This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. This Accepted Manuscript will be replaced by the edited, formatted and paginated article as soon as this is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Recent Applications of Intramolecular Diels-Alder Reaction in Total Synthesis of Natural Products

Majid M. Heravi,* Vaezeh Fathi Vavsari

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

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Abstract

Diels-Alder (D-A) reaction undoubtedly is the most powerful [4+2] cycloaddition reaction in organic synthesis. It has been always considered as a model and symbol of cycloaddition 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 .......................................................................................................................................................... 2
2. Terpenoids ............................................................................................................................................................ 3
   2.1. Sesquiterpenoids .............................................................................................................................................. 4
       2.1.1. Total synthesis of ent-ledol .................................................................................................................. 4
       2.1.2. Total synthesis of khusiol ................................................................................................................... 5
       2.1.3. Synthesis of (−)-presilphiperfolan-1-ol and (−)-9-epi-presilphiperfolan-1-ol ............................................ 6
       2.1.4. Synthesis of 3,5,5,7-Sesquiterpenoids echinopine A and B ................................................................. 8
   2.2. Diterpenoids ....................................................................................................................................................... 9
1. Introduction
The thermal 1,4-cycloaddition of a double/triple bond to a conjugated diene is recognized as Diels-Alder (D-A) reaction.\textsuperscript{1-3} Commonly, Diels-Alder adducts are employed to create synthons, often, exceptionally advantaged for being used in the synthesis of complex targets.\textsuperscript{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.\textsuperscript{7-13} Significantly, the D-A reaction can be conducted in asymmetric fashion (ADA reaction) with high stereoselectivity due to proceeding via concreteness manner.\textsuperscript{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.\textsuperscript{22-24} Due to resourcefulness and exceptional privileged nature of IMDA

2.2.1. Total Synthesis of (-)-Scabronines A and G, and (-)-Episcabronine A ....................................................... 9
2.2.2. Synthesis of (±)-atisine and (±)-isoazitine ................................................................................................ 11
2.2.3. Synthesis of Maoecrystal V core .............................................................................................................. 12
2.2.4. Total synthesis of Caribenol A ................................................................................................................. 15
2.2.5. Total synthesis of Vinigrol ....................................................................................................................... 16
2.2.6. Synthesis of Salvinorin A core ................................................................................................................ 17
2.2.7. Total synthesis of Taxanes ........................................................................................................................ 18
2.3. Meroterpenoids ................................................................................................................................................ 19
2.3.1. Synthesis of (-)-Isoglaziovianol ................................................................................................................ 19
2.3.2. Synthesis of Andibenin B core ................................................................................................................. 20
3. Alkaloids............................................................................................................................................................. 22
3.1. Total Synthesis of (-)-Himandrine ................................................................................................................... 23
3.2. Total Synthesis of (+)- and (−)-Fusarisetin A .................................................................................................. 25
3.3. Synthesis of the Decalin core of Codinaeopsin ........................................................................................... 28
3.4. Synthesis of Isopalhinine A core ...................................................................................................................... 29
3.5. Synthesis of Borreverine alkaloids ................................................................................................................... 31
3.6. \textit{Daphniphyllum} alkaloids synthesis ........................................................................................................... 32
3.7. \textit{Lycopodium lucidulum} alkaloids synthesis ............................................................................................... 34
3.8. Synthesis of Uncialamycin core ....................................................................................................................... 35
4. Summary ................................................................................................................................................................. 36
5. Acknowledgment ..................................................................................................................................................... 36
6. References ............................................................................................................................................................... 37
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.\textsuperscript{25-27} In fact, due to the high degree of chemo-, regio- and diastereo-selectivity, attained from this reaction,\textsuperscript{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\textsuperscript{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\textsuperscript{11,34-36}. Due to our interest in the applications of name reactions in organic synthesis,\textsuperscript{37-41} total synthesis of natural products\textsuperscript{42-47} and asymmetric synthesis,\textsuperscript{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.\textsuperscript{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.\textsuperscript{51}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Taxol.png}
\caption{Taxol (1) a diterpene}
\end{figure}

2.1. Sesquiterpenoid

2.1.1. Total synthesis of \textit{ent}-ledol

Ledol 2 is a toxic sesquiterpenoid isolated from \textit{Rhododendron tomentosum} (\textit{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.\textsuperscript{52,53} \textit{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.

Kündig and co-workers reported the total synthesis of ent-ledol 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$_2$Cl$_2$ 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. These kinds of Ru-catalysis were previously employed in IMDA reactions of enals with various dienes.

**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.
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. 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. Notably, this reaction was improved by Banwell group for the total synthesis of sesquiterpenoid khusiol 9 which is illustrated in Scheme 2.

![Scheme 2: Total synthesis of Khusiol](image)

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 isoprenoldervied carbamate 18. After several reaction steps, the provided \(\text{gem}\)-dimethyl acyclopentene 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 \(\alpha\)-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).\(^{63}\)
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. Its total synthesis was reported by Peixoto and co-workers. 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). Spectroscopic data of tricycle 34 were compared to those of the reported previously 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$_2$O (7:3) provided scabronine A 36 as a colorless amorphous solid. Scabronine G 35 was purified likewise to scabronine A. They were traditionally used for the reduction of Alzheimer, Parkinson, and Huntington disease symptoms. 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.  

Figure 2
2.2.2. Synthesis of (±)-atisine and (±)-isoazitine

The plant *Aconitum heterophylhum* (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.  

Atisine 44 and isoazitine 45 (Scheme 6) are two members of atisine-type C\textsubscript{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 \( \text{ortho} \)-quinone was submitted to thermal activation (150 °C) to furnish 51 which is a pentacyclic compound as a single isomer in good yield. The form of \( \text{endo} \) 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).

![Scheme 6](image)

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 \( \text{Isodon eriocalyx} \), 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. 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 \textit{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). Dong and his group applied the Nicolaou’s pathway for the synthesis of highly functionalized tetracyclic lactone 63 and 64 (Scheme 8). In another work, an effective and stereo-selective pathway was employed for the synthesis of tricyclic core structure of maoecrystal V from a simple aromatic precursor. A tandem oxidative dearomatization of suitably appended \textit{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). 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).

![Figure 3: *Isodon eriocalyx* and Maoecrystal V](image)
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.\(^3\) The first total synthesis of caribenol A (77) was performed and revealed in 2010.\(^4\) 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.\(^5\) 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 \(n\) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{88}
2.2.6. Synthesis of Salvinorin A core

Neoclerodane diterpenes, such as salvinorin A (Fig. 4), show fascinating biological activities. Salvinorin A is the first isolated and identified diterpene hallucinogen, isolated from *Salvia divinorum* (Labiatae). For isolation, dried leaves of *Salvia divinorum*, 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 as colorless crystals. Applying a highly diastereoselective acrylate IMDA cycloaddition as the crucial step, a relatively short pathway starting from 3-furaldehyde reaching to a bicyclic framework 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 was found, fruitful. For this purpose, 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 was found to be the major product. The relative configurations of four possible diastereomers were characterized by NOESY experiments (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 BF₃·OEt₂ 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 tricyclic system 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.\(^3\)

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. Isoglaziovianol 98 synthesis was started by Tsuji–Trost asymmetric alkylation 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 happens 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).

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. 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 toluene via Diels–Alder cycloaddition. The yield of isolated product of this reaction was high. The allylic alcohol 108, gives 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](image)

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 \( \text{113} \), 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 (\( \cdot \))-Himandrine

The galbulimima alkaloid (\( \cdot \))-himandrine (\( \text{114} \)) is a topologically interesting substance. It is initially isolated from the bark of \( \text{Galbulimima belgraveana} \), 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, himandravin, himgravine, himbosine, himandrine.\(^{104, 105}\) Movassaghi and co-worker performed and reported the total synthesis of (\( \cdot \))-himandrine \( \text{114} \) 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 \( \text{trans} \)-decalin \( \text{117} \) bearing tricycle (\( \cdot \))-\( \text{118} \) in an enantiomerically pure form. Solution of tetraenal (\( \cdot \))-\( \text{116} \) at 95 °C gave the desired \( \text{trans} \)-decalin aldehyde (\( \cdot \))-\( \text{117} \) as the major endo Diels-Alder product (75%, \( \text{dr} = 5:1 \)). The reaction of aldehyde (\( \cdot \) )-\( \text{117} \) with titanium tetrachloride gave the corresponding Mukaiyama aldol product,\(^{107}\) which upon treatment with Martin sulfurane\(^{108}\) gave the oxygen and acid sensitive enone (\( \cdot \))-\( \text{118} \) 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 \( \text{114} \) in Scheme 17) with whole.
diastereoselectivity and thriving accomplishment of this biogenetically motivated oxidative spirocyclization in converting $\text{118}$ to $\text{(-)-114}$.\textsuperscript{106} Upon oxidative cyclization of dienic sulfonamides $\text{119}$ in the presence of iodobenzene diacetate in TFA, followed by a tandem IMDA reaction, desymmetrization of a “locally symmetrical” dienone $\text{120}$ (Scheme 18) with good levels of diastereoselectivity is achieved, resulting in precious synthetic intermediates for the himandrine alkaloids (Scheme 19).\textsuperscript{109,110}

![Scheme 17](image)

Scheme 17

![Scheme 18](image)

Scheme 18: Model tandem phenolic oxidative amidation-IMDA reaction giving the framework of himandrine
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. BF₃.OEt₂ 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 Et₂AlCl-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**

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](image_url)
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 alkoxyaminial 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.\(^\text{120}\)

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](image)

**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. 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. Employing cyclohexenone 152, as starting material, enone 153 was provided (Scheme 35). The IMDA reaction of enone 153 imposing the conditions A (TMSOTf, Et3N) 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 Et3N) 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
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 CCl₄ 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.\(^{126}\)
3.6. *Daphniphyllum* alkaloids synthesis

Recently, several new alkaloids containing atypical framework such as calyciphyllines C-M have been isolated from *Daphniphyllum calycinum*. 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). 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 Et2AlCl, 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$_2$AlCl-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.$^{130}$

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$_2$AlCl 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).\textsuperscript{135}

![Scheme 29](image)

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 \textsuperscript{174} and structurally appropriate dihydrolycolucine \textsuperscript{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 \textsuperscript{174} and a dihydrolycolucin \textsuperscript{175}.\textsuperscript{136,137} An approach to the synthesis of the Lycopodium alkaloid dihydrolycolucine \textsuperscript{175} has been studied. Appropriate synthetic pathways were achieved based on *N*-acylpyridinium salt \textsuperscript{176} chemistry to synthesize the target fragments \textsuperscript{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 \textsuperscript{183} was synthesized \textit{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).\textsuperscript{138}
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 streptomyetc obtained from the surface of a lichen Cladonia uncialis. 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/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](image)

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.

5. Acknowledgment

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

54 A. Judžentienė, J. Būdienė, A. Misiūnas and R. Butkienė, *chemija*, 2012, **23**.


140 V. V. Kouznetsov, *Tetrahedron*, 2009, **65**, 2721-2750.

Majid M. Heravi was born in 1952 in Mashhad, Iran. He received his B.Sc. degree from the National University of Iran in 1975 and his M.Sc. and Ph.D. degrees from Salford University England in 1977 and 1980. He completed his doctoral thesis under supervision of late Jim Clarck in Salford University. He started his career as a research fellow in Daroupakksh (a pharmaceutical company) in 1981 Tehran, Iran and joined as an assistant professor to Ferdowsi University of Mashhad Iran. In 1999 he moved to Alzahra University Tehran, Iran as professor of chemistry where he is still working in. He has previously been a visiting professor at UC Riverside, California, USA and Hamburg University, Hamurg, Germany. His research interests focus on heterocyclic chemistry, catalysis and organic methodology.

Vaezeh Fathi Vavsari was born in 1983 in Sari, Iran. She received her B.Sc. degree in Applied Chemistry from Ferdowsi University of Mashhad, Iran (2009) and her MSc. degree in Organic Chemistry at Khaje Nasir Toosi University of Technology, Tehran, Iran (2013) under the supervision of Dr. Saeed Balalaie. She is currently working towards her PhD. in Organic chemistry at Alzahra University under the supervision of Dr. Ghodsi Mohammadi Ziarani. Her research field is organic synthesis by the using of amino acids in the presence of nanostructure silicas as catalysts.