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Recent Applications of Intramolecular Diels-Alder Reaction in Total Synthesis of Natural Products

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Abstract

Diels-Alder (D-A) reaction undoubtedly is the most powerful [4+2] cycloaddition reaction in organic synthesis. I has been always considered as a model and symbol of cycloaddtion reactions. Intramolecular D-A reactions (IMDA) are also well-recognized and can be employed in one or more steps of total synthesis of several natural products. In this report we wish to highlight the recent applications of IMDA as a key step in the total synthesis of biologically active natural products including alkaloids and terpenes.

Keywords: Intramolecular Diels-Alder reaction, Natural products, Asymmetric synthesis, Alkaloids and Terpenes.

Contents

1. Introduction

The thermal 1,4-cycloaddition of a double/triple bond to a conjugated diene is recognized as Diels-Alder (D-A) reaction.[1-3] Commonly, Diels-Alder adducts are employed to create synthons, often, exceptionally advantaged for being used in the synthesis of complex targets.[4-6] Intramolecular D-A reactions (IMDA) are also well-established as a versatile and useful reactions and found to have several applications in synthetic organic chemistry.[7-13] Significantly, the D-A reaction can be conducted in asymmetric fashion (ADA reaction) with high stereo-selectivity due to proceeding via concreteness manner.[14-21] These ADA reactions are very appealing and valuable, since, they can generate four chiral centers in the desired product, simultaneously. Notably, ADA reactions can also be employed in intramolecular fashion (AIMDA reaction) purposely, which often proceed with high enantio- and diastereoselectivities.[22-24] Due to resourcefulness and exceptional privileged nature of IMDA

reaction, it is anticipated as a prevailing and versatile approach, being employed in one or more steps of total synthesis of some important naturally occurring products, especially, those bearing bridged polycyclic moieties.[25-27] In fact, due to the high degree of chemo-, regio- and diastereo-selectivity, attained from this reaction,[28-30] it still is strategy of choice when , construction of ring with high level of stereo-selectivity is required. Thus this reaction has attracted much attention of organic synthetic chemists, documented by every day over mounting citation of associated articles in the chemical literatures. AIMDA reaction also has been common reaction in the laboratories where asymmetric synthesis is prevailed. It is still stirring up the interest of asymmetric organic chemists, particularly the chemists who are chiefly engaged with the total synthesis of naturally occurring products, especially those exhibiting various biological potencies.

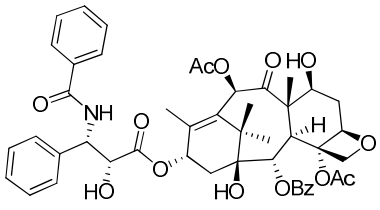
The theme has always been enough highly fascinating and striking being attended and thus reviewed comprehensively and broadly in years[31-33] These reports are covering, virtually all relevant endeavors and accomplishments on the applications of D-A reaction as the key and decisive step in the total synthesis of a wide variety of natural products. Especially when a high stereo-selectivity along with ring formation is required in a part of total synthesis of natural products, the D-A reaction is employed, often as a key step.

The role of IMDA in the total synthesis of naturally occurring products has been previously reviewed[11,34-36] . Due to our interest in the applications of name reactions in organic synthesis,[37-41] total synthesis of natural products[42-47] and asymmetric synthesis,[48,49] herein, we wish to underscore the recent and current applications of IMDA reaction as a key step in the total synthesis of biologically active natural products, mainly, alkaloids and terpenes This includes a number of recently achieved total syntheses of some important biologically and pharmacologically active natural products that their total synthesis were much desirable. It should be mentioned that, the minutiae of all steps of total synthesis of selected targets, are out of the scope of this review and not discussed in detail, basically due to space limitation. However, they are obtainable from the primary source provided in this report in the reference section. Nevertheless, due to the importance of the stereo-chemical outcomes of the total synthesis and especially when the enantio-selective D-A reaction is required, a systematic and precise description is given.

2. Terpenoids

Terpenoids are one of the most important and widespread classes of natural products in the plant kingdom and have several uses in human fitness, health and sustenance. Their molecular diversity has resulted in the finding more than 40,000 various structures, with numerous classes, found being important pharmaceutical agents and aids, such as the known and well-established anticancer agent paclitaxel (Taxol) **1** (Figure 1) and terpenoid-derived indole alkaloids. Notably a majority of terpenoids can be isolated only in low yield from natural sources. To circumvent this deficiency and back draw, the plant cell cultures have been modified as alternating production tactic. Metabolic engineering and modification of whole plants and plant cell cultures is an efficient and successful strategy. It enhances both terpenoid abundance and amend terpenoid supply to achieve desired properties such as increased flavor, enhanced fragrance and intensify color. Current advances in essential terpenoid metabolic routes, especially in secondary metabolism, increased knowledge regarding direction of terpenoid build up. Applications of promising plant systems biology approaches, have also enabled metabolic modifications for terpenoid assembly.[50]

Terpenoids constitute the most abundant natural products in the plant kingdom and are most rich and resourceful candidates as compounds for drug innovation. Current endeavors into the research, improvement and development of anti-cancer drugs derived from natural products have resulted in the identification of various terpenoids that inhibit cancer cell propagation and metastasis *via* different mechanisms.[51]



Taxol (1)
a diterpene

Figure 1

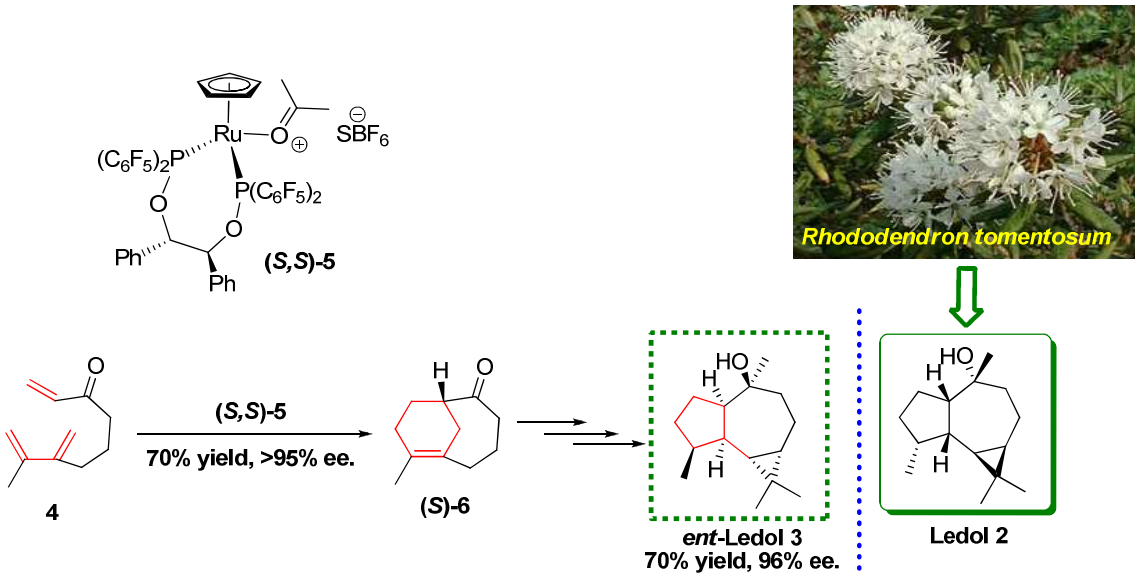
2.1. Sesquiterpenoid

2.1.1. Total synthesis of *ent*-ledol

Ledol **2** is a toxic sesquiterpenoid isolated from *Rhododendron tomentosum* (*Ledum palustre*), marsh rosemary which is a scented evergreen bush originate in peaty soils in northern Europe, Asia and North America. It shows expectorant and antitussive potency.[52,53] *Rhododendron*

tomentosum L. plants were usually collected at the flowering stage The essential oils were prepared *via* hydrodistillation of air-dried all aerial parts in a Clevenger-type apparatus in accordance with the European Pharmacopoeia. *Ent*-ledol was obtained from this extract as a yellow-greyish oily-like mass with a distinctive oil flavor and aroma. Quantitative analysis of this essential oil was achieved using GC and GC-Mass.[54]

Kündig and co-workers reported the total synthesis of *ent*-ledo **3** manipulating asymmetric IMDA reaction of triene **4** (Scheme 1). Initially, Rh catalyst ,(*S*,*S*)-**5** was employed to catalyze reaction of 2,6-lutidine and triene **4** in CH_2Cl_2 to obtain a yellow–orange solution. After further stirring at ambient temperature (r.t.) under N_2 atmosphere, the solution was evaporated to give a crude which gave pure (*S*)-**6** after flash column chromatography. The latter was then transformed into desired *ent*-ledol **3** in several steps.[55] These kinds of Ru- catalysis were previously employed in IMDA reactions of enals with various dienes.[56, 57]

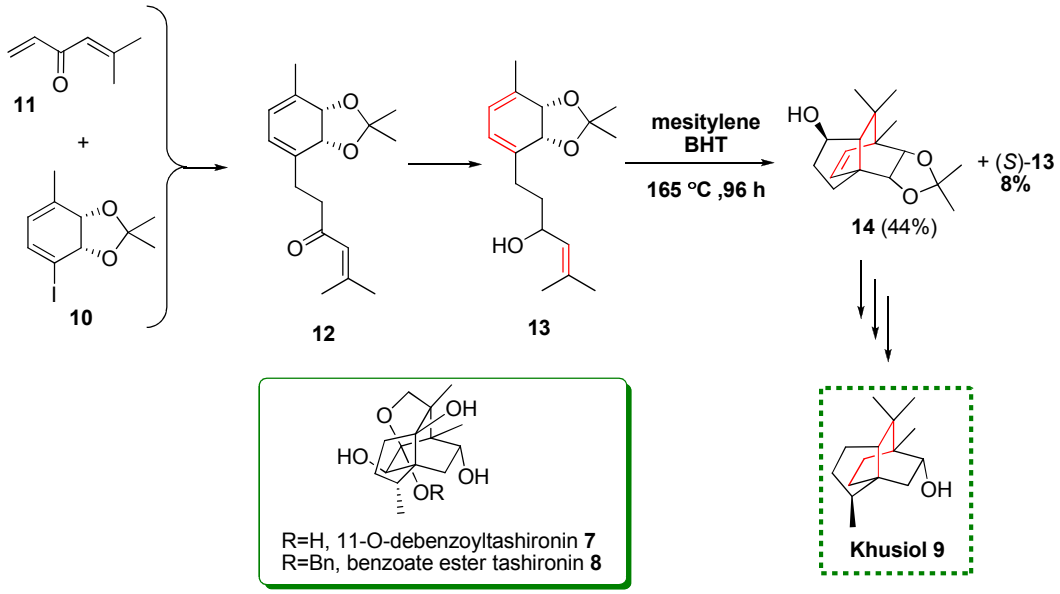


Scheme 1: Total synthesis of *ent*-ledol

2.1.2. Total synthesis of khusiol

The sesquiterpenoid natural product 11-*O*-debenzoyltashironin and the corresponding benzoate ester tashironin were isolated from the pericaps of the eastern Asian plant *Illicium merrillianum*. The pericarps of I. merrillianum were dried, powdered and then extracted with MeOH at ambient temperature to afford a pale yellow crude. Upon column chromatography on silica gel seven fractions (A-G) were obtained. 11-*O*-debenzoyltashironin **7** was then isolated from fraction B

and characterized by NMR and HRMS.[58] Sharma and co-workers attempted the total synthesis of khusiol 9. They started from chemoenzymatic approach to achieve a tricyclic carbon framework of 11-*O*-benzoyltashironin, fruitfully **7** and **8**. In this line they presented the first enantio-selective total synthesis of the sesquiterpenoid khusiol **9**.[59] An effective and versatile approach for the synthesis of 1,2-cyclopentannulated and 1,2-cyclopentannulated bicyclo[2.2.2]octanes albeit in enantiomeric form was reported by Australian researchers. The key elements were based on the initial transformation of the enzymatically-derived and enantiomerically pure *cis*-1,2-hydrocatechol **10** into the respected alkene-tethered system **12** and then **13**. The latter was then subjected into IMDA reactions upon heating in mesitylene in the presence of butylated hydroxytoluene as a free radical chain inhibitor to give the adducts **14** in reasonable yield.[60] Notably, this reaction was improved by Banwell group for the total synthesis of sesquiterpenoid khusiol **9** which is illustrated is Scheme 2.[59]

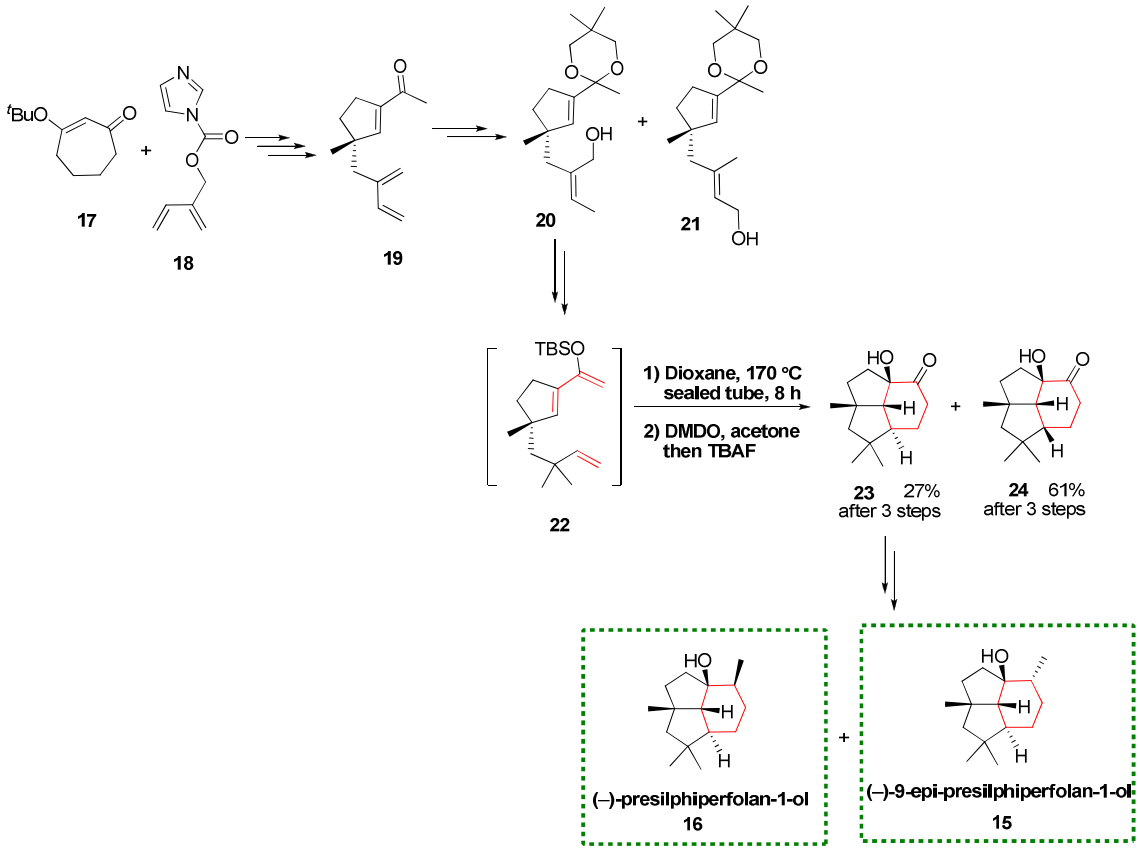


Scheme 2: Total synthesis of Khusiol

2.1.3. Synthesis of (−)-presilphiperfolan-1-ol and (−)-9-epi-presilphiperfolan-1-ol

(−)-epi-Presilphiperfolan-1-ol **15**, a triquinane sesquiterpene, was initially isolated from the essential oil of *Anemia tomentosa* var. *anthriscifolia*. The leaves of *Anemia tomentosa* are specifically utilized as a remedy for bronchitis in Brazil as a traditional medicine. *Anemia tomentosa* var. *anthriscifolia* leaves are also habitually used as a digestive abettor, expectorant, and antigripal in Argentina. In order to characterize the structure of **15** the essential oils of *A.*

tomentosa var. *anthriscifolia* were separated using silica-gel column chromatography to obtain initially 18 fractions. From these fractions compound **15** was obtained. The structure revelation was achieved using far-reaching 1D- and 2D-NMR analyses, as well as using GC–MS, chiral bidimensional GC, dehydration reactions, and a comparative (GIAO/DFT) theoretical study of the ^{13}C NMR chemical shifts of **15** with that of its well-known isomers (presilphiperfolan-1-ol **16**).[61,62] Hong and Stoltz and co-workers reported the novel asymmetric total synthesis of the (−)-epi-Presilphiperfolan-1-ol **15**. Their synthetic approach commenced with simultaneous acylation/alkylation of commercially available 3-isobutoxycycloheptenone **17**, utilizing methyl iodide and isoprenolderived carbamate **18**. After several reaction steps, the provided *gem*-dimethyl acylcyclopentene **19** was transformed into the respective silyl dienol ether **22**, followed by IMDA bicyclization which was progressed efficiently and smoothly to provide a mixture of diastereomers **23** and **24**. After chromatographic separation, having pure α-hydroxyketone **23** available, the latter was subjected to Wittig methylenation and several other transformations to give **15** and **16** including, PtO_2-catalyzed hydrogenation and desilylation using TBAF (Scheme 3).[63]

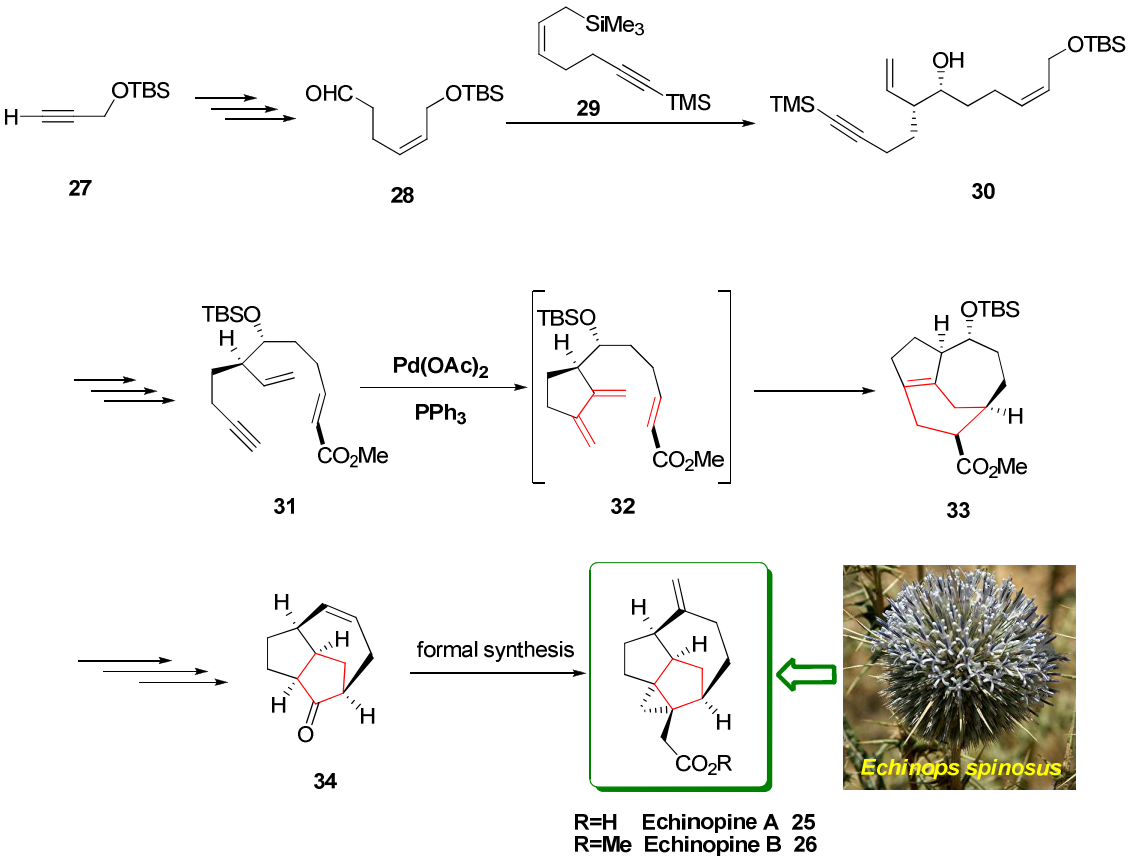


Scheme 3

2.1.4. Synthesis of 3,5,5,7-Sesquiterpenoids echinopine A and B

3,5,5,7-Sesquiterpenoids echinopine A and B (**25** and **26**), initially isolated from the root of *Echinops spinosus*. The roots of *E. spinosus* were initially dried, chopped into small pieces and then extracted with MeOH. The extract was subjected to silica gel normal phase column chromatography (CC) and RP-HPLC to provide compounds **25** and **26**.[64] Its total synthesis was reported by Peixoto and co-workers.[65] Alkenyl aldehyde **28** initially was prepared from alkyne **27** *via* its conjugate addition to acrolein with subsequent partial hydrogenation employing Lindlar catalyst. Compound **28** was subjected to Hosomi–Sakurai reaction, providing alcohol **30** in a 75% yield albeit as an inseparable diastereomeric mixture in favor of the *syn* isomer (*syn/anti* ca. 3:1). After several steps **30** was converted to compound **31**. The planned cycloisomerization/IMDA occurred efficiently and cleanly to afford diene enoate **32** as the sole noticeable component in the crude reaction mixture. This *in situ* created intermediate was subjected subsequently into IMDA at elevated temperature upon prolonged heating (160 °C), to

afford [5,6,7] tricycle **33** with an 75% overall yield from **33**. An endo transition state, which can be electronically stabilized *via* secondary orbital interactions, was occupied during the IMDA process. More importantly the configuration of the TBS ether (C10) had no appreciable effect on the competence and selectivity of either the cycloisomerization or the Diels–Alder reaction. Subsequently, compound **34** was synthesized from **33** in several steps manipulating functional group transformations (Scheme 4).[65] Spectroscopic data of tricycle **34** were compared to those of the reported previously[66] and found being identical . Therefore the pathway was established as a formal synthesis of echinopine A (**25**) and B (**26**).



Scheme 4

2.2. Diterpenoids

2.2.1. Total Synthesis of (-)-Scabronines A and G, and (-)-Episcabronine A

(-)-Scabronines G (**35**) and A (**36**) (Figure 2) are two well-known members of diterpenoids family. They were initially isolated from the bitter mushroom, *Sarcodon scabrosus*. The fruit

part of *S. scabrosus* can be extracted with MeOH. After several fractionation, the fraction obtained with chloroform-MeOH elution was purified *via* reverse-phase HPLC on ODS. Finally elution using MeOH-H_2O (7:3) provided scabronine A **36** as a colorless amorphous solid. Scabronine G **35** was purified likewise to scabronine A.[67] They were traditionally used for the reduction of Alzheimer, Parkinson, and Huntington disease symptoms.[68,69] The first total synthesis of (-)-episcabronine A (**37**) involves a highly stereoselective cascade. The total synthesis starts from salicyl aldehyde derivative **38**. Initially, the latter was transformed into the terminal alkyne phosphate **39** followed by treatment with isopropylmagnesium chloride. Removal of the TIPS group provided a chiral allene **40**. Treatment of the latter with phenyliodine (III) diacetate (PIDA) gave an *o*-benzoquinone mono-dimethylacetal **41**. In the following an intramolecular Inverse-Electron-Demand Diels–Alder (IEDDA) reaction made progress sluggishly at ambient temperature and notably required seven days for being completed to afford **41** as the sole product in 95% ee. Subsequently, the latter was used in the synthesis of compound **42** which is the key intermediate for the total synthesis of (-)-scabronines G **35** and A **36**, and (-)-episcabronine A **37** (Scheme 5). Significantly, the total synthesis of (-)-scabronine G **35** presents a highly stereoselective oxidative dearomatization/IEDDA reaction cascade, as the first ever reported total synthesis of (-)-scabronine A **36** presenting a highly stereoselective oxa-Michael/protonation/acetalization cascade. The first reported total synthesis of (-)-episcabronine A **37** comprises yet another highly stereoselective cascade.[70]

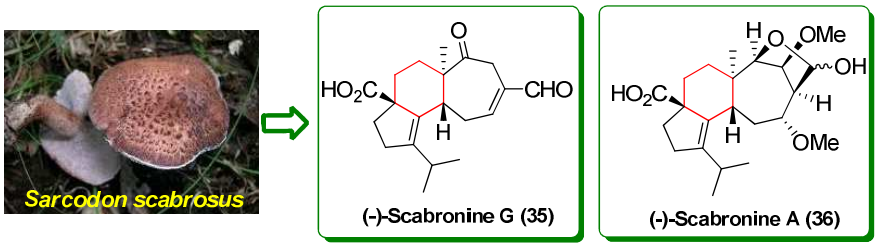
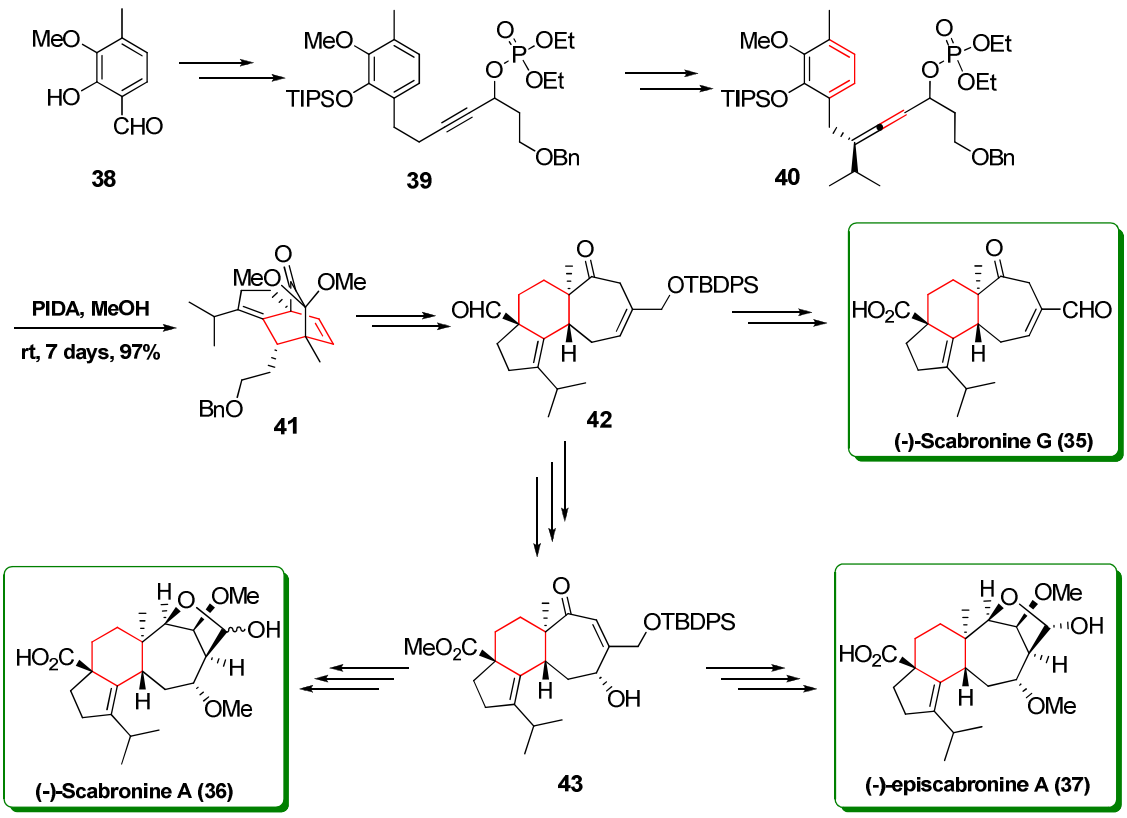


Figure 2

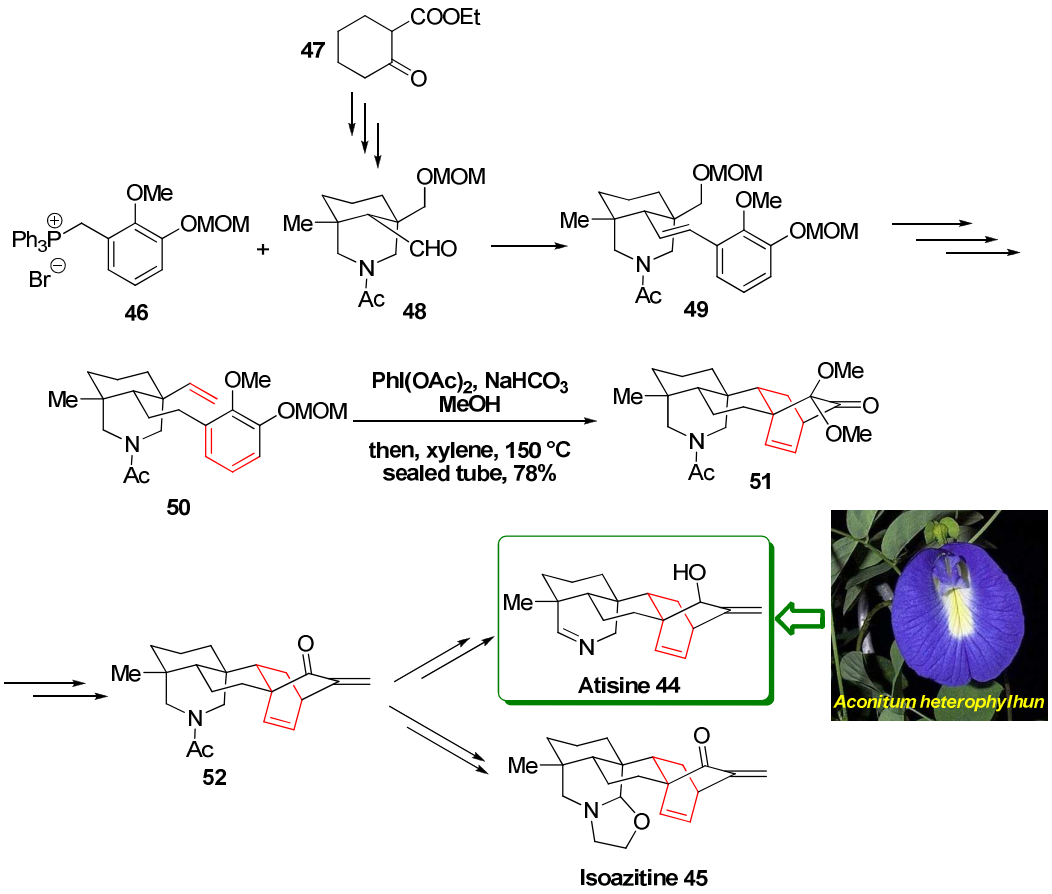


Scheme 5

2.2.2. Synthesis of (±)-atisine and (±)-isoazitine

The plant *Aconitum heterophylhun* (Atis) were found in the Himalaya Mountain at high altitudes. Interestingly, the root of this plant has been used as a traditional medicine native Indian as anti-fevers and anti-malaria for a long time. It is also known for a long time that the aforementioned root contains , atisine **44**, belongs in the category of simpler aconite alkaloids family. A finely-powdered batch *heterophyllum* roots was initially extracted exhaustively using common organic solvents such as ethanol. The extract was subjected to repeated fractional column chromatography. One of the fractions contained a bulk of the alkaloids chiefly consist atisine **44**.[71-75] Atisine **44** and isoazitine **45** (Scheme 6) are two members of atisine-type C_{20}-diterpenoid alkaloids, bearing a pentacyclic scaffold, characteristic of azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane moieties. Assembly of azabicyclo[3.3.1]nonane and bicyclo[2.2.2]octane ring systems has been the chief challenge and main endeavors in several laboratories. Liu and his research group utilized a cascade of oxidative dearomatization/IMDA cycloaddition to envisage the construction of the bicyclo[2.2.2]octane ring system for total synthesis of diterpenoid

alkaloids **44** and **45**. In this line, **48** was treated with a Wittig reagent **46** being subjected to olefination to provide the *E*-isomer of styrene **49**. In the following, **50** is provided *via* a series of chemical transformation involving functional group conversion. The latter, after oxidation of phenolic hydroxyl group, was subjected to an oxidative dearomatization/IMDA cascade reaction. When xylenes was used as solvent, the obtained masked *ortho*-quinone was submitted to thermal activation (150 ℃) to furnish **51** which is a pentacyclic compound as a single isomer in good yield. The form of *endo* for **51** was established and confirmed by NOESY spectrum (due to the vital correlation between H-14 and H-20) and single crystal X-ray of the product. The same strategy has been used for the assemblage of (±)-isoazitine **45** in 22 steps (Scheme 6).[76]



Scheme 6

2.2.3. Synthesis of Maoecrystal V core

Recently Maoecrystal V **53** a gifted terpenoide with potency and selective cytotoxic activities and novel architectural moiety was isolated and its structure was revealed. It was initially isolated from the traditional medicinally used Chinese herb *Isodon eriocalyx*, composed from the

Jiangchuan prefecture of Yunnan province. Leaves of *I. eriocalyx* (Dunn.) were collected in China, on September 10, 1994, for the first time. After meticulous extraction using methanol, the extract was fractionally column chromatographed on silica to give several fractions. Further column chromatography gave the purest natural product which was first identified by Prof. H. W. Li. Dried.[77] Nicolaou and co-workers initially approached to the pentacyclic scaffold of this target. They envisaged this hypothesis that the target could be constructed from a bicyclic precursor *via* an IMDA of intermediate **56** which can introduce two additional rings simultaneously, with subsequent intramolecular cyclopropanation/dearomatization/ring opening cascade to create the final target **58** (Scheme 7).[78] Dong and his group applied the Nicolaou's pathway for the synthesis of highly functionalized tetracyclic lactone **63** and **64** (Scheme 8).[79] In another work, an effective and stereo-selective pathway was employedfor the synthesis of tricyclic core structure of maoecrystal V from a simple aromatic precursor. A tandem oxidative dearomatization of suitably appended *o*-hydroxymethylphenol **65** under IMDA conditions afforded a tricyclic adduct, bearing bridged bicyclo[2.2.2]octanone scaffold **67** annulated with the lactone ring. Manipulation of the oxirane ring and the double bond provided the desired intermediate **68** (Scheme 9).[80] Later, Peng and Danishefsky designed a sequence including, IMDA reaction of a less poly- functionalized and symmetrical precursor. Their pathway to provide the IMDA precursor **74** ,started from typical vinylogous acylaiont, from substrates **69** and **70**, which led to intermediate **71**, bearing one of the requisite quaternary carbon centers. The latter was then transformed to the target IMDA substrate **74** after several steps. In this occasion, compound **74** easily was thermally subjected to IMDA cyclization in fair yield to create the expected cycloadduct **75** which then afforded maoecrystal V core **76** (Scheme 10).[81]

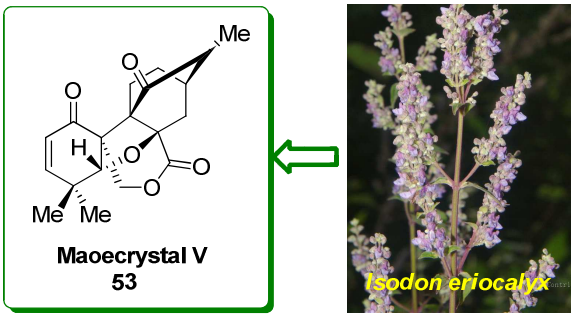
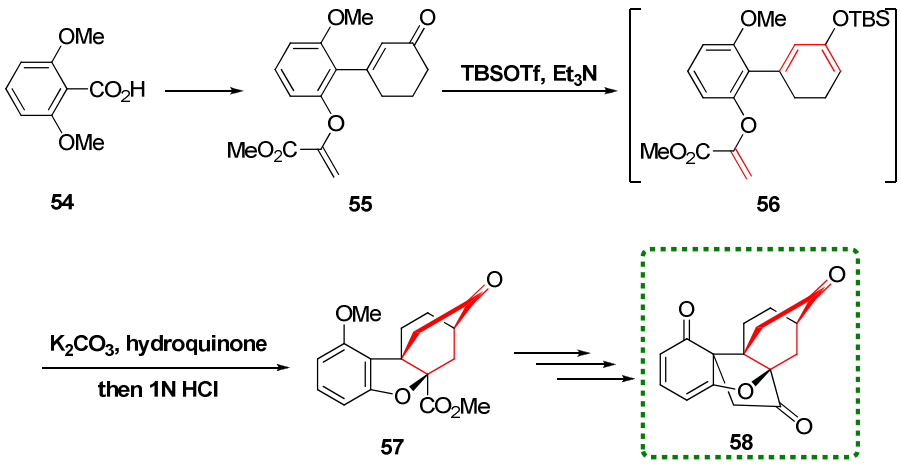
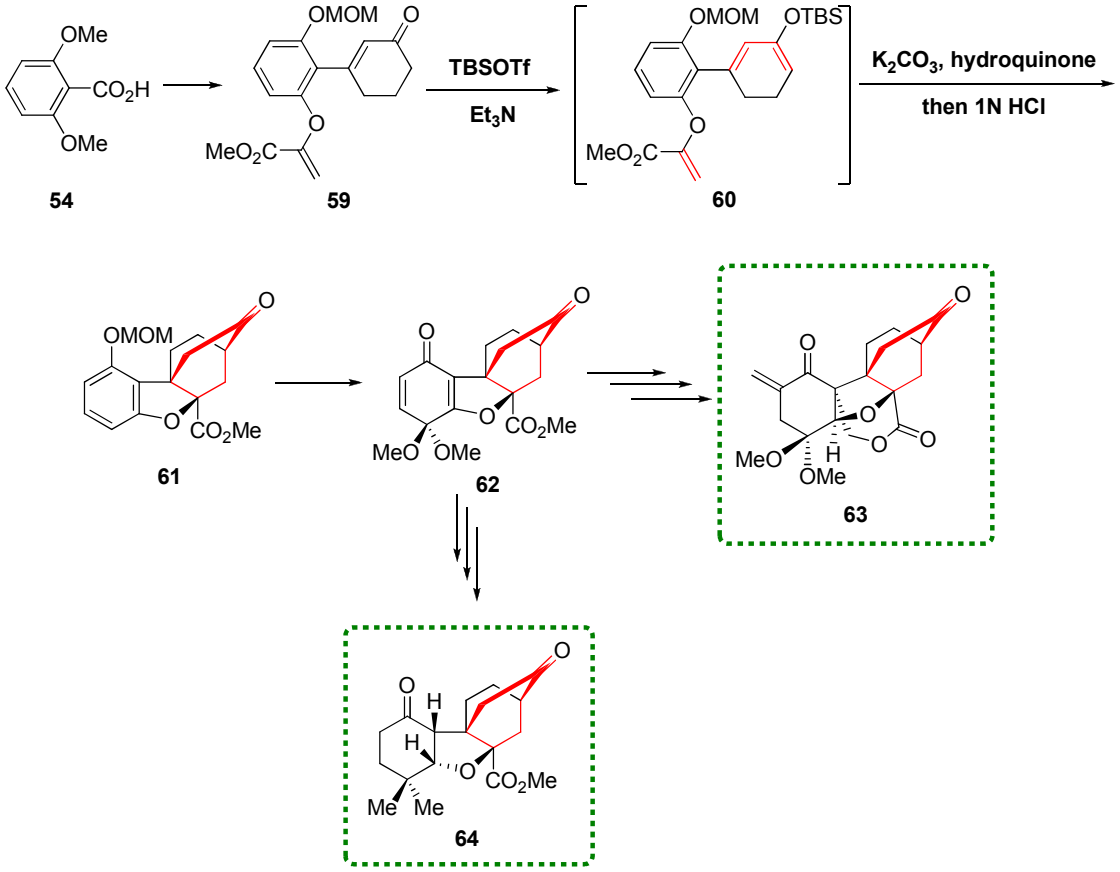


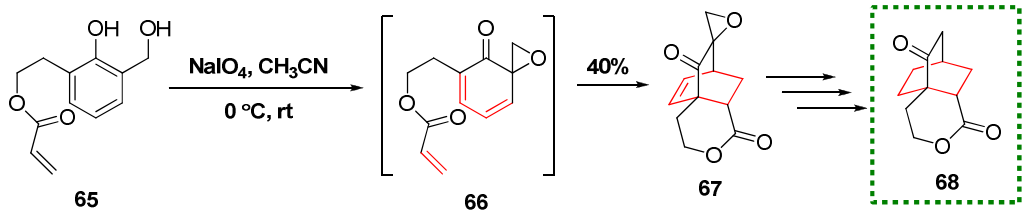
Figure 3: *Isodon eriocalyxi*[82]and Maoecrystal V



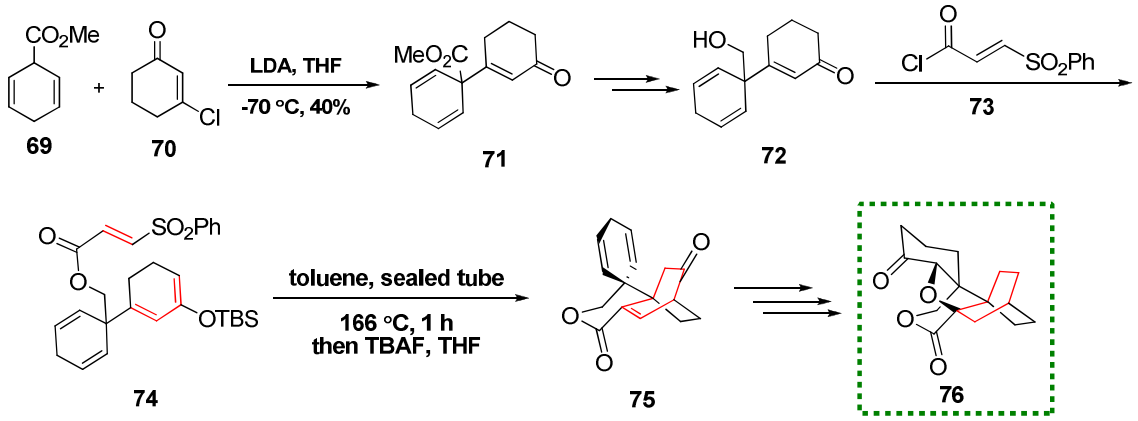
Scheme 7



Scheme 8



Scheme 9

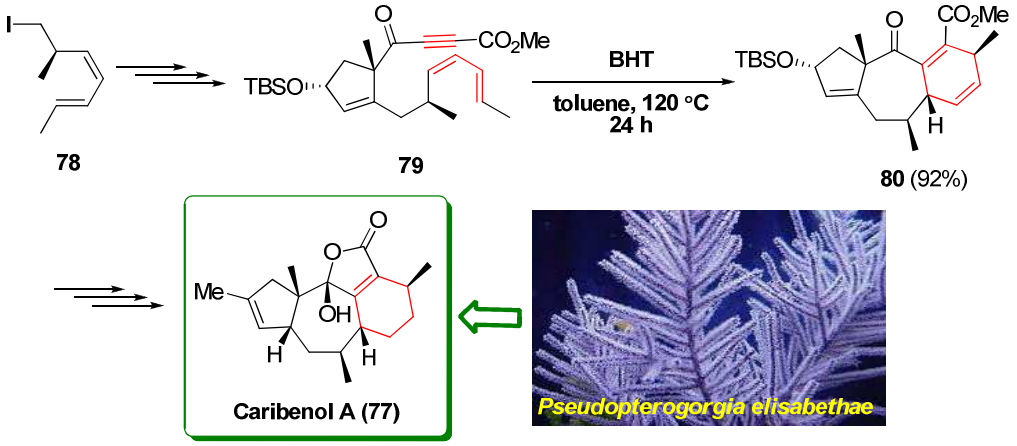


Scheme 10

2.2.4. Total synthesis of Caribenol A

Caribenol A (**77**) was initially isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae*. It is a member of a family of new norditerpenes with important biological properties. In a research project focused on finding novel anticancer two *P. elisabethae* chemotypes collected from Colombia were studied. From these species a myriad of structurally diverse terpenoids, were isolated. They showed many interesting structural features as well as exhibiting biological activities. The extract subjected to size exclusion chromatography with subsequent flash column chromatography and normal-phase HPLC to obtain Caribenol A and B .[83] The first total synthesis of caribenol A (**77**) was performed and revealed in 2010.[84] The research group have completed their work by conducting the asymmetric construction of the [5−7−6]tricyclic core of caribenol A (**77**) *via* the IMDA reaction as the key step in their approach.[85] Due to the reactivity and selectivity, proven for IMDA reactions, they are often highly substrate-dependent, especially when 1,3-butadienes used as the substrates. The reaction was started with testing the IMDA reaction of **79**, which could be easily synthesized *via* the reaction sequence illustrated in Scheme 11. The desired and planned IMDA product could

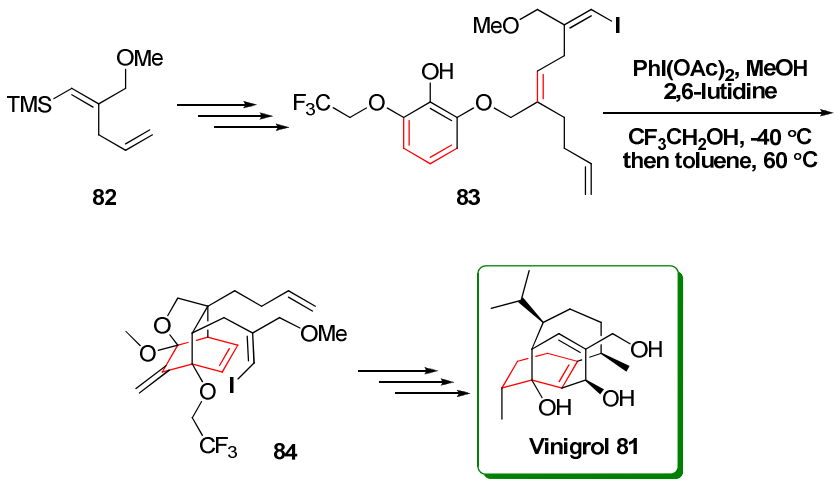
be constructed in the presence of a catalytic amount of 2,6-di-tert-butyl-4-methylphenol (BHT), resulting in the generation of **80** in excellent yield. In the following, the D-A product **80** was transformed into the caribenol A (**77**) in several steps, manipulating different functional group transformations.[84, 85]



Scheme 11

2.2.5. Total synthesis of Vinigrol

Vinigrol **81** was initially isolated from *Virgaria nigra*, a fungus, as an antihypertensive and platelet aggregation-inhibiting substance. For isolation, fermentation broth initially was filtered and the then mycelium was extracted by discontinuous mixing. The solvent extract was concentrated under reduced pressure. After adjusting to pH 7.0, active component was extracted with EtOAc (3 liters). The concentrated extract was subjected to a silica gel column chromatography. For further purification the separated vinigrol was crystallized from a mixture of EtOAc/n-heptane.[86,87] After optimization of the oxidative dearomatization reaction, starting from compound **82**, Yang and co-worker were pleased with high yields of IMDA cycloadduct **83** (Scheme 12). In the following, the latter was coupled via Heck cyclization cascade, giving the carbocyclic core of vinigrol in just two steps from a simple and common precursor. The synthesis includes a number of distinguished conversions such as: a) a straight hydrogenation in a very complex and over-involved surroundings, b) selenium-dioxide-mediated deprotection along with olefin isomerization, c) Wharton fragmentation, and eventually d) exceptional tactical applications and deprotection of a trifluoroethyl ether.[88]



Scheme 12

2.2.6. Synthesis of Salvinorin A core

Neoclerodanediterpenes, such as salvinorin A (Fig. 4), show fascinating biological activities.[89] Salvinorin A **85** is the first isolated and identified diterpene hallucinogen, isolated from *Salvia divinorum* (Labiatae). For isolation, dried leaves of *Salvia divinorurn*, which was collected from Mexico, were extracted with chloroform .The extract as a green residue separated to thirteen fractions by chromatography. The sixth and seventh fractions were found to have salvinorin A as ascertained detected by TLC .Further purification achieved by crystallization from methanol affording, salvinorin A **85** as colorless crystals.[90] Applying a highly diastereoselective acrylate IMDA cycloaddition as the crucial step, a relatively short pathway starting from 3-furaldehyde **86** reaching to a bicyclic frame work for the synthesis of were developed. An initial attempt involving a conjugate methylation of a dienyl lactone was unsuccessful. However, streamlined sequence employing an all-surrounding IMDA reaction of an even sterically overcrowded 1,3-diene **89** was found, fruitful. For this purpose, **89** was heated under pressure at 180 °C in a sealed tube in the presence of small amounts of BHT to provide 61% yield of cycloadducts. In this reaction diastereomer **90** was found to be the major product. The relative configurations of four possible diastereomers were characterized by NOESY experiments (Scheme 13).[91]

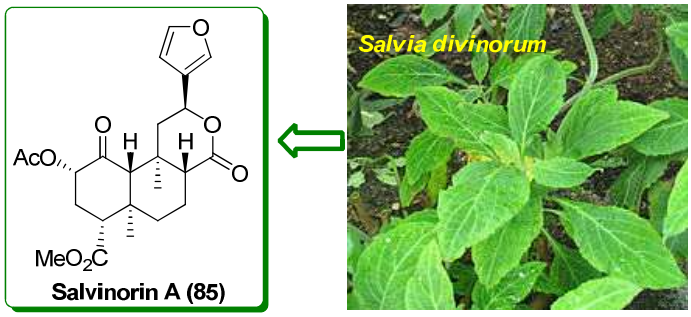
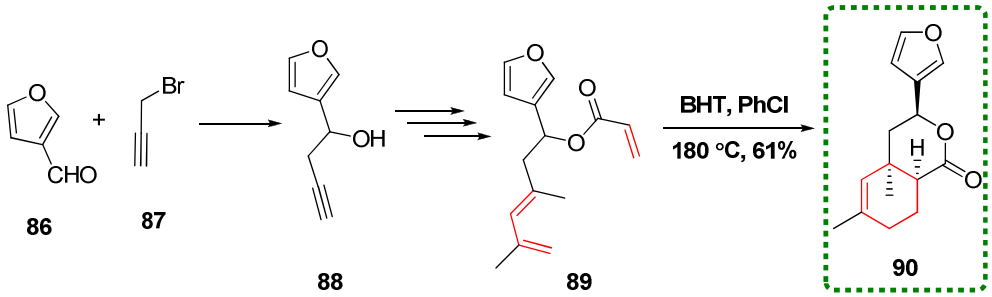


Figure 4

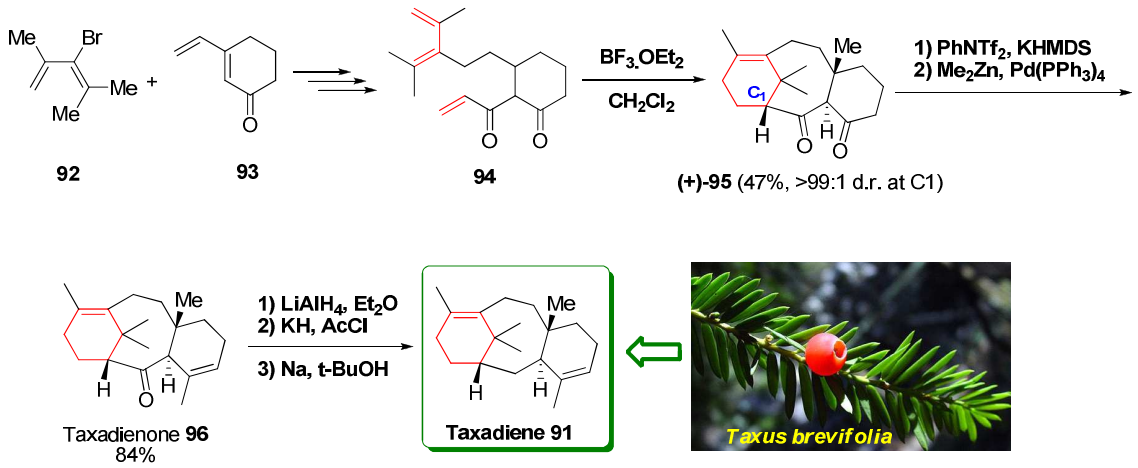


Scheme 13

2.2.7.Total synthesis of Taxanes

Taxanes form a large family of terpenes comprising over 350 members, the most famous of which is Taxol (paclitaxel), a billion-dollar anticancer drug. The extract from *Taxus brevifolia* bark powder, was silica gel chromatographed to provide a hydrocarbon fraction. This fraction, are very complex mixture of sesquiterpene and diterpene hydrocarbons. was then purified by column chromatography to give an oily material. Further passage through silica gel with subsequent reversed-phase column chromatography gave taxadiene **91** in relatively pure form.[92] Mendoza and co-workers reported the first practical and operational scalable synthetic procedure towards these natural products through the succinct synthesis of (1)-taxa-4(5),11(12)-dien-2-one **91**.The latter has a suitable functional handle being converted to more oxidized members of its family. Enantio-selective approach to the taxane family of natural products, interestingly, was achieved as short as seven steps, commencing from a commercially purchasable common starting material **92,** in 18–20% overall yield. Compound **94** treated with $BF_3.OEt_2$ to afford a tricyclic compound **(+)-95**. The desired diketone **95** was provided in reasonable yield, along with its diastereomer albeit in low yield, but with complete diastereo-selectivity. Now, only one more

carbon remained to be assembled to complete the taxane scaffold: this was accomplished *via* enol triflate generation, followed by Negishi coupling to give taxadienone **96** in high yield over two steps which can then transform to taxadiene **91**. To this end, a three-step deoxygenation sequence was performed in reasonable yield (Scheme 14). This pathway provides a gram-scale synthesis of the 'parent' taxane—taxadiene—which is the delightfully, the largest amount of this natural terpene ever either isolated or synthesized in fairly pure form. The characteristic 6-8-6 tricyclicsystem of the taxane family, bearing a bridgehead alkene, is fake *via* a vicinal difunctionalization D–A strategy. Asymmetry is induced *via* an enantio-selective conjugate addition which generates a full-carbon quaternary stereogenic center, from which all other stereocentres are unchanged *via* full substrate control. This study lays an important foundation for an intended access to partially oxidized taxane analogues and a bench scale laboratory synthesis of Taxol itself.[93]



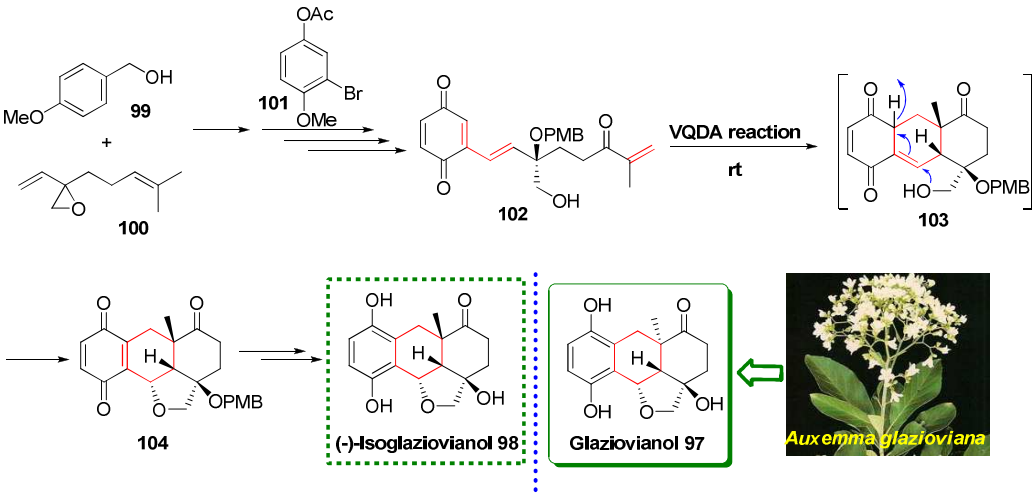
Scheme 14

2.3. Meroterpenoids

2.3.1. Synthesis of (-)-Isoglaziovianol

The cordiachromes, an abnormal class of meroterpenoids can be formed and found either as the quinone or quinol form. Most of them bear a *cis*-fused decalin motif with one noticeable exclusion: that is glaziovianol **97**, which is the only member of the family recognized to date that carries a transfused decalin. The aforementioned natural product was initially isolated from the trunk Heartwood of *Auxemma glazioviana*, a tree endemic in the district of the north east of

Brazil. Dried and powdered Heartwood initially was thoroughly extracted with EtOH at ambient temperature. Repetitive chromatography on Silica gel afforded glaziovianol **97**.[94] Isoglaziovianol **98** synthesis was started by Tsuji–Trost asymmetric alkylation[95,96] of para-methoxybenzyl alcohol **99** with the easily prepared known racemic vinyl epoxide **100**. The provided tertiary allylic ether initially was transformed to respective quinone **102** in high regio- and enantio-selectivity (85% isolated yield and 93% ee), *via* several steps. It is worthwhile to mention, that the latter,, is inaccessible since it is simultaneously and rapidly is subjected into intramolecular vinyl quinone D-A (VQDA) reaction at ambient temperature. It most probably happenes through generation of endo transition state, with subsequent nucleophilic trapping of the resulting isoquinone methide **103**. Over oxidation of the resulting hydroquinone provided the tetracyclic quinone **104** in relatively poor overall yield. Oxidative removal of the PMB group, followed by reduction then afforded hydroquinone **98**. The latter carries the foundation of glaziovianol **97** (Scheme 15).[97]



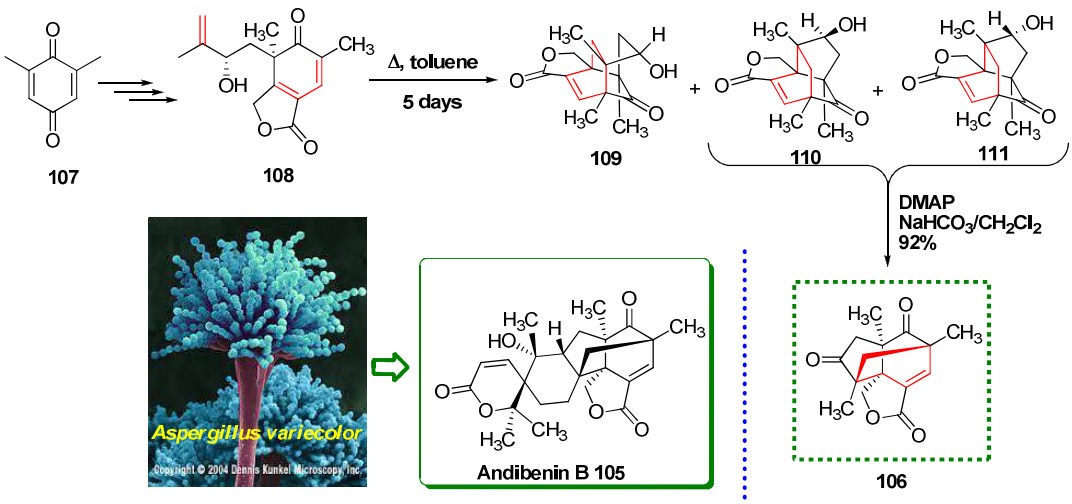
Scheme 15

2.3.2. Synthesis of Andibenin B core

In 1976, Dunn and co-workers for the first time obtained, and reported the crystallographic structure of a novel metabolite meroterpenoids, andibenin B (**105**), isolated from the static cultures of *Aspergillus variecolor*. Practically the mother liquors from static cultures of the fungus was extracted, providing a brown semi-solid oil,

Which first was isolated and purified by crystallization.[98] A concise synthesis of the bicyclo[2.2.2]octane **106** cores of andibenin B through a nature-inspired IMDA was disclosed by Spangler and Sorensen, accomplished, only in 10 steps obtaining 14% overall yield based on 2,6-dimethylbenzoquinone **107**. The latter was converted to allylic alcohol, **108** in several steps. Compound **108** was transformed to epimeric mixture of carbinols **109**, **110** and **111** upon heating to 80 °C in toluehene *via* Diels–Alder cycloaddition. The yield of isolated product of this reaction was high. The allylic alcohol **108** , gives gi the both possible Diels–Alder regioisomers in a 1:1.8 ratio (**109**/**110**),.slightly favoring the desired regioisomer **110**. This cycloaddition allows the assembly of a sterically overcrowded bicycle and

concurrently generates three new all-carbon quaternary chiral centers in a highly well-organized manner. Oxidation of **110** and **111** using Dess–Martin periodinane (DMP) subsequently performed to give the corresponding ketone **106** in good yield.[99]



Scheme 16

3. Alkaloids

Alkaloids are a group of natural chemical compounds which contain chiefly, basic nitrogen atoms.[100] However, this group also may contain some interrelated compounds with neutral and even weak acidic properties. Some synthetic compounds of similar structure are also termed alkaloids.[101] In addition to carbon, hydrogen and nitrogen, alkaloids may also contain oxygen, sulfur and more infrequently other elements such as chlorine, bromine, and phosphorus.[102] In the of alkaloids in a wide variety of organisms such as bacteria, fungi, plants, and animals are involved. They are usually purified from crude extracts of these organisms commonly by acid-base extraction. Interestingly, many alkaloids are toxic to other organisms. They often have biological and pharmacological activities and are usually used as prescribed recreational drugs, and in entheogenic rituals. Examples are the local anesthetic and stimulant cocaine, the psychedelic psilocin, the stimulants caffeine and nicotine.[103] Notorious morphine **112** is the major active constituent of opium, which is actually extraction of the immature seed capsule of the opium poppy. Morphine **112** and linked opiates are generally analgesics. In spite of grim side

effects, including physical and psychological addiction, it remains to be clinically as one of the most extensively used drugs to treat severe pain. Codeine **113**, methylated morphine, is frequently used in cough medicines as antitussive agent. It is also a weak analgesic (Fig. 5).[103] Acetylated morphine, heroin, which not while ago had been used as an analgesic, nowadays is a street drug.

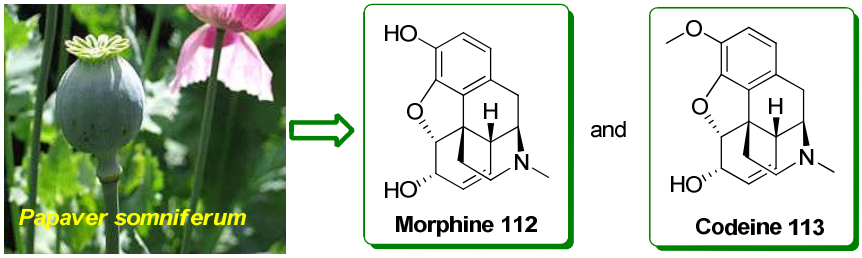
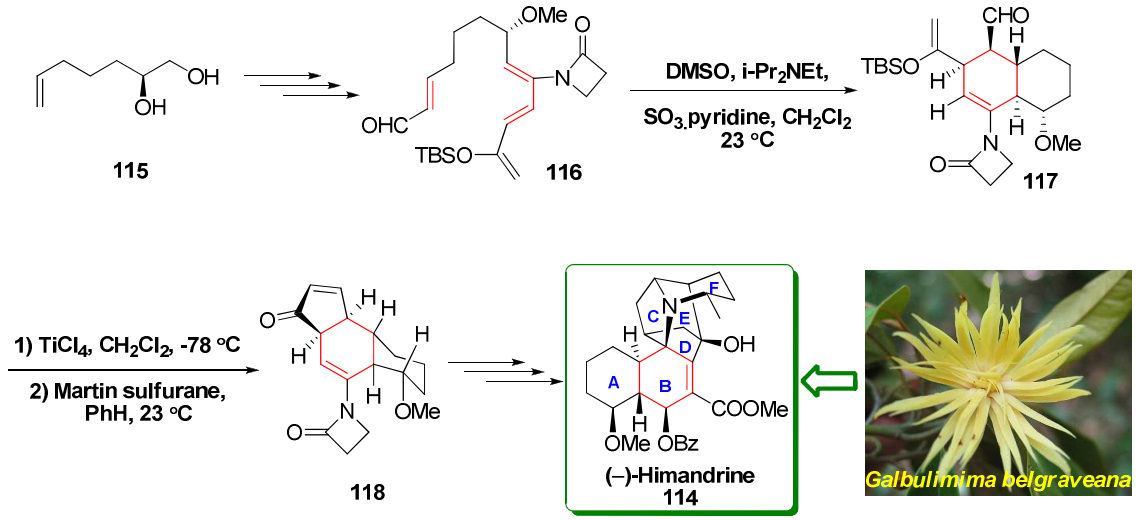


Figure 5

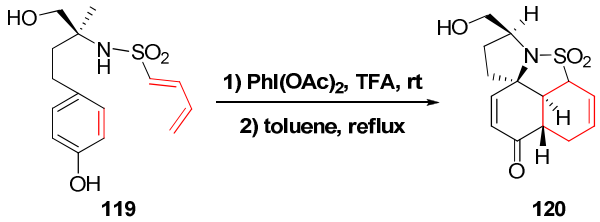
3.1. Total Synthesis of (-)-Himandrine

The galbulimima alkaloid (-)-himandrine (**114**) is a topologically interesting substance. It is initially isolated from the bark of *Galbulimima belgraveana*, a tree indigenous grown in New Guinea and northern Australia. The neutral fraction provided by exhaustive extraction with methanol. Basic material which was recovered from methanol solution gave a small amount of himbosine. The bases in the mother liquor were also recovered and purified by column chromatography on alumina. The major alkaloid fraction was then separated into those desired alkaloids, namely himbacine, himbeline, himandravine, himgravine, himbosine, himandrine.[104, 105] Movassaghi and co-worker performed and reported the total synthesis of (-)-himandrine **114** for the first time. They started from an enone and an iminium chloride and followed annulations methodology.[106] Remarkable appearance of this chemistry, include the diastereoselective D-A reaction for an efficient synthesis of the *trans*-decalin **117** bearing tricycle (-)-**118** in an enantiomerically pure form. Solution of tetraenal (-)-**116** at 95 °C gave the desired *trans*-decalin aldehyde (-)-**117** as the major endo Diels-Alder product (75%, dr = 5:1). The reaction of aldehyde (-) -**117** with titanium tetrachloride gave the corresponding Mukaiyama aldol product,[107] which upon treatment with Martin sulfurane[108] gave the oxygen and acid sensitive enone (-)-**118** in good yield over two steps. This formal [3+3] annulation protocol to secure the formation of CDE-ring system (See A-F rings of Himandrine **114** in Scheme 17) with whole

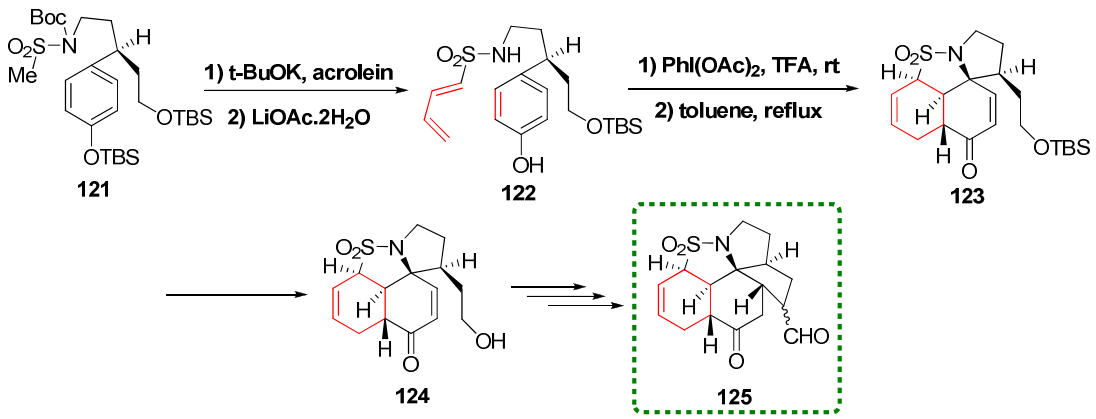
diastereoselectivity and thriving accomplishment of this biogenetically motivated oxidative spirocyclization in converting **118** to (-)-**114**.[106] Upon oxidative cyclization of dienic sulfonamides **119** in the presence of iodobenzene diacetate in TFA, followed by a tandem IMDA reaction, desymmetrization of a "locally symmetrical" dienone **120** (Scheme 18) with good levels of diastereoselectivity is achieved, resulting in precious synthetic intermediates for the himandrine alkaloids (Scheme 19).[109,110]



Scheme 17



Scheme 18: Model tandem phenolic oxidative amidation-IMDA reaction giving the framework of himandrine

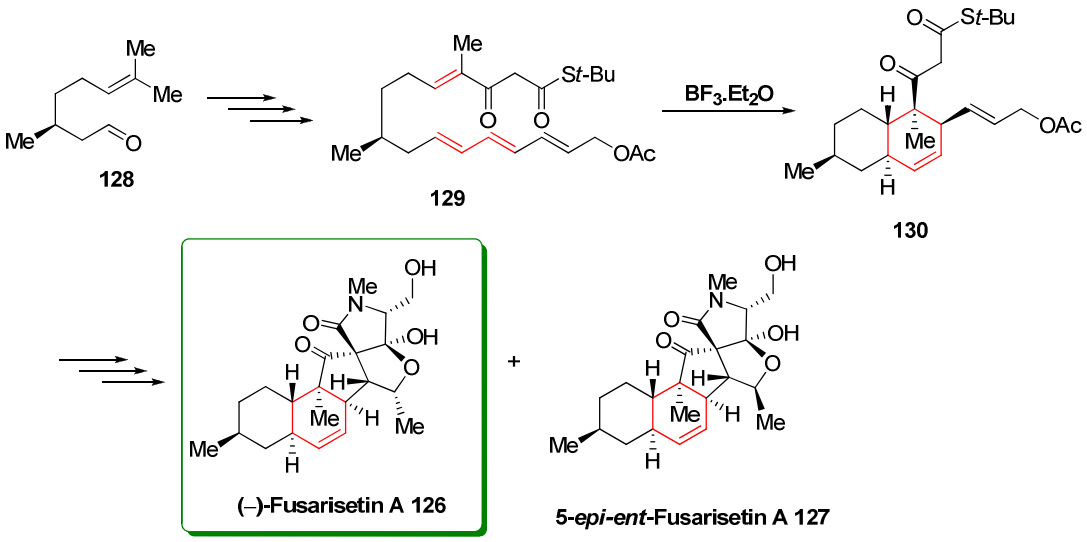


Scheme 19

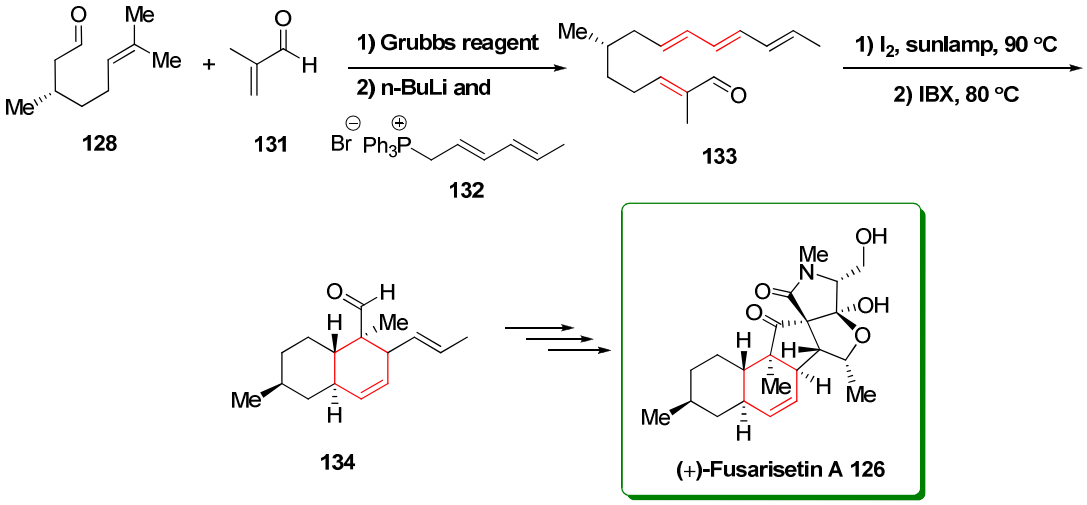
3.2. Total Synthesis of (+)- and (−)-Fusarisetin A

Ahn and co-workers attempted the successful isolation of a biologically intriguing natural product, fusarisetin A, from a soil fungus, *Fusarium sp*. This compound showed remarkable inhibition of acinar morphogenesis as well as cell migration and incursion with no appreciable cytotoxicity. *Fusarimu* sp. was inoculated of seed culture medium PD broth. This culture broth was filtered and extracted. The extract was column chromatographed to obtain seven fractions. One of the fractions was purified by reverse-phase HPLC to yield **126**.[111]. The total synthesis of (−)-fusarisetin A **126** was firstly reported, had been achieved in 13 steps, resulting in the re-assignment of the absolute configuration of the actual natural product. The synthesis involved a Lewis acid- mediated IMDA reaction, along with Pd-catalyzed O→C allylic rearrangement, followed by a chemo-selective Wacker oxidation, and sequential Dieckmann condensation/hemiketalization cascade. Compound **130** is believed to derive from a linear precursor such as **129** *via* a diastereo-selective IMDA reaction. $BF_3.OEt_2$ was recognized as an efficient promoter for this conversion. Transdecalin **130** was transformed to **126** as a sole isolable diastereomer in several steps to give 63% yield. The desired target of D-A substrate **129** could be installed from the reaction of known (*S*)-(−)-citronellal **128** and phosphonates *via* double Horner−Wadsworth−Emmons (H-W-E) olefinations.[112] In another alternative work, polyene *ent*-**133** was selected as the precursor for the IMDA reaction. It was provided from the reaction of (*S*)-(−)-citronellal **128** in 62% overall yield expectedly as a mixture of *E*–*Z* isomers. Interestingly, this mixture can be subjected to photochemical-induced isomerisation in the presence of catalytic amount of iodine to give the *trans* polyene **133** as the sole product.

Skipping purification, this isomer can be submitted to a Et_2AlCl-catalyzed IMDA reaction, which produced the desired *trans*-decalin aldehyde *ent*-**134** with high stereoselectivity (dr > 10:1, 82% yield). The latter was transformed into (+)-fusarisetin A **126** in several further steps.[113,114]



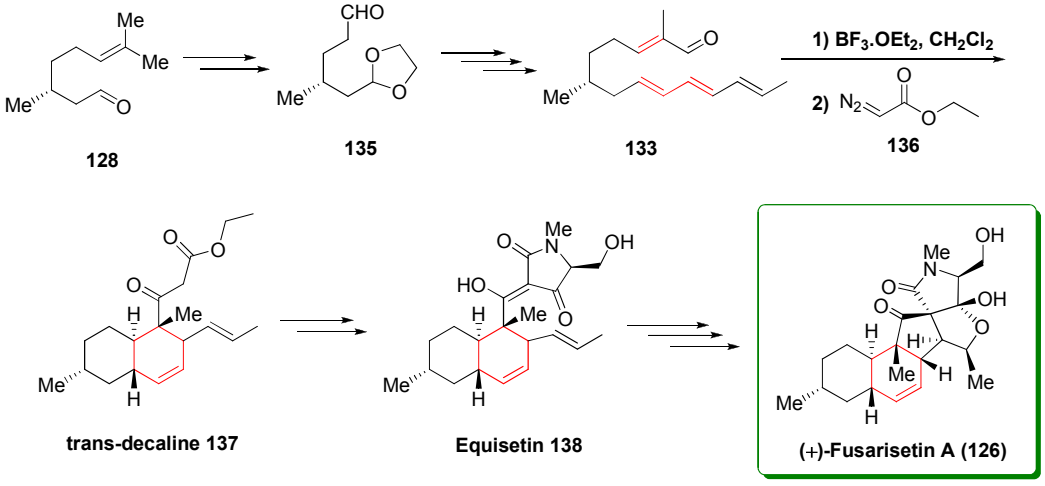
Scheme 20



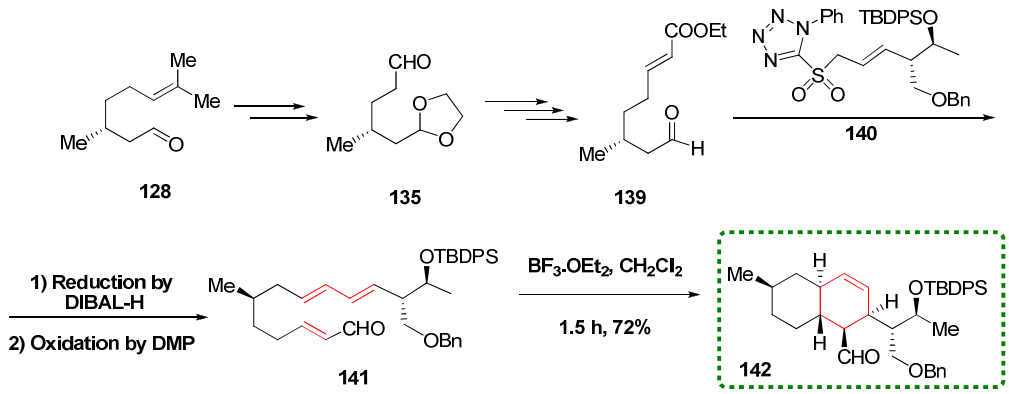
Scheme 21

Equisetin **138**, a fungal metabolite, was initially isolated from the white mold *Fusarium equisetii*. *Fusarium equiseti* initially was grown on an autoclaved white corn grit medium at ambient temperature, upon extraction afforded a substance that shown to inhibit some gram-positive bacteria including mycobacteria.[115] Employing a two-step procedure, (+)-citronellal **128** was transformed into aldehyde **135**. Conversion of **135** to unsaturated aldehyde *ent*-**133** was achieved

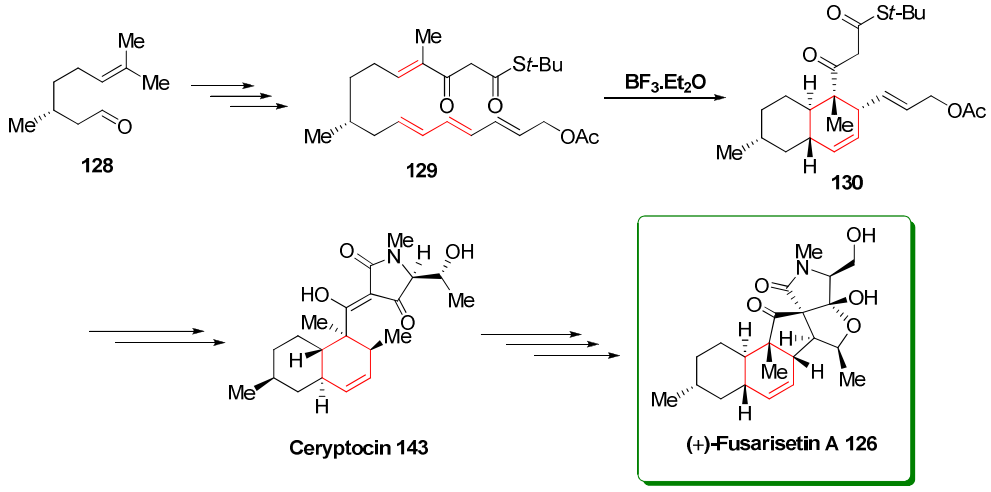
by using a sequential Wittig reaction, diisobutylaluminium hydride (DIBAL-H) reduction/Dess–Martin periodinane (DMP) oxidation. The IMDA reaction efficiently and easily transformed aldehyde *ent*-**133** to trans-decalin **137** mediated by $BF_3.OEt_2$ which then in turn was converted to equisetin **138** *via* four step reactions using different organic transformation methodologies.[116, 117] The conversion of equisetin **138** to (+)-fusarisetin A **126** could be conducted in a one-pot reaction fashion *via* straight addition of Zn to the O_2-scavenger oxidative radical sequence and **126** was obtained in fair yield over the sequential (Scheme 22).[117] An Indian researcher group synthesized compound **139** beginning from (+)-citronellal **128**. The next objective of Julia-Kocienski olefination between aldehyde **139** and sulphone **140** was stereo-selective in the presence of KHMDS to furnish a triene ester which was converted to the Diels-Alder precursor **141** in two steps. The endo transition state favored IMDA reaction of **141** under Lewis acid catalysis ($BF_3.OEt_2$) furnished the fully functionalized decalin **142** with *trans* ring junction and seven out of ten chiral centers with 72% yield (Scheme 23).[118] Kong and co-workers used (+)-citronellal **128** for the synthesis of other triene *ent*-**129** which was converted to *trans*-decalin *ent*-**130** (dr = 8:1) through an IMDA reaction promoted by $BF_3.OEt_2$. Then, *trans*-decalin *ent*-**130** was used for the synthesis of cryptocin **143** and then for the synthesis (+)-fusarisetin A **126**.[119]



Scheme 22



Scheme 23



Scheme 24

3.3. Synthesis of the Decalin core of Codinaeopsin

Codinaeopsin **144** (Fig. 6), a tryptophan-polyketide hybrid is a natural product with auspicious antimalarial properties. It belongs to family of fungal metabolites that have a decalin scaffold derived from a linear polyketide united with an alkoxyaminal segment to provide α-acyl-γ-hydroxy lactams. A novel tryptophan-polyketide hybrid, codinaeopsin, was initially isolated from an endophytic fungus which was fermented. Upon extraction of the fermentation broth followed by silica gel flash column chromatography several fractions were obtained. Fractions containing the active component, identified by TLC were collected and purified further by reverse-phase HPLC. In this way a pure codinaeopsin **144**, the active ingredient, was obtained.[120] Ramanathan and co-workers reported the synthesis of the decalin core of codinaeopsin, *via* an IMDA reaction. A convergent synthesis was accessible to synthesize the precursors for the

IMDA reaction in 10 steps commenced from trimethylphenol **145**. The exo cycloadducts **149a-b** were obtained from thermal, IMDA reactions of the substrates carrying a Weinreb amide or ester conjugated dienophile, and the endo adducts **149c-d** were obtained from Lewis acid-catalyzed reactions of the substrates with a formyl group (Scheme 25).[121]

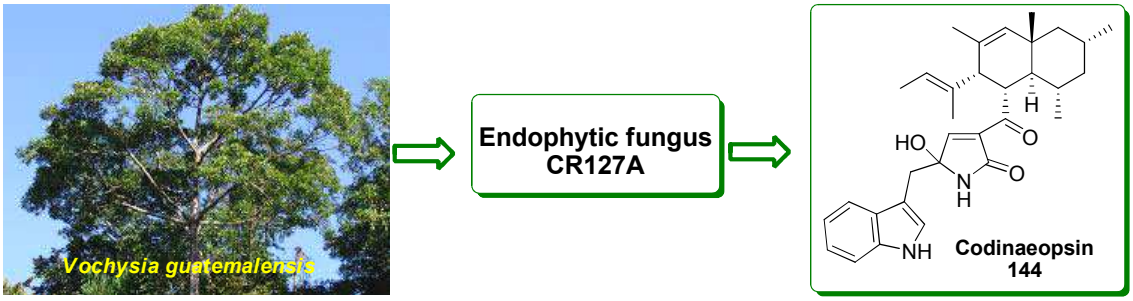
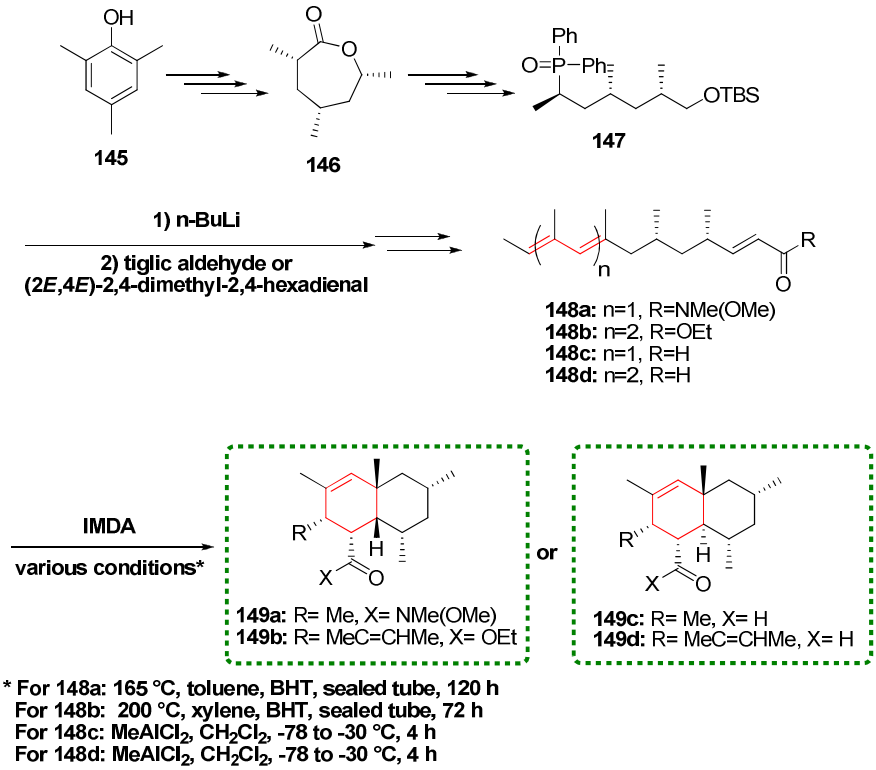


Figure 6



Scheme 25

3.4. Synthesis of Isopalhinine A core

Isopalhinine A (**150**), is one of the most complex member of the palhinin family, is a lycopodium alkaloid which was initially isolated from *Palhinhaea cernua*, carrying an extraordinary pentacyclic architecture. (Figure 7). The whole plant of *P. cernua* was initially collected. A

sample of being already air-dried and powdered was then extracted for several times. After being partitioned using common procedure, the alkaloid parts were subjected to column chromatography to afford four fractions. The third fraction was then subjected to further column chromatography on silica gel to give four sub-fractions. When the first fraction further chromatographed on silica gel to afford isopalhinine A **150**.[122] The latter has a C4−C16 linkage resulting in a tricyclo[4.3.1.0]decane (isotwistane) core. In 2014, Sizemore and co-workers presented a synthetic pathway to the isotwistane core **151** using a sequential Morita−Baylis−Hillman/intramolecular Diels−Alder (IMDA) protocol.[123] Employing cyclohexenone **152**, as starting material, eneone **153** was provided (Scheme 35). The IMDA reaction of enone **153** imposing the conditions A (TMSOTf, Et_3N) with subsequent heating in dichlorobenzene has resulted in a mixture of regioisomers containing mainly isotwistane **156** which is not appropriate for the synthesis of palhinine lycopodiums. Thus, in alternative attempt, conditions B (heating enone **153** to 90 °C in DMF mediated by excess TMSCl and Et_3N) was employed to gain the desired IMDA products as diastereomeric isotwistanes **151a** and **151b** in relatively high yield (Scheme 26). This region-selectivity of the IMDA reaction is induced by the conditions used for silyl enol ether **155** formation, imposing a set of conditions obtaining the core of cardionine and alternative conditions producing the desired isotwistane core of isopalhinine.[123]

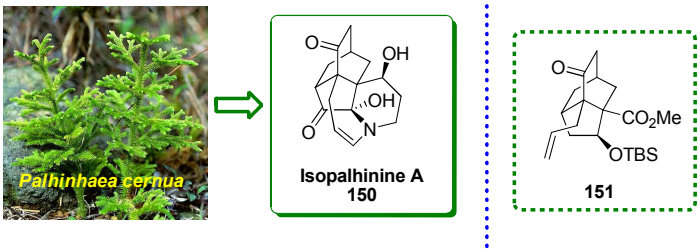
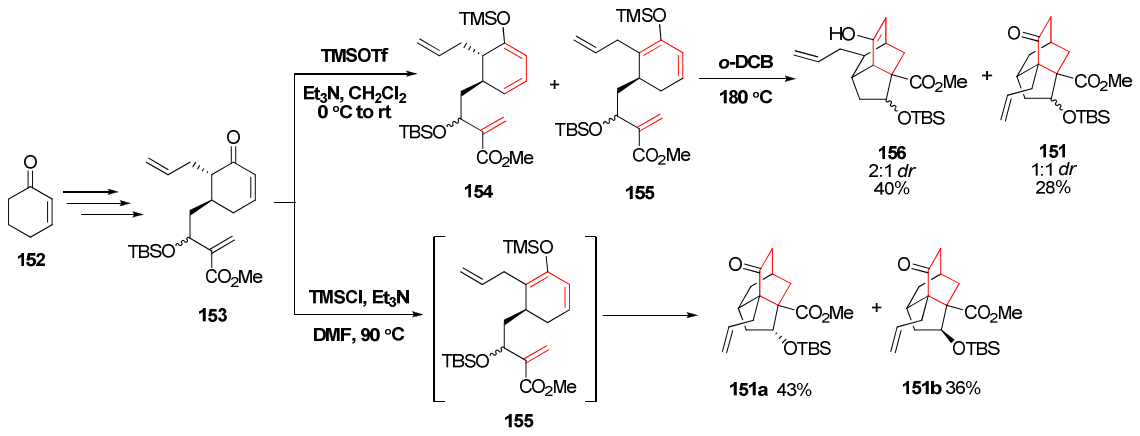


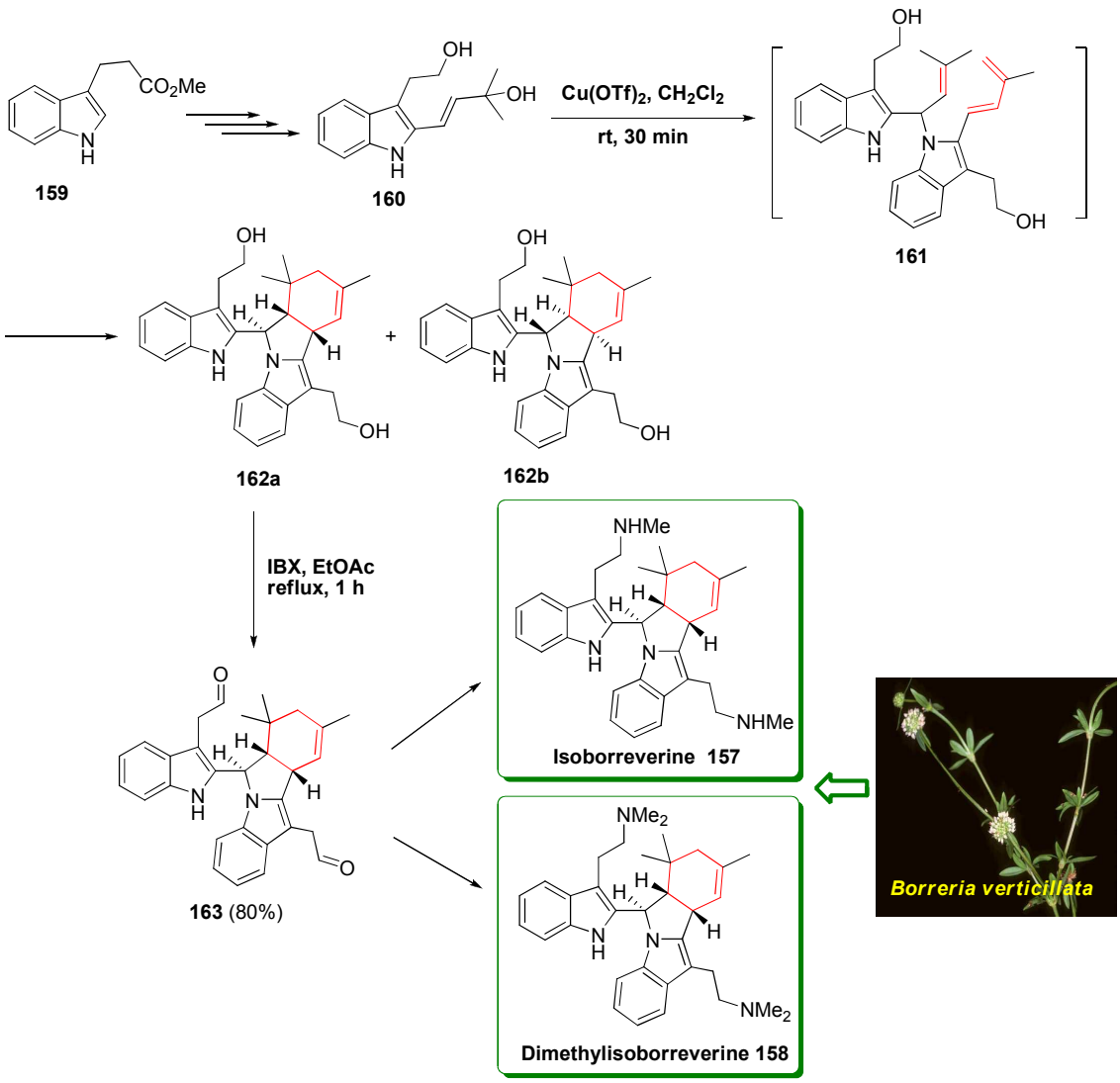
Figure 7



Scheme 26

3.5. Synthesis of Borreverine alkaloids

Borreria verticillata, a very communal tropical plant, is used in outdated pharmacopeia to recuperate cutaneous infections. The Borreverine alkaloids extracted from this plant showed an antimicrobial action in vitro.[124] Isoborreverine **157**, and dimethylisoborreverine **158**, exhibited anti-malarial properties, and were initially isolated from *F. Ambiosis* by Riche and co-workers in 1977.[125] Dethe and co-workers reported a relatively brief total synthesis of isoborreverine **157** and dimethylisoborreverine **158**. The reaction of methyl ester of indole acetic acid **159** with NBS in CCl_4 at ambient temperature afforded the bromination product which then under Stille coupling and subsequent reduction of the ester group in the latter employing, LAH as reductive agent provided the crucial intermediate **160** in good yield. The tertiary alcohol **160** could generate the intermediate **161** followed by an IMDA reaction resulted in isoborreverine analogue **162a** and **162b**. Compound **162a** was then transformed into the desired target natural products **157** and **158** through two steps.[126]

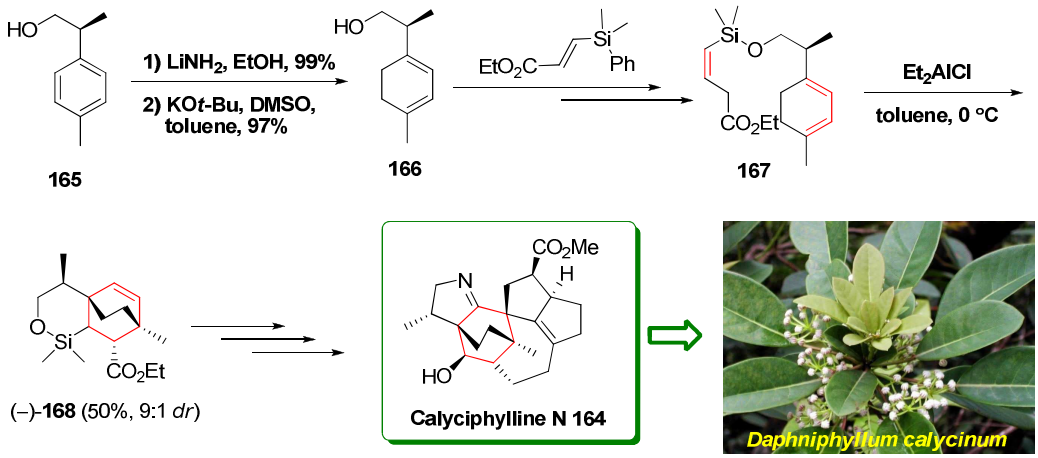


Scheme 27

3.6. *Daphniphyllum* alkaloids synthesis

Recently, several new alkaloids containing atypical framework such as calyciphyllines C-M have been isolated from *Daphniphyllum calycinum*.[127,128] Further work on the obtained extracts has led to the isolation of three new alkaloids, calyciphyllines N-P. The crude alkaloids passed over an amino silica gel column, with subsequent purification using column chromatography, to afford calyciphyllines N (**164**, 0.00031% yield).[129] The total synthesis of the structurally complex *Daphniphyllum* alkaloid (−)-calyciphylline N **164** has been accomplished with a relatively linear sequence of 37 steps starting from known alcohol (−)-**165**. The synthesis was performed in the presence of Et_2AlCl, to accomplish a highly stereo-selective, substrate-

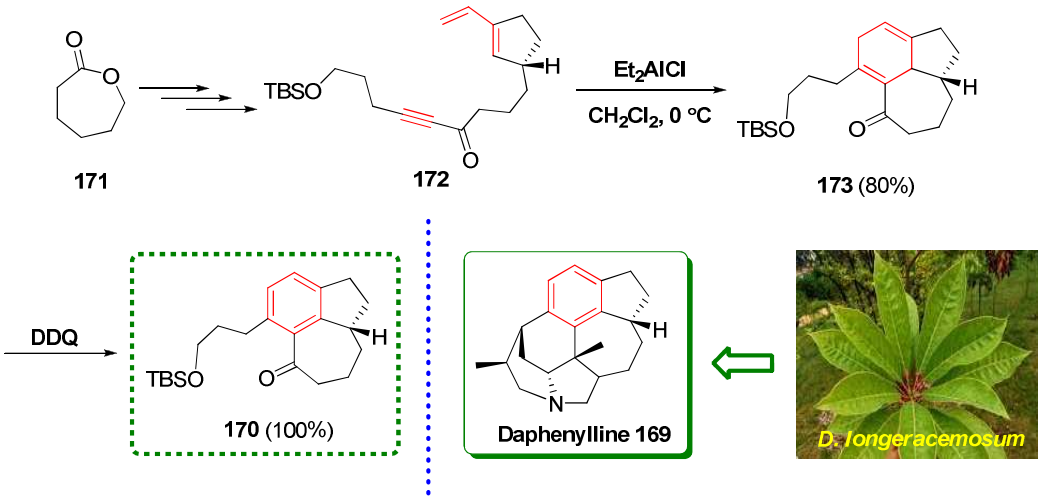
controlled IMDA reaction. Due to the instability of **167** on silica gel, the mixture was further forwarding without column chromatography separation. Whereas the thermal D-A reaction resulted in a mixture of all possible diastereomers as could be determined by ^{1}H NMR spectroscopy, interestingly, Et_2AlCl-catalyzed cyclization afforded a 9:1 mixture of diastereomers in which the desired cycloadduct (−)-**168** was the major compound. Subsequently a transannular enolate alkylation, followed by an efficient sequential Stille carbonylation/Nazarov cyclization was performed. Finally a high-risk diastereo-selective hydrogenation of a fully substituted conjugated diene ester **164** was conducted.[130]



Scheme 28

The *Daphniphyllum* alkaloids, was initially isolated from the genus of *Daphniphyllum* (Daphniphyllaceae), represent a huge and growing group of structurally complex natural products.[131-133] Daphenylline **169**, with an extraordinary rearranged 22-nor-calyciphylline framework, was initially isolated from the fruits of *Daphniphyllum longeracemosum*. This fruit was extracted after work up was subjected to, column silica gel chromatography to give three parts. The third fraction was further subjected to column chromatography to afford daphenylline **169**.[134] An efficient sequential DA/oxidative aromatization strategy for the synthesis of the fused all-carbon DEF tricyclic skeleton **170** of the structurally novel *Daphniphyllum* alkaloid daphenylline **169** has been achieved. A Lewis acid-promoted IMDA reaction with subsequent oxidative aromatization was performed to synthesize the demanding poly-substituted aryl ring as well as the 5/6/7 tricyclic skeleton. Remarkably, Et_2AlCl was found effective to promote the desired D–A reaction, and provided **173** along with a trace amount of oxidative aromatization

product. That was determined by ^{1}H NMR spectroscopy. Worthy to mention that other Lewis acids, examined were found to be ineffective and fruitless (Scheme 29).[135]



Scheme 29

3.7. *Lycopodium lucidulum* alkaloids synthesis

The Lycopodium alkaloids were initially extracted from club moss *Lycopodium lucidulum*. The Lycopodium alkaloids symbolize a structurally complex family of heterocyclic natural products with different structural types. Within the *Lycopodium* family, there is a plentiful subclass of compounds, including lycolucine **174** and structurally appropriate dihydrolycolucine **175** (Fig. 8). Separation of the weak bases of *L. lucidulum* was achieved by exhaustive distribution between a moving phase and stationary phase followed by widespread by TLC and column chromatography over alumina. Finally, two isomeric alkaloids namely lucidine A and lucidine B, were obtained, as well as lycolucine **174** and a dihydrolycolucin **175**.[136,137] An approach to the synthesis of the Lycopodium alkaloid dihydrolycolucine **175** has been studied. Appropriate synthetic pathways were achieved based on *N*-acylpyridinium salt **176** chemistry to synthesize the target fragments **179** that could finally meet the natural product. Key and crucial reactions involve IMDA cycloadditions and retro-Mannich ring-openings to form both the AB and the EF ring segments. The ring C precursor **183** was synthesized *via* pyridine substitution along with directed lithiation chemistry. Subsequent Suzuki cross-coupling of rings C and EF resulted in the CEF ring segment. Notably, preliminary attempts for the closure of the seven-membered D ring were unproductive (Scheme 30).[138]

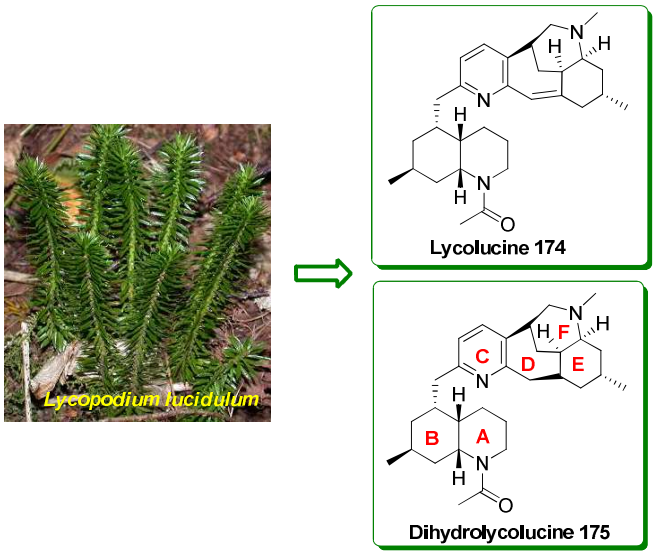
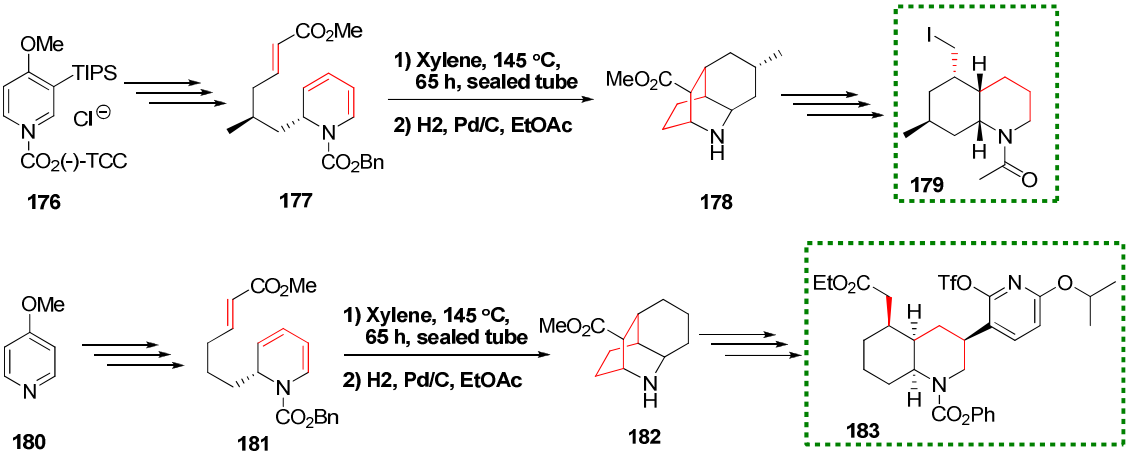


Figure 8

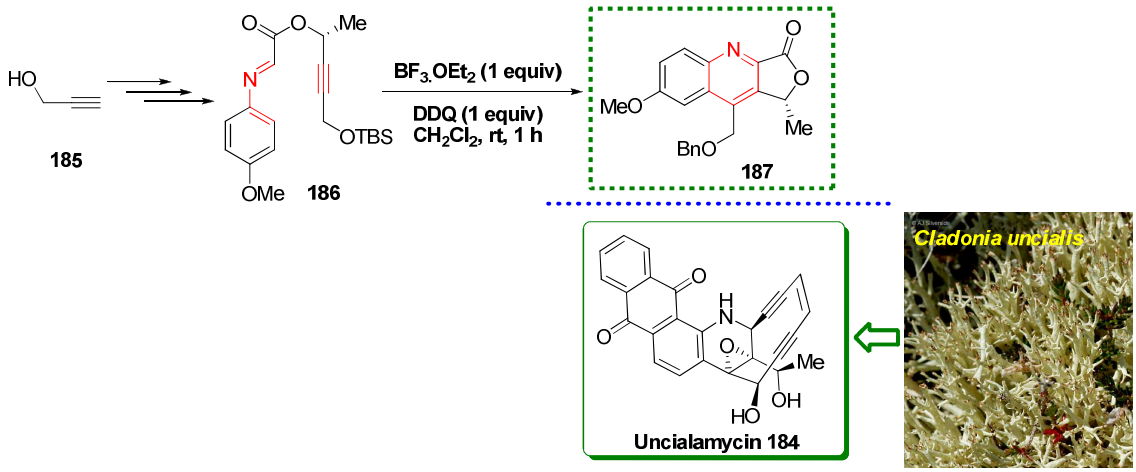


Scheme 30

3.8. Synthesis of Uncialamycin core

In 2005, Davies, and co-workers revealed the structure of uncialamycin **184**, a new "enediyne" natural product which was isolated from an unknown streptomycete obtained from the surface of a lichen *Cladonia uncialis*.[139] Imino IMDA reaction permits a fast access to polysubstituted quinolines in a facile and direct way. By using this procedure the chiral quinoline motif of the uncialamycin can be prepared. Desrat and co-workers discovered that $BF_3.OEt_2$ in the presence of DDQ can promote intramolecular sequential Povarov reaction[140]/oxidative aromatization providing substituted quinolones **187**. The dienophile used, could be either an alkene or an alkyne without the appreciable effect on the yield of cyclization. However, only one equiv of

DDQ is enough in the case of the cycloaddition reaction with the alkynes while two equiv for the reaction with alkenes is necessary. In the absence of DDQ, the cycloaddition reaction still takes place, but the obtained quinoline is in the mixture which an amine resulted from a hydrogen atom transfer from the dihydro- or tetrahydroquinoline to the starting imine **186**. These reaction conditions were employed to synthesize the chiral quinoline motif **187** of the enediyne uncialamycin **184**. The C26 stereogenic center of the uncialamycin was set at the start of the synthesis from a well-established enantio-selective reduction of α-alkyne ketone.[141]



Scheme 31

4. Summary

Diels-Alder (DA) reaction is known as a symbol of the powerful [4+2] cycloaddition reactions in organic synthesis. Intramolecular DA reactions (IMDA) are also well-established and frequently used as a versatile methodology in organic synthesis and also found several applications in the total synthesis of natural products. IMDA plays an important role in the total synthesis of natural products since it forms a 6-membered ring often found in many natural products. This reaction permits the construction of polycyclic molecules that can also include a heterocycle. Furthermore, the obtained products are often enantio or diastereo rich compounds which confirm the weight of this reaction in the asymmetric synthesis. A variety of catalysts promote IMDA reaction in which $BF_3.OEt_2$ is the most used one.

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