. Fukuyo, *Chem. Res. Toxicol.*, 2004, **17**, 1265-1271.

255 Y. Kasai, T. Ito and M. Sasaki, *Organic letters.*, 2012, **14**, 3186-3189.

256 J. D. White, P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge and D. J. Wardrop, *J. Am. Chem. Soc.*, 2001, **123**, 8593-8595.

257 P. R. Blakemore, C. C. Browder, J. Hong, C. M. Lincoln, P. A. Nagornyy, L. A. Robarge, D. J. Wardrop and J. D. White, *J. Org. Chem.*, 2005, **70**, 5449-5460.

258 K. C. Nicolaou, S. P. Seitz and D. P. Papahatjis, *J. Am. Chem. Soc.*, 1983, **105**, 2430-2434.

259 L. A. Paquette, L. Barriault and D. Pissarnitski, *J. Am. Chem. Soc.*, 1999, **121**, 4542-4543.

260 L. A. Paquette, L. Barriault, D. Pissarnitski and J. N. Johnston, *J. Am. Chem. Soc.*, 2000, **122**, 619-631.

261 Y. Kasai, T. Ito and M. Sasaki, *Org. Lett.*, 2012, **14**, 3186-3189.

262 N. M. Nasir, K. Ermanis and P. A. Clarke, *Org. Biomol. Chem.*, 2014, **12**, 3323-3335.

263 J. H. Frank and K. Kanamitsu, *J. Med. Entomol.*, 1987, **24**, 155-191.

264 S. A. Norton and C. Lyons, *Lancet.*, 2002, **359**, 1950.

265 F. Netolitzky, *Z. Angew. Entomol.*, 1919, **5**, 252-257.

266 C. Cardani, D. Ghiringhelli, R. Mondelli and A. Quilico, *Tetrahedron Lett.*, 1965, **6**, 2537-2545.

267 A. Furusaki, T. Watanabé, T. Matsumoto and M. Yanagiya, *Tetrahedron Lett.*, 1968, **9**, 6301-6304.

268 J. C. Jewett and V. H. Rawal, *Angew. Chem. Int. Ed.*, 2007, **46**, 6502-6504.

269 J. C. Jewett and V. H. Rawal, *Angew. Chem. Int. Ed. Engl.*, 2007, **46**, 6502-6504.

270 T. McMahon and J. Silke, *Harmful. Algae. News.*, 1996, **14**, 1998.

271 M. Satake, K. Ofuji, H. Naoki, K. J. James, A. Furey, T. McMahon, J. Silke and T. Yasumoto, *J. Am. Chem. Soc.*, 1998, **120**, 9967-9968.

272 A. Furey, C. Moroney, A. Brana-Magdalena, M. J. Saez, M. Lehane and K. J. James, *Environ. Sci. Technol.*, 2003, **37**, 3078-3084.

273 K. C. Nicolaou, W. Qian, F. Bernal, N. Uesaka, P. M. Pihko and J. Hinrichs, *Angew. Chem.*, 2001, **40**, 4068-4071.

274 R. G. Carter, T. C. Bourland, X.-T. Zhou and M. A. Gronemeyer, *Tetrahedron.*, 2003, **59**, 8963-8974.

275 C. J. Forsyth, J. Xu, S. T. Nguyen, I. A. Samdal, L. R. Briggs, T. Rundberget, M. Sandvik and C. O. Miles, *J. Am. Chem. Soc.*, 2006, **128**, 15114-15116.

276 X. Li, J. Li and D. R. Mootoo, *Org. Lett.*, 2007, **9**, 4303-4306.

277 D. A. Evans, L. Kvaerno, T. B. Dunn, A. Beauchemin, B. Raymer, J. A. Mulder, E. J. Olhava, M. Juhl, K. Kagechika and D. A. Favor, *J. Am. Chem. Soc.*, 2008, **130**, 16295-16309.

278 K. C. Nicolaou, D. Y. Chen, Y. Li, W. Qian, T. Ling, S. Vyskocil, T. V. Koftis, M. Govindasamy and N. Uesaka, *Angew. Chem.*, 2003, **42**, 3649-3653.

279 K. C. Nicolaou, D. Y. Chen, Y. Li, N. Uesaka, G. Petrovic, T. V. Koftis, F. Bernal, M. O. Frederick, M. Govindasamy, T. Ling, P. M. Pihko, W. Tang and S. Vyskocil, *J. Am. Chem. Soc.*, 2006, **128**, 2258-2267.

280 K. Takai, T. Kakiuchi, Y. Kataoka and K. Utimoto, *J. Org. Chem.*, 1994, **59**, 2668-2670.

281 S.-G. Ma, R.-M. Gao, Y.-H. Li, J.-D. Jiang, N.-B. Gong, L. Li, Y. Lü, W.-Z. Tang, Y.-B. Liu, J. Qu, H.-N. Lü, Y. Li and S.-S. Yu, *Org. Lett.*, 2013, **15**, 4450-4453.

282 S. Koser, H. M. R. Hoffmann and D. J. Williams, *J. Org. Chem.*, 1993, **58**, 6163-6165.

283 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115-136.

284 I. Kim, S. G. Kim, J. Choi and G. H. Lee, *Tetrahedron.*, 2008, **64**, 664-671.

285 Y. R. Lee and T. V. Hung, *Tetrahedron.*, 2008, **64**, 7338-7346.
286 L. Wei, M. Xiao and Z. Xie, *Org. Lett.*, 2014, **16**, 2784-2786.
287 Y. Sakai, T. Tsujita, T. Akiyama, T. Yoshida, T. Mizukami, S. Akinaga, S. Horinouchi, M. Yoshida and T. Yoshida, *J. Antibiot.*, 2002, **55**, 863-872.
288 A. K. Ghosh and G. B. Ren, *J. Org. Chem.*, 2012, **77**, 2559-2565.
289 A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *Angew. Chem.*, 1999, **38**, 2398-2400.
290 D. E. Chavez and E. N. Jacobsen, *Org. Synth.*, 2005, 34-42.
291 A. K. Ghosh, N. Ma, K. A. Effenberger and M. S. Jurica, *Org. Lett.*, 2014, **16**, 3154-3157.
292 S. G. Ma, R. M. Gao, Y. H. Li, J. D. Jiang, N. B. Gong, L. Li, Y. Lu, W. Z. Tang, Y. B. Liu, J. Qu, H. N. Lu, Y. Li and S. S. Yu, *Org. Lett.*, 2013, **15**, 4450-4453.
293 V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299-5358.
294 S. P. Roche and J. A. Porco, Jr., *Angew. Chem.*, 2011, **50**, 4068-4093.
295 L. F. Silva, Jr. and B. Olofsson, *Nat. Prod. Rep.*, 2011, **28**, 1722-1754.
296 H. Yao, L. Song and R. Tong, *J. Org. Chem.*, 2014, **79**, 1498-1504.
297 L. Song, H. Yao and R. Tong, *Org. Lett.*, 2014, **16**, 3740-3743.
298 D. Gouiffès, S. Moreau, N. Helbecque, J. L. Bernier, J. P. Hénichart, Y. Barbin, D. Laurent and J. F. Verbist, *Tetrahedron.*, 1988, **44**, 451-459.
299 B. M. Degnan, C. J. Hawkins, M. F. Lavin, E. J. McCaffrey, D. L. Parry and D. J. Watters, J. *Med. Chem.*, 1989, **32**, 1354-1359.
300 A. V. Statsuk, D. Liu and S. A. Kozmin, *J. Am. Chem. Soc.*, 2004, **126**, 9546-9547.
301 D. Riou, C. Roussakis, J. F. Biard and J. F. Verbist, *Anticancer. Res.*, 1993, **13**, 2331-2334.
302 A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem. Int. Ed.*, 2003, **42**, 5361-5364.
303 A. Fürstner, F. Feyen, H. Prinz and H. Waldmann, *Angew. Chem.*, 2003, **115**, 5519-5522.
304 X. Han and P. E. Floreancig, *Angew. Chem.*, 2014, **126**, 11255-11258.
305 A. E. Wright, J. C. Botelho, E. Guzmán, D. Harmody, P. Linley, P. J. McCarthy, T. P. Pitts, S. A. Pomponi and J. K. Reed, *J. Nat. Prod.*, 2007, **70**, 412-416.
306 W. Youngsaye, J. T. Lowe, F. Pohlki, P. Ralifo and J. S. Panek, *Angew. Chem.*, 2007, **119**, 9371-9374.
307 M. Valeria D'Auria, A. Zampella, L. G. Paloma, L. Minale, C. Debitus, C. Roussakis and V. Le Bert, *Tetrahedron.*, 1996, **52**, 9589-9596.
308 A. K. Ghosh, K. A. Shurrush and Z. L. Dawson, *Org. Biomol. Chem.*, 2013, **11**, 7768-7777.
309 R. Furuta, S. Naruto, A. Tamura and K. Yokogawa, *Tetrahedron Lett.*, 1979, **20**, 1701-1704.
310 K. Gademann, D. E. Chavez and E. N. Jacobsen, *Angew. Chem,*. 2002, **41**, 3059-3061.

311 M. Quitschalle, M. Christmann, U. Bhatt and M. Kalesse, *Tetrahedron Lett.*, 2001, **42**, 1263-1265.

312 D. Giguère, J. Martel, T. C. Shiao and R. Roy, *J. Org. Chem.*, 2011, **76**, 9687-9698.

313 S. J. Danishefsky, M. P. DeNinno and S. H. Chen, *J. Am. Chem. Soc.*, 1988, **110**, 3929-3940.

314 I. Robina, A. T. Carmona, A. J. Moreno-Vargas and E. Moreno-Clavijo, *Chimia. Int. J. Chem.*, 2011, **65**, 85-90.

315 D. A. Evans and J. S. Johnson, *J. Am. Chem. Soc.*, 1998, **120**, 4895-4896.

316 D. A. Evans, J. S. Johnson and E. J. Olhava, *J. Am. Chem. Soc.*, 2000, **122**, 1635-1649.

317 J. Thorhauge, M. Johannsen and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 1998, **37**, 2404-2406.

318 H. Audrain, J. Thorhauge, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, 2000, **65**, 4487-4497.

319 C. J. Henrich, E. I. Goncharova, J. A. Wilson, R. S. Gardella, T. R. Johnson, J. B. McMahon, K. Takada, H. R. Bokesch and K. R. Gustafson, *Chem Biol Drug Des.*, 2007, **69**, 321-330.

320 N. Oku, K. Takada, R. W. Fuller, J. A. Wilson, M. L. Peach, L. K. Pannell, J. B. McMahon and K. R. Gustafson, *J. Am. Chem. Soc.*, 2010, **132**, 10278-10285.

321 L. Bialy and H. Waldmann, *Chemistry.*, 2004, **10**, 2759-2780.

322 B. G. Lawhorn, S. B. Boga, S. E. Wolkenberg, D. A. Colby, C. M. Gauss, M. R. Swingle, L. Amable, R. E. Honkanen and D. L. Boger, J. *Am. Chem. Soc.*, 2006, **128**, 16720-16732.

323 Y. Watanabe, T. Nakamura and H. Mitsumoto, *Tetrahedron Lett.*, 1997, **38**, 7407-7410.

324 C. K. Skepper, T. Quach and T. F. Molinski, *J. Am. Chem. Soc.*, 2010, **132**, 10286-10292.

325 R. Fröde, C. Hinze, I. Josten, B. Schmidt, B. Steffan and W. Steglich, *Tetrahedron lett.*, 1994, **35**, 1689-1690.

326 T. Hashimoto, Y. Akiyo, K. Akazawa, S. Takaoka, M. Tori and Y. Asakawa, *Tetrahedron Lett.*, 1994, **35**, 2559-2560.

327 A. Fürstner, H. Krause and O. R. Thiel, *Tetrahedron.*, 2002, **58**, 6373-6380.

328 C. Hinze, A. Kreipl, A. Terpin and W. Steglich, *Synthesis.*, 2007, **2007**, 608-612.

329 L. Fu and G. W. Gribble, *Tetrahedron Lett.*, 2010, **51**, 537-539.

330 D. L. Boger, *Tetrahedron.*, 1983, **39**, 2869-2939.

331 D. L. Boger, *Chem. Rev*. 1986, **86**, 781-793.

332 D. K. Heldmann and J. Sauer, *Tetrahedron Lett.*, 1997, **38**, 5791-5794.

333 J. Sauer, D. K. Heldmann, J. Hetzenegger, J. Krauthan, H. Sichert and J. Schuster, *Eur. J. Org. Chem.*, 1998, **1998**, 2885-2896.

334 T. Sakamoto, N. Funami, Y. Kondo and H. Yamanaka, *Heterocycles.*, 1991, **32**, 1387-1390.

335 J. S. Oakdale and D. L. Boger, *Org. Lett.*, 2010, **12**, 1132-1134.

336 Y. Hayakawa, K.-y. Sohda, K. Shin-Ya, T. Hidaka and H. Seto, *J. Antibiot.*, 1995, **48**, 954-961.

337 M. T. Crimmins and B. W. King, *J. Am. Chem. Soc.*, 1998, **120**, 9084-9085.

338 M. J. Plater, S. Aiken and G. Bourhill, *Tetrahedron.*, 2002, **58**, 2415-2422.

339 E. R. Jarvo, B. M. Lawrence and E. N. Jacobsen, *Angew. Chem. Int. Ed.*, 2005, **44**, 6043-6046.

340 T. K. Chakraborty, R. K. Goswami and M. Sreekanth, *Tetrahedron Lett.*, 2007, **48**, 4075-4078.

341 S. Bonazzi, O. Eidam, S. G ttinger, J.-Y. Wach, I. Zemp, U. Kutay and K. Gademann, *J. Am. Chem. Soc.*, 2010, **132**, 1432-1442.

342 I. De Albuquerque, C. Galeffi, C. Casinovi and G. Marini-Bettolo, *Gazz. Chim. Ital.*, 1964, **94**, 287-295.

343 C. Galeffi, C. Giulio Casinovi and G. Marini-Bettolo, *Gazz. Chim. Ital.*, 1965, **95**, 95-100.

344 A. A. Craveiro, A. da Costa Prado, O. Gottlieb and P. W. de Albuquerque, *Phytochemistry*. 1970, **9**, 1869-1875.

345 A. d. C. Alcantara, M. Souza and D. Piló-Veloso, *Fitoterapia.*, 2000, **71**, 613-615.

346 L. Jurd and R. Wong, *Aust. J. Chem.*, 1984, **37**, 1127-1133.

347 F. Colobert, R. D. Mazery, G. Solladié and M. C. Carreno, *Org. Lett.*, 2002, **4**, 1723-1725.

348 M. C. Carreño, R. Des Mazery, A. Urbano, F. Colobert and G. Solladié, *J. Org. Chem.*, 2003, **68**, 7779-7787.

349 P. A. Clarke and W. H. Martin, *Tetrahedron Lett.*, 2004, **45**, 9061-9063.

350 P. A. Clarke and W. H. Martin, *Tetrahedron.*, 2005, **61**, 5433-5438.

351 M. Pham, A. Allatabakhsh and T. G. Minehan, *J. Org. Chem.*, 2008, **73**, 741-744.

352 T. Takeuchi, M. Matsuhashi and T. Nakata, *Tetrahedron Lett.*, 2008, **49**, 6462-6465.

353 P. A. Evans, J. Cui and S. J. Gharpure, *Org. Lett.*, 2003, **5**, 3883-3885.

354 S. Marumoto, J. J. Jaber, J. P. Vitale and S. D. Rychnovsky, *Org. Lett.*, 2002, **4**, 3919-3922.

355 M. Dziedzic and B. Furman, *Tetrahedron Lett.*, 2008, **49**, 678-681.

356 W. Chaładaj, P. Kwiatkowski and J. Jurczak, *Tetrahedron Lett.*, 2008, **49**, 6810-6811.

357 C. F. Nutaitis and J. E. Bernardo, *Synth. Commun.*, 1990, **20**, 487-493.

358 W. Chaładaj, R. Kowalczyk and J. Jurczak, *J. Org. Chem.*, 2010, **75**, 1740-1743.

359 K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi and T. Kusumi, *Org. Lett.*, 2008, **10**, 225-228.

360 T. Nagasawa and S. Kuwahara, *Org. Lett.*, 2009, **11**, 761-764.

361 K. E. Maloneyhuss, *Synth. Commun.*, 1985, **15**, 273-277.

362 S. Baker, *J. Am. Chem. Soc.*, 1952, **74**, 827-828.

363 S. Danishefsky, *Org. Syn.* 1990, **7**, 312-315.

364 S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, 1974, **96**, 7807-7808.

365 K. Ohmori, *Bull. Chem. Soc. Jpn.*, 2004, **77**, 875-885.

366 R. C. Larock and T. R. Hightower, *J. Org. Chem.*, 1993, **58**, 5298-5300.

367 J. D. Panarese and S. P. Waters, *Org. Lett.*, 2009, **11**, 5086-5088.

368 J. H. Butterworth and E. Morgan, *Chem. Commun. (London)*., 1968, 23-24.

369 A. Jennifer Mordue Luntz, M. S. Simmonds, S. V. Ley, W. M. Blaney, W. Mordue, M. Nasiruddin and A. J. Nisbet, *Pestic. Sci.*, 1998, **54**, 277-284.

370 A. J. Mordue and A. Blackwell, *J. Insect Physiol.*, 1993, **39**, 903-924.

371 G. E. Veitch, A. Boyer and S. V. Ley, *Angew. Chem. Int. Ed.*, 2008, **47**, 9402-9429.

372 G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, C. Ayats and S. V. Ley, *Angew. Chem.*, 2007, **119**, 7777-7779.

373 G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen and S. V. Ley, *Angew. Chem. Int. Ed.*, 2007, **46**, 7629-7632.

374 G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, C. Ayats and S. V. Ley, *Angew. Chem. Int. Ed.*, 2007, **46**, 7633-7635.

375 G. E. Veitch, A. Pinto, A. Boyer, E. Beckmann, J. C. Anderson and S. V. Ley, *Org. Lett.*, 2008, **10**, 569-572.

376 H. Watanabe, T. Watanabe, K. Mori and T. Kitahara, *Tetrahedron Lett.*, 1997, **38**, 4429-4432.

377 T. Fukuzaki, S. Kobayashi, T. Hibi, Y. Ikuma, J. Ishihara, N. Kanoh and A. Murai, *Org. Lett.*, 2002, **4**, 2877-2880.

378 H. Watanabe, N. Mori, D. Itoh, T. Kitahara and K. Mori, *Angew. Chem. Int. Ed.*, 2007, **46**, 1512-1516.

379 S. V. Ley, A. Abad-Somovilla, J. C. Anderson, C. Ayats, R. Bänteli, E. Beckmann, A. Boyer and e. al, *Chem. -Eur. J.*, 2008, **14**, 10683-10704.

380 C. F. Morrison and D. J. Burnell, *Tetrahedron Lett.*, 2001, **42**, 7367-7369.

381 S. Kii, T. Hashimoto and K. Maruoka, *Synlett.*, 2002, **2002**, 0931-0932.

382 M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro and S. Hashimoto, *Angew. Chem.*, 2004, **116**, 2719-2722.

383 M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro and S. Hashimoto, *Angew. Chem. Int. Ed.*, 2004, **43**, 2665-2668.

384 T. Washio, R. Yamaguchi, T. Abe, H. Nambu, M. Anada and S. Hashimoto, *Tetrahedron.*, 2007, **63**, 12037-12046.

385 A. Boyer, G. E. Veitch, E. Beckmann and S. V. Ley, *Angew. Chem. Int. Ed.*, 2009, **48**, 1317-1320.

386 X. Tian, J. J. Jaber and S. D. Rychnovsky, *J. Org. Chem.* 2006, **71**, 3176-3183.

387 H. M. Ko, D. G. Lee, M. A. Kim, H. J. Kim, J. Park, M. S. Lah and E. Lee, *Org. Lett*. 2007, **9**, 141-144.

388 I. Paterson and N. A. Miller, *Chem. Commun. (Camb.)*., 2008, 4708-4710.

389 W. B. Jennings, B. M. Farrell and J. F. Malone, *J. Org. Chem.*, 2006, **71**, 2277-2282.

390 J. Yin, K. Kouda, Y. Tezuka, Q. Le Tran, T. Miyahara, Y. Chen and S. Kadota, *Planta Med*. 2004, **70**, 54-58.

391 G. Sabitha, P. Padmaja and J. S. Yadav, *Helv. Chim. Acta.*, 2008, **91**, 2235-2239.

392 S. Chandrasekhar, T. Shyamsunder, S. J. Prakash, A. Prabhakar and B. Jagadeesh, *Tetrahedron Lett.*, 2006, **47**, 47-49.

393 H. Wang, B. J. Shuhler and M. Xian, *Synlett.*, 2008, **2008**, 2651-2654.

394 I. Muhammad, X.-C. Li, M. R. Jacob, B. L. Tekwani, D. C. Dunbar and D. Ferreira, *J. Nat. Prod.*, 2003, **66**, 804-809.

395 I. Muhammad, X. C. Li, D. C. Dunbar, M. A. ElSohly and I. A. Khan, , *J. Nat. Prod.*, 2001, **64**, 1322-1325.

396 A. G. Chittiboyina, C. R. Reddy, E. B. Watkins and M. A. Avery, *Tetrahedron Lett.*, 2004, **45**, 1689-1691.

397 H. J. Lee, Y. R. Lee and S. H. Kim, *Helv. Chim. Acta.*, 2009, **92**, 1404-1412.

398 O. Miyata, N. Takeda and T. Naito, *Organic letters.*, 2004, **6**, 1761-1763.

399 N. Takeda, O. Miyata and T. Naito, *Eur. J. Org. Chem.*, 2007, **2007**, 1491-1509.

400 N. H. G. R. I. Geran , M. M. Mac Donald , A. M. Schumacher , B. J. Abbott, *Cancer Chemother. Rep.*, **1972 3**, 1 –103.

401 L. Zeng, Q. Ye, N. H. Oberlies, G. Shi, Z.-M. Gu, K. He and J. L. McLaughlin, *Nat. Prod. Rep.*, 1996, **13**, 275-306.

402 X.-p. Fang, J. E. Anderson, X.-x. Qiu, J. F. Kozlowski, C.-j. Chang and J. L. McLaughlin, *Tetrahedron.*, 1993, **49**, 1563-1570.

403 C. Mukai, H. Yamashita, S. Hirai, M. Hanaoka and J. L. McLaughlin, *Chem. Pharm. Bull. (Tokyo).*, 1999, **47**, 131-132.

404 A. A. E. El-Zayat, N. R. Ferrigni, T. G. McCloud, A. T. McKenzie, S. R. Byrn, J. M. Cassady, C.-j. Chang and J. L. McLaughlin, *Tetrahedron Lett.*, 1985, **26**, 955-956.

405 A. Alkofahi, W.-W. Ma, A. McKenzie, S. Byrn and J. McLaughlin, *J. Nat. Prod.*, 1989, **52**, 1371-1373.

406 Z. Tian, S. Chen, Y. Zhang, M. Huang, L. Shi, F. Huang, C. Fong, M. Yang and P. Xiao, *Phytomedicine.*, 2006, **13**, 181-186.

407 P. Tuchinda, B. Munyoo, M. Pohmakotr, P. Thinapong, S. Sophasan, T. Santisuk and V. Reutrakul, *J. Nat. Prod.*, 2006, **69**, 1728-1733.

408 S. Talapatra, D. Basu, T. Deb, S. Goswami and B. Talapatra, *Indian. J. Chem. B*., 1985, **24**, 29.

409 X.-p. Fang, J. E. Anderson, C.-j. Chang and J. L. McLaughlin, *Tetrahedron.*, 1991, **47**, 9751-9758.

410 J. Loder and R. Nearn, *Heterocycles.*, 1977, **7**, 113-118.

411 M. Deligny, F. Carreaux and B. Carboni, *Synlett.*, 2005, 1462-1464.

412 F. Carreaux, A. Favre, B. Carboni, I. Rouaud and J. Boustie, *Tetrahedron Lett.*, 2006, **47**, 4545-4548.

413 A. Favre, F. Carreaux, M. Deligny and B. Carboni, *Eur. J. Org. Chem.*, 2008, **2008**, 4900-4907.

414 S.-T. Lu, Y.-C. Wu and S.-P. Leou, *Phytochemistry.*, 1985, **24**, 1829-1834.

415 M. A. Blazquez, A. Bermejo, M. C. Zafra-Polo and D. Cortes, *Phytochem. Anal.*, 1999, **10**, 161-170.

416 X.-p. Fang, J. E. Anderson, D. L. Smith, J. L. McLaughlin and K. V. Wood, *J. Nat. Prod.*, 1992, **55**, 1655-1663.

417 Y.-H. Lan, F.-R. Chang, J.-H. Yu, Y.-L. Yang, Y.-L. Chang, S.-J. Lee and Y.-C. Wu, *J. Nat. Prod.*, 2003, **66**, 487-490.

418 D. A. Digoniodiol, *Planta Med.*, 2005, **71**, 153-159.

419 K. Gademann, D. E. Chavez and E. N. Jacobsen, *Angew. Chem.*, 2002, **114**, 3185-3187.

420 M. Deligny, F. Carreaux, L. Toupet and B. Carboni, *Adv. Synth. Catal.*, 2003, **345**, 1215-1219.

421 P. A. Horton, F. E. Koehn, R. E. Longley and O. J. McConnell, *J. Am. Chem. Soc.*, 1994, **116**, 6015-6016.

422 A. K. Ghosh and G. Gong, *Organic letters.*, 2007, **9**, 1437-1440.

423 A. K. Ghosh and G. Gong, *Chem.-Asian. J.*, 2008, **3**, 1811-1823.

424 C. R. Harris and S. J. Danishefsky, *J. Org. Chem.*, 1999, **64**, 8434-8456.

425 E. Lee, H. Y. Song, J. W. Kang, D.-S. Kim, C.-K. Jung and J. M. Joo, *J. Am. Chem. Soc.*, 2002, **124**, 384-385.

426 S. H. Kang, S. Y. Kang, H.-w. Choi, C. M. Kim, H.-S. Jun and J.-H. Youn, *Synthesis.*, 2004, 1102-1114.

427 T. Yoshimura, F. Yakushiji, S. Kondo, X. Wu, M. Shindo and K. Shishido, *Org. Lett.*, 2006, **8**, 475-478.

428 K. B. Sawant, F. Ding and M. P. Jennings, *Tetrahedron Lett.*, 2006, **47**, 939-942.

429 J. C. Medina, M. Salomon and K. S. Kyler, *Tetrahedron Lett.*, 1988, **29**, 3773-3776.

430 M. T. Mujica, M. M. Afonso, A. Galindo and J. A. Palenzuela, *Tetrahedron.*, 1996, **52**, 2167-2176.

431 I. Paterson and E. A. Anderson, *Science.*, 2005, **310**, 451.

432 A. K. Ghosh and G. Gong, *Org. Lett.*, 2007, **9**, 1437-1440.

433 K.-S. Yeung and I. Paterson, *Chem. Rev.*, 2005, **105**, 4237-4313.

434 R. Noyori, *Angew. Chem.*, 2002, **114**, 2108-2123.

435 D. W. Custar, T. P. Zabawa and K. A. Scheidt, *J. Am. Chem. Soc.*, 2008, **130**, 804-805.

436 H. Fuwa, S. Naito, T. Goto and M. Sasaki, *Angew. Chem. Int. Ed.*, 2008, **47**, 4737-4739.

437 V. V. Vintonyak and M. E. Maier, *Org. Lett.*, 2008, **10**, 1239-1242.

438 I. Paterson and M. Tudge, *Tetrahedron.*, 2003, **59**, 6833-6849.

439 A. G. Dossetter, T. F. Jamison and E. N. Jacobsen, *catalyst.*, 1999, **1**, 2.

440 O. A. Ulanovskaya, J. Janjic, M. Suzuki, S. S. Sabharwal, P. T. Schumacker, S. J. Kron and S. A. Kozmin, *Nat. Chem. Biol.*, 2008, **4**, 418-424.

441 I. Paterson and N. A. Miller, *Chem. Commun.*, 2008, 4708-4710.

442 U. Gräfe, W. Schade, M. Roth, L. Radics, M. Incze and K. Ujszaszy, *J. Antibiot.*, 1984, **37**, 836-846.

443 H. A. Brooks, D. Gardner, J. P. Poyser And T. J. King, *J. Antibiot.*, 1984, **37**, 1501-1504.

444 E. Tonew, M. Tonew, U. Graefe and P. Zopel, *Pharmazie.*, 1988, **43**, 717-719.

445 K. Komatsu, K. Tanino and M. Miyashita, *Angew. Chem. Int. Ed. Engl.*, 2004, **43**, 4341-4345.

446 L.-L. Wei, R. P. Hsung, H. Xiong, J. A. Mulder and N. T. Nkansah, *Org. Lett.*, 1999, **1**, 2145-2148.

447 L. L. Wei, H. Xiong and R. P. Hsung, *Acc. Chem. Res.*, 2003, **36**, 773-782.

448 J. E. Antoline, R. P. Hsung, J. Huang, Z. Song and G. Li, *Org. Lett.*, 2007, **9**, 1275-1278.

449 L. Shen, R. P. Hsung, Y. Zhang, J. E. Antoline and X. Zhang, *Org. Lett.*, 2005, **7**, 3081-3084.

450 J. Huang and R. P. Hsung, *J. Am. Chem. Soc*. 2005, **127**, 50-51.

451 F. Gohier, K. Bouhadjera, D. Faye, C. Gaulon, V. Maisonneuve, G. Dujardin and R. Dhal, *Org. Lett.*, 2007, **9**, 211-214.

452 A. Palasz, *Org. Biomol. Chem.*, 2005, **3**, 3207-3212.

453 Z. Song, R. P. Hsung, T. Lu and A. G. Lohse, *J. Org. Chem.*, 2007, **72**, 9722-9731.

454 C. Araujo, L. Alegrio and L. Leon, *Phytochemistry.*, 1998, **49**, 751-754.

455 M. S. Ali, A. H. Banskota, Y. Tezuka, I. Saiki and S. Kadota, *Biol. Pharm. Bull.*, 2001, **24**, 525-528.

456 J. Yin, K. Kouda, Y. Tezuka, Q. Le Tran, T. Miyahara, Y. Chen and S. Kadota, *Planta Med.*, 2004, **70**, 54-58.

457 S. P. Cakir and K. T. Mead, *Tetrahedron Lett.*, 2006, **47**, 2451-2454.

458 N. Kawai, S. M. Hande and J. i. Uenishi, *Tetrahedron.*, 2007, **63**, 9049-9056.

459 P. A. Clarke and S. Santos, *Eur. J. Org. Chem.*, 2006, **2006**, 2045-2053.

460 M. C. Carreno, R. Des Mazery, A. Urbano, F. Colobert and G. Solladié, *J. Org. Chem.*, 2003, **68**, 7779-7787.

461 G. Sabitha, K. Bhaskar Reddy, G. Kiran Kumar Reddy, N. Fatima and J. Yadav, *Synlett.*, 2005, **2005**, 2347-2351.

462 K. R. Prasad and P. Anbarasan, *Tetrahedron.*, 2007, **63**, 1089-1092.

463 M. A. Sanz, T. Voigt and H. Waldmann, *Adv. Synth. Catal.*, 2006, **348**, 1511-1515.

464 M. Anada, T. Washio, N. Shimada, S. Kitagaki, M. Nakajima, M. Shiro and S. Hashimoto, *Angew. Chem.*, 2004, **116**, 2719-2722.

465 M. Valenzuela, M. P. Doyle, C. Hedberg, H. WENHAO and A. Holmstrom, *Synlett.*, 2004, 2425-2428.

466 H.-J. Knölker, B. Ahrens, P. Gonser, M. Heininger and P. G. Jones, *Tetrahedron.*, 2000, **56**, 2259-2271.

467 N. Takeuchi, T. Nakano, K. Goto and S. Tobinaga, *Heterocycles.*, 1993, **35**, 289-297.

468 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467-4470.

469 B. Figadere, A. W. Norman, H. L. Henry, H. P. Koeffler, J.-Y. Zhou and W. Okamura, *J. Med. Chem.*, 1991, **34**, 2452-2463.

470 T.-S. Lee, J. Kim and J.-Y. Bae, *Polymer.*, 2004, **45**, 5065-5076.

471 A. Cutignano, I. Bruno, G. Bifulco, A. Casapullo, C. Debitus, L. Gomez-Paloma and R. Riccio, *Eur. J. Org. Chem.*, 2001, **2001**, 775-778.

472 A. B. Smith and I. G. Safonov, *Org. Lett.*, 2002, **4**, 635-637.

473 C. C. Sanchez and G. E. Keck, *Org. Lett.*, 2005, **7**, 3053-3056.

474 T. R. Hoye and M. Hu, *J. Am. Chem. Soc.*, 2003, **125**, 9576-9577.

475 F. Ding and M. P. Jennings, *Org. Lett.*, 2005, **7**, 2321-2324.

476 D. L. Aubele, S. Wan and P. E. Floreancig, *Angew. Chem.*, 2005, **117**, 3551-3554.

477 I. Louis, N. L. Hungerford, E. J. Humphries and M. D. McLeod, *Org. Lett.*, 2006, **8**, 1117-1120.

478 K. Shimanaka, Y. Takahashi, H. Iinuma, H. Naganawa And T. Takeuchi, *J. Antibiot.*, 1994, **47**, 1145-1152.

479 K. Shimanaka, Y. Takahashi, H. Iinuma, H. Naganawa and T. Takeuchi, *J. Antibiot.*, 1994, **47**, 1153-1159.

480 M. C. Bagley, J. W. Dale, E. A. Merritt and X. Xiong, *Chem. Rev.*, 2005, **105**, 685-714.

481 R. A. Hughes, S. P. Thompson, L. Alcaraz and C. J. Moody, *Chem. Commun.*, 2004, 946-948.

482 M. J. Burk, G. Casy and N. B. Johnson, *J. Org. Chem.*, 1998, **63**, 6084-6085.

483 R. A. Hughes, S. P. Thompson, L. Alcaraz and C. J. Moody, *J. Am. Chem. Soc.*, 2005, **127**, 15644-15651.

484 H. Koshino, H. Takahashi, H. Osada And K. Isono, *J. Antibiot.*, 1992, **45**, 1420-1427.

485 H. Osada, H. Koshino, K. Isono, H. Takahashi And G. Kawanishi, *J. Antibiot.*, 1991, **44**, 259-261.

486 T. Shimizu, T. Masuda, K. Hiramoto and T. Nakata, *Org. Lett.*, 2000, **2**, 2153-2156.

487 T. Shimizu, R. Kobayashi, K. Osako, H. Osada and T.-i. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6755-6758.

488 K. E. Drouet, T. Ling, H. V. Tran and E. A. Theodorakis, *Org. Lett.*, 2000, **2**, 207-210.

489 M. El Sous and M. A. Rizzacasa, *Tetrahedron Lett.*, 2000, **41**, 8591-8594.

490 M. El Sous, D. Ganame, P. A. Tregloan and M. A. Rizzacasa, *Org. Lett.*, 2004, **6**, 3001-3004.

491 F. Perron and K. F. Albizati, *Chem. Rev.*, 1989, **89**, 1617-1661.

492 H. Osada, H. Koshino, K. Isono, H. Takahashi and G. Kawanishi, *J Antibiot (Tokyo).*, 1991, **44**, 259-261.

493 H. Takahashi, H. Osada, H. Koshino, T. Kudo, S. Amano, S. Shimizu, M. Yoshihama and K. Isono, *J. Antibiotics.*, 1992, **45**, 1409-1413.

494 H. Koshino, H. Takahashi, H. Osada and K. Isono, *J Antibiot (Tokyo).*, 1992, **45**, 1420-1427.

495 A. N. Cuzzupe, C. A. Hutton, M. J. Lilly, R. K. Mann, K. J. McRae, S. C. Zammit and M. A. Rizzacasa, *J. Org. Chem.*, 2001, **66**, 2382-2393.

496 M. D'Ambrosio, A. Guerriero, F. Pietra and C. Debitus, *Helv. Chim. Acta.*, 1996, **79**, 51-60.

497 K. R. Hornberger, C. L. Hamblett and J. L. Leighton, *J. Am. Chem. Soc.*, 2000, **122**, 12894-12895.

498 Y. Wang, J. Janjic and S. A. Kozmin, *J. Am. Chem. Soc.*, 2002, **124**, 13670-13671.

499 P. Wipf and J. T. Reeves, *Chem. Commun.*, 2002, 2066-2067.

500 S. A. Kozmin, *Org. Lett.*, 2001, **3**, 755-758.

501 P. A. Searle and T. F. Molinski, *J. Am. Chem. Soc.*, 1995, **117**, 8126-8131.

502 P. A. Searle, T. F. Molinski, L. J. Brzezinski and J. W. Leahy, *J. Am. Chem. Soc.*, 1996, **118**, 9422-9423.

503 F. Ahmed and C. J. Forsyth, *Tetrahedron Lett.*, 1998, **39**, 183-186.

504 D. A. Evans, D. M. Fitch, T. E. Smith and V. J. Cee, *J. Am. Chem. Soc.*, 2000, **122**, 10033-10046.

505 A. B. Smith, K. P. Minbiole, P. R. Verhoest and M. Schelhaas, *J. Am. Chem. Soc.*, 2001, **123**, 10942-10953.

506 A. B. Smith, K. P. Minbiole, P. R. Verhoest and T. J. Beauchamp, *Org. Lett.*, 1999, **1**, 913-916.

507 H. Huang and J. S. Panek, *Org. Lett.*, 2001, **3**, 1693-1696.

508 J. V. Schaus and J. S. Panek, *Org. Lett.*, 2000, **2**, 469-471.

509 I. Paterson and E. A. Arnott, *Tetrahedron Lett.*, 1998, **39**, 7185-7188.

510 I. Paterson and C. A. Luckhurst, *Tetrahedron Lett.*, 2003, **44**, 3749-3754.

511 G. Shi, Z.-m. Gu, K. He, K. V. Wood, L. Zeng, Q. Ye, J. M. MacDougal and J. L. McLaughlin, *Bioorg. Med. Chem.*, 1996, **4**, 1281-1286.

512 D. J. Dixon, S. V. Ley and D. J. Reynolds, *Chem.-Eur. J.*, 2002, **8**, 1621-1636.

513 B. M. Trost and T. J. J. Muller, *J. Am. Chem. Soc.*, 1994, **116**, 4985-4986.

514 M. T. Crimmins and R. O'Mahony, *J. Org. Chem.*, 1989, **54**, 1157-1161.

515 D. G. Lynn, N. J. Phillips, W. C. Hutton, J. Shabanowitz, D. Fennell and R. Cole, *J. Am. Chem. Soc.*, 1982, **104**, 7319-7322.

516 C. T. Gnewuch and G. Sosnovsky, *Chem. Rev*., 1997, **97**, 829-1014.

517 H. Hamacher, *Arzneim.-Forsch*., 1979, **29**, 463-466.

518 G. Guanti, L. Banfi, E. Narisano and M. T. Zannetti, *J. Org. Chem.*, 1993, **58**, 1508-1514.

519 L. Tietze and G. Kettschau, in *Top Curr Chem*, ed. P. Metz, Springer Berlin Heidelberg, 1997, vol. 189, ch. 1, pp. 1-120.

520 J. D. White, N.-S. Kim, D. E. Hill and J. A. Thomas, *Synthesis.*, 1998, 619-626.

521 L. F. Tietze and C. Schneider, *J. Org. Chem.*, 1991, **56**, 2476-2481.

522 M. Bartz, J. Küther, R. Seshadri and W. Tremel, *Angew. Chem. Int. Ed.*, 1998, **37**, 2466-2468.

523 L. F. Tietze, G. Schneider, J. Wölfling, A. Fecher, T. Nöbel, S. Petersen, I. Schuberth and C. Wulff, *Chem.-Eur. J.*, 2000, **6**, 3755-3760.

524 Z. F. Mahmoud, T. M. Sarg, M. E. Amer and S. M. Khafagy, *Pharmazie*., 1983, **38**, 486-487.

525 M. M. Kady, L. Brimer, P. Furu, E. Lemmich, H. M. Nielsen, S. T. Thiilborg, O. Thastrup and S. B. Christensen, *Planta Med*., 1992, **58**, 334-337.

526 F. Bohlmann and C. Zdero, *Phytochemistry*., 1977, **16**, 1092-1095.

527 F. Bohlmann and C. Zdero, *Phytochemistry*., 1982, **21**, 2263-2267.

528 E. L. I. Kiøller Larsen , S. T. Thilborg , H. M. Nielsen , M. Fatima , M. Piedade , M. M. Kady , S. Brøgger Christensen , *Acta Chem. Scand.*, **1992** 750-756.

529 G. Appendino, G. Cravotto, A. Minassi and G. Palmisano, *Eur. J. Org. Chem.*, 2001, **2001**, 3711-3717.

530 J. R. Rocca, J. H. Tumlinson, B. M. Glancey and C. S. Lofgren, *Tetrahedron Lett.*, 1983, **24**, 1889-1892.

531 T. Sakan, S. Isoe and S. B. Hyeon, *Tetrahedron Lett.*, 1967, **8**, 1623-1627.

532 G. V. Subbaraju, M. S. Manhas and A. K. Bose, *Tetrahedron Lett.*, 1991, **32**, 4871-4874.

533 K. Mori and V. Khlebnikov, *Liebigs Ann. Chem.*, 1993, **1993**, 77-82.

534 L. Strekowski, M. Visnick and M. A. Battiste, *J. Org. Chem.*, 1986, **51**, 4836-4839.

535 J. Bricout, R. Viani, F. Müggler-Chavan, J. P. Marion, D. Rwymond and R. H. Egli, *Helv. Chim. Acta.*, 1967, **50**, 1517-1522.

536 M. Johannsen and K. A. Joergensen, *J. Org. Chem.*, 1995, **60**, 5757-5762.

537 M. Johannsen and K. A. Jørgensen, *Tetrahedron.*, 1996, **52**, 7321-7328.

538 S. Yao, M. Johannsen and K. A. Jørgensen, *J. Chem. Soc., Perkin Trans. 1.*, 1997, 2345-2350.

539 S. Yao, M. Johannsen, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 1998, **63**, 118-121.

540 S. O¯mura, A. Nakagawa, H. Aoyama, K. Hinotozawa and H. Sano, *Tetrahedron Lett.*, 1983, **24**, 3643-3646.

541 M. Murata, T. Miyasaka, H. Tanaka And S. Omura, *J. Antibiot.*, 1985, **38**, 1025-1033.

542 T. R. Kelly, J. A. Field and Q. Li, *Tetrahedron Lett.*, 1988, **29**, 3545-3546.

543 B. Serckx-Poncin, A.-M. Hesbain-Frisque and L. Ghosez, *Tetrahedron Lett.*, 1982, **23**, 3261-3264.

544 S. Satsumabayashi, K. Nakajo, R. Soneda and S. Motoki, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 1586-1588.

545 P. Nebois, R. Barret and H. Fillion, *Tetrahedron Lett.*, 1990, **31**, 2569-2572.

546 J. Pérez, C. Avendaño and J. C. Menéndez, *Tetrahedron Lett.*, 1997, **38**, 4717-4720.

547 J. Pérez, P. López-Alvarado, C. Avendaño and J. C. Menéndez, *Tetrahedron Lett.*, 1998, **39**, 673-676.

548 A. Goldmann, B. Message, D. Tepfer, R. J. Molyneux, O. Duclos, F.-D. Boyer, Y. Pan and A. D. Elbein, *J. Nat. Prod.*, 1996, **59**, 1137-1142.

549 J. Streith and A. Defoin, *Synthesis.*, 1994, **1994**, 1107-1117.

550 F.-D. Boyer and J.-Y. Lallemand, *Tetrahedron.*, 1994, **50**, 10443-10458.

551 T. Faitg, J. Soulié, J.-Y. Lallemand and L. Ricard, *Tetrahedron: Asymmetry.*, 1999, **10**, 2165-2174.

552 J. Soulié, T. Faitg, J.-F. Betzer and J.-Y. Lallemand, *Tetrahedron.*, 1996, **52**, 15137-15146.

553 M. E. Ferreira, H. Nakayama, A. R. de Arias, A. Schinini, N. V. de Bilbao, E. Serna, D. Lagoutte, F. Soriano-Agatón, E. Poupon and R. Hocquemiller, *J. Ethnopharmacol.*, 2007, **109**, 258-263.

554 J.-H. Li and J. K. Snyder, *Tetrahedron Lett.*, 1994, **35**, 1485-1488.

555 L. Mitscher, M. Shipchandler, H. Showalter and M. Bathala, *Heterocycles.*, 1975, **3**, 7-14.

556 H. J. Rosenkranz, G. Botyos and H. Schmid, *Justus Liebigs Ann. Chem.*, 1966, **691**, 159-164.

557 R. Oehl, G. Lenzer and P. Rosenmund, *Chem. Ber.*, 1976, **109**, 705-709.

558 M. Cain, O. Campos, F. Guzman and J. M. Cook, *J. Am. Chem. Soc.*, 1983, **105**, 907-913.

559 B. Harirchian and N. L. Bauld, *J. Am. Chem. Soc.*, 1989, **111**, 1826-1828.

560 M. Sainsbury and N. L. Uttley, *J. Chem. Soc., Perkin Trans. 1*., 1977, 2109-2115.

561 J. Laronze, J. Laronze, M. Garnier, C. Trentesaux And J. Levy, *Bull. Soc. Chim. Fr.*, 1992, 303-307.

562 C. F Gürtler, S. Blechert and E. Steckhan, *Chem.-Eur. J.*, 1997, **3**, 447-452.

563 U. Rößler, S. Blechert and E. Steckhan, *Tetrahedron Lett.*, 1999, **40**, 7075-7078.

564 S. B. King and B. Ganem, *J. Am. Chem. Soc.*, 1994, **116**, 562-570.

565 T. Aoyagi, T. Yamamoto, K. Kojiri, H. Morishima, M. Nagai, M. Hamada, T. Takeuchi And H. Umezawa, *J. Antibiot.*, 1989, **42**, 883-889.

566 S. Katsumura, S. Fujiwara and S. Isoe, *Tetrahedron Lett.*, 1985, **26**, 5827-5830.

567 S. Katsumura, S. Fujiwara and S. Isoe, *Tetrahedron Lett.*, 1988, **29**, 1173-1176.

568 M. E. Garst, E. A. Tallman, J. N. Bonfiglio, D. Harcourt, E. B. Ljungwe and A. Tran, *Tetrahedron Lett.*, 1986, **27**, 4533-4536.

569 P. Bury, G. Hareau, P. Kocieński and D. Dhanak, *Tetrahedron*., 1994, **50**, 8793-8808.

570 A. Pommier and P. J. Kocieński, *Chem. Commun.*, 1997, 1139-1140.

571 J. Coombs, E. Lattmann and H. Hoffmann, *Synthesis.*, 1998, 1367-1371.

572 T. L. B. Boivin, *Tetrahedron.*, 1987, **43**, 3309-3362.

573 F. Perron and K. F. Albizati, *J. Org. Chem.*, 1989, **54**, 2044-2047.

574 L. F. Tietze and C. Schneider, *J. Org. Chem.*, 1991, **56**, 2476-2481.

575 W. Borsche, *Ber.*, 1914, **47**, 2902.

576 Z. Israili and E. Smissman, *J. Org. Chem.*, 1976, **41**, 4070-4074.

577 T. Izawa and T. Mukaiyama, *Chem. Lett.*, 1975, 161-164.

578 S. Castellino and J. J. Sims, *Tetrahedron Lett.*, 1984, **25**, 4059-4062.

579 H. Umezawa, K. Maeda, T. Takeuchi and Y. Okami, *J. Antibiotics*,. 1966, **19**, 200.

580 S. N. Roy and S. B. Horwitz, *Cancer Res.*, 1984, **44**, 1541-1546.

581 大塚雅巳, 成田昌稔, 吉田誠, 小林進, 大野雅二, 梅沢洋二, 森島甫, 斉藤清一, 滝田智久 and 梅沢浜夫, *Chem. Pharm. Bul.*, 1985, **33**, 520-526.

582 Y. Aoyagi, M. S. Chorghade, A. A. Padmapriya, H. Suguna and S. M. Hecht, *J. Org. Chem.*, 1990, **55**, 6291-6298.

583 D. L. Boger, T. Honda and Q. Dang, *J. Am. Chem. Soc.*, 1994, **116**, 5619-5630.

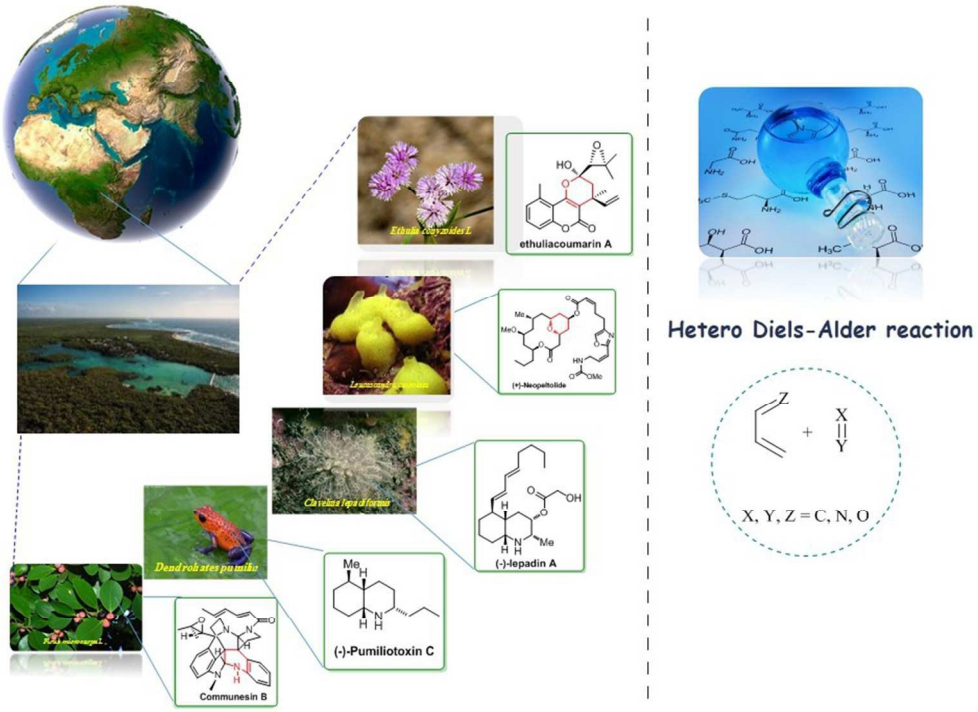
584 D. L. Boger, R. F. Menezes and T. Honda, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 273-275.

585 A. S. Duerfeldt and D. L. Boger, *J. Am. Chem. Soc.*, 2014, **136**, 2119-2125.

586 M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi and T. Naito, *Alkaloids Chem Biol*, 2000, vol. Volume 54, pp. 191-257.

587 A. Stoll, A. Hofmann and F. Troxler, *Helvetica Chimica Acta*., 1949, **32**, 506-521.

588 K. Lee, Y. B. Poudel, C. M. Glinkerman and D. L. Boger, *Tetrahedron*., 2015, **71**, 5897-5905.



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