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Masked *o*-benzoquinone strategy in organic synthesis: Short and efficient construction of *cis*-decalins and linear triquinanes from 2-methoxyphenols*

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Abstract: The inter- and intramolecular Diels–Alder reactions of masked *o*-benzoquinones generated in situ from the oxidation of easily accessible 2-methoxyphenols with diacetoxyiodobenzene or bis(trifluoroacetoxy)iodobenzene provided cycloadducts in excellent regio- and stereoselectivity and good yields. A general approach to the synthesis of highly substituted *cis*-decalins and triquinanes with complete stereocontrol from the cycloadducts has been developed. The applicability of our methodology is demonstrated by the total syntheses of several natural products.

Keywords: Diels–Alder reactions; *o*-benzoquinones; *cis*-decalins; triquinanes; total synthesis.

INTRODUCTION

Masked *o*-benzoquinones (MOBs) [1] are a synthetically useful class of cyclohexa-2,4-dienone derivatives that can serve in the rapid elaboration of complex structural motifs. In contrast to their counterparts, masked *p*-benzoquinones (MPBs) derived from *p*-benzoquinones, MOBs are a relatively underutilized class of compounds mainly because of self-dimerization [2] and lack of efficient methods for the preparation of MOBs (Fig. 1). By virtue of their structure, MOBs can behave both as a diene and a dienophile in the Diels–Alder reaction to produce the corresponding dimers. The rate laws for the competing self-dimerization and the desired Diels–Alder reaction can be represented by eqs. 1–3. As from eq. 3, the ratio of the required Diels–Alder reaction with external dienophile to rate of dimerization of MOB is directly proportional to [dienophile] and inversely to [MOB]. To suppress the undesired dimerization event, [MOB] in the reaction mixture should be reduced. In this direction, our laboratory has employed a high dilution technique, and a syringe pump was used to maintain an appropriate concentration of transiently generated MOB all through the course of the reaction. The MOBs were trapped by various dienophiles through the Diels–Alder reactions. Over the years, we have been working on the chemistry of these linearly conjugated cyclohexadienones, and their synthetic potential has been exploited. We have developed new synthetic methodologies especially based on the dual Diels–Alder reactivity of these synthons. It is worthwhile mentioning here that the first example [3] of MOB was reported by Deslongchamps et al., who used Diels–Alder reaction of an MOB as one of the key steps in their elegant total synthesis of (+)-ryanodol [4].

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$$\text{Rate}_{DI} = k_{DI}[MOB]^2 \tag{1}$$

$$\text{Rate}_{DA} = k_{DA}[MOB][\text{Dienophile}] \tag{2}$$

$$\frac{\text{Rate}_{DA}}{\text{Rate}_{DI}} = \frac{k_{DA}}{k_{DI}} \times \frac{[\text{Dienophile}]}{[MOB]} \tag{3}$$

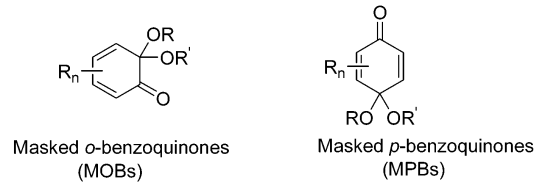
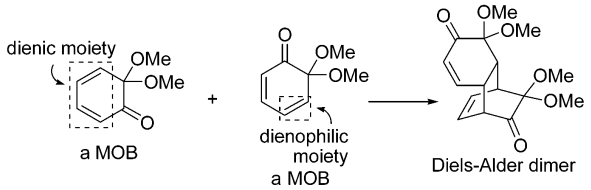


Fig. 1 General structures of MOBs and MPBs.

We describe here the MOB methodology for rapid and efficient construction of various ring skeleta, especially *cis*-decalins and linear triquinanes, and their synthetic applications toward natural products that took place in our laboratory based on these two skeleta (Scheme 1).



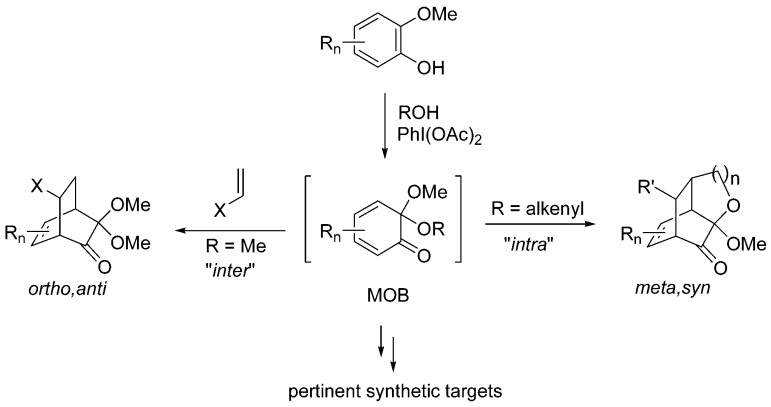
Scheme 1 Dimerization of a MOB.

DIELS–ALDER REACTIONS

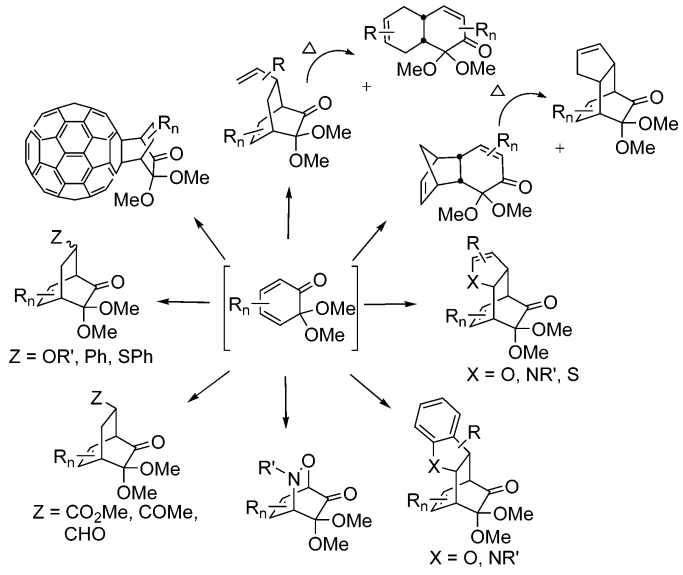
The Diels–Alder reaction enjoyed widespread use in organic synthesis owing to its ability of forming two bonds in a cyclohexenyl system and simultaneous creation of up to four stereogenic centers in a highly stereoselective and predictable manner [5–7]. The MOBs, generated in situ by the oxidation of the corresponding 2-methoxyphenols in MeOH, undergo rather facile intermolecular Diels–Alder reaction when trapped with an external dienophile to furnish bicyclo[2.2.2]oct-5-en-2-ones with complete *ortho*,*anti*-selectivity [2,8a–c]. When the oxidation of 2-methoxyphenols was carried out in the presence of an allylic or a homoallylic alcohol, the resultant MOBs undergo intramolecular Diels–Alder (IMDA) reactions via a tandem oxidative acetalization process to provide oxacyclic compounds with complete *meta,syn*-selectivity [9]. In the initial stages of our studies, the oxidations of 2-methoxyphenols were carried out with thallium trinitrate. Later, the advent of hypervalent iodine reagents [10] for the oxidations prompted us to use oxidants such as diacetoxyiodobenzene (DAIB) and bis(trifluoroacetoxy)iodobenzene (BTIB) for the generation of MOBs.

A wide variety of dienophiles were used in the intermolecular Diels–Alder reactions with MOBs to provide the corresponding bicyclo[2.2.2]octenones with high regio- and stereoselectivity (Scheme 2). The electron-deficient dienophiles such as methyl acrylate [2], methyl vinyl ketone [2], methyl methacrylate [2], acrolein [11], methacrolein [11], and even [60]fullerene [12] participated in the Diels–Alder reactions with in situ generated MOBs to afford the corresponding cycloadducts in high yields (Scheme 3). The electron-rich dienophiles such as benzyl vinyl ether, dihydrofuran, phenyl vinyl sulfide, and conjugative dienophile styrene [8a–c] underwent Diels–Alder cycloaddition with MOBs to furnish highly functionalized bicyclo[2.2.2]octenones in high yields (Scheme 3). Despite the fact that the MOBs are electron-deficient dienes, they readily underwent both normal and inverse electron-de-

mand Diels–Alder reactions. The high reactivity of MOBs compelled the five-membered heteroaromatics such as furans [13], pyrroles [14], and thiophenes [15] to act as dienophiles in the Diels–Alder reactions (Scheme 3). The hetero- Diels–Alder reactions of transiently generated nitroso compounds and MOBs [16] proceeded efficiently to form bicyclo[2.2.2]octenones embedded with heteroatoms (Scheme 3) that are potential precursors for the synthesis of naturally occurring alkaloids from simple 2-methoxyphenols.



Scheme 2 Inter- and intramolecular Diels–Alder reactions of MOB.

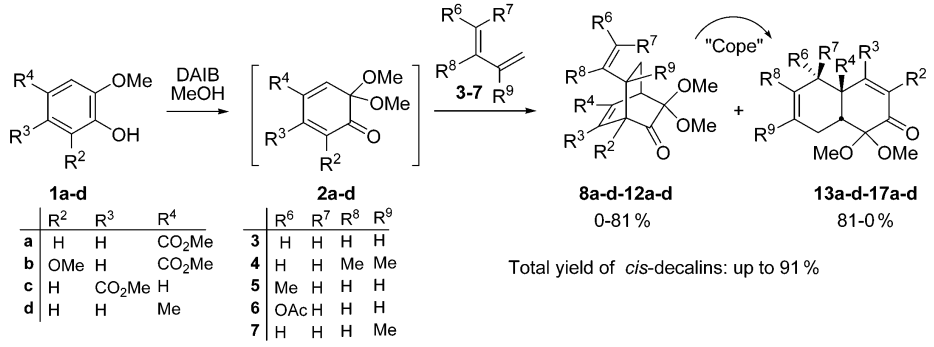


Scheme 3 MOB as a versatile diene in DA reactions.

The IMDA reaction is a versatile tool for the rapid construction of polycyclic ring systems with a high degree of structural and stereochemical complexity. We have found that the oxidation of 2-methoxyphenols in the presence of allylic/homoallylic alcohol underwent a tandem oxidative acetalization-intramolecular Diels–Alder cycloaddition to produce highly functionalized 4-oxatricyclo[4.3.1.$0^{3,8}$]decenones and 4-oxatricyclo[4.4.1.$0^{3,8}$]undecenones in high yields [9]. When acrylic acids were tethered to 2,4-cyclohexadienone moiety of MOBs, the corresponding IMDA adducts were obtained in moderate yields [9].

SYNTHESIS OF *CIS*-DECALINS

A large variety of natural products of biological activities contain decalin skeleton as an integral part of their structures [17–19]. Owing to their importance in nature, synthesis of decalins has become a major focal point of synthetic chemistry. Consequently, a flurry of reports appeared recently [20,21,22b]. We have identified the Diels–Alder protocol of MOBs as an efficient method for the synthesis of stereochemically rich and multifunctional decalins.



	R^2	R^3	R^4
a	H	H	CO_2Me
b	OMe	H	CO_2Me
c	H	CO_2Me	H
d	H	H	Me

	R^6	R^7	R^8	R^9
3	H	H	H	H
4	H	H	Me	Me
5	Me	H	H	H
6	OAc	H	H	H
7	H	H	H	Me

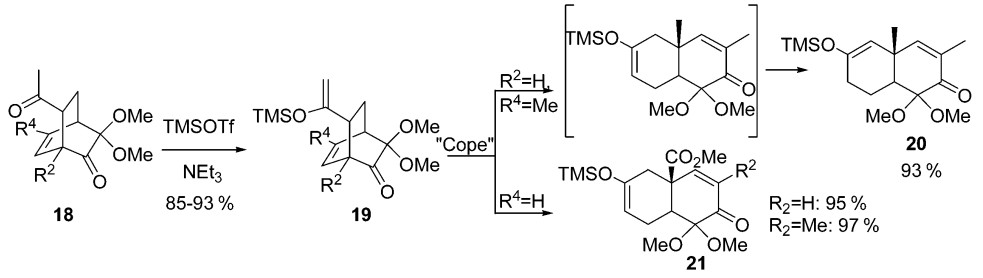
Scheme 4 Stereo- and regioselective intermolecular DA reactions of MOBs with 1,3-butadienes for the synthesis of *cis*-decalins.

Diels–Alder reactions with 1,3-butadienes

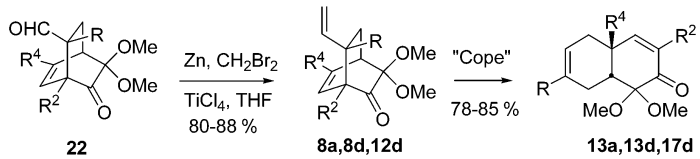
The MOBs, being dual role players, participated in the intermolecular Diels–Alder reactions with acyclic 1,3-dienes to give bicyclo[2.2.2]octenones and *cis*-decalins [20]. 2-Methoxyphenols such as **1a–d** when oxidized in the presence of acyclic dienes **3–7** resulted in the formation of vinylbicyclo[2.2.2]octenones **8–12** and *cis*-decalins **13–17**; the formers underwent Cope rearrangements to afford the corresponding *cis*-decalins, thus, providing a simple and efficient method for the synthesis of the *cis*-decalins from commercially available 2-methoxyphenols in excellent yields (Scheme 4). The extent of dienophilicity or the diene character apparently depends on the nature and/or position of the substituents present on the MOBs and also on the structures of the added acyclic dienes.

Cope rearrangement of 1,5-dienes derived from cycloadducts of MOBs

Bicyclo[2.2.2]octenones **18** prepared by the Diels–Alder reactions of methyl vinyl ketone, acrolein, and methacrolein with MOBs generated in situ by the oxidation of 2-methoxyphenols with DAIB were converted to silyl enol ethers **19**, which upon heating in mesitylene at 220 °C underwent Cope rearrangement smoothly to provide *cis*-decalins **20** or **21** in excellent yields [11] (Scheme 5). In a similar vein, another set of vinylbicyclo[2.2.2]octenones **8a**, **8d**, and **12d** were prepared from formylbicyclo[2.2.2]octenones **22** under Lambardo conditions (Scheme 6). Even these 1,5-dienes could undergo Cope rearrangement smoothly at 250 °C to provide *cis*-decalins **13a**, **13d**, and **17d**, respectively, in high yields [11].



Scheme 5 Silyloxy-1,5-dienes as substrates for Cope rearrangement for synthesis of *cis*-decalins.

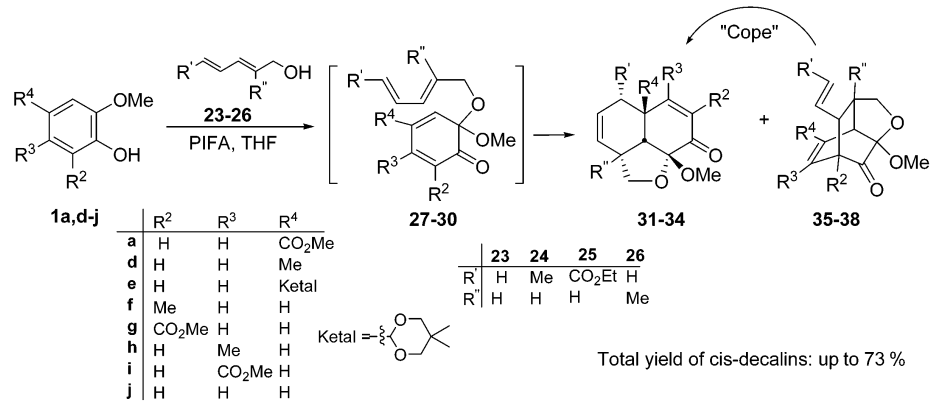


Scheme 6 Selective olefination followed by Cope rearrangement for synthesis of *cis*-decalins.

Thus, an efficient and stereocontrolled four-step preparation of highly oxygenated *cis*-decalins is developed employing bicyclo[2.2.2]octenones with 2-silyloxy-1,5-diene unit as a substrate for Cope rearrangement for the first time.

IMDA reactions of MOBs of tethered dienes

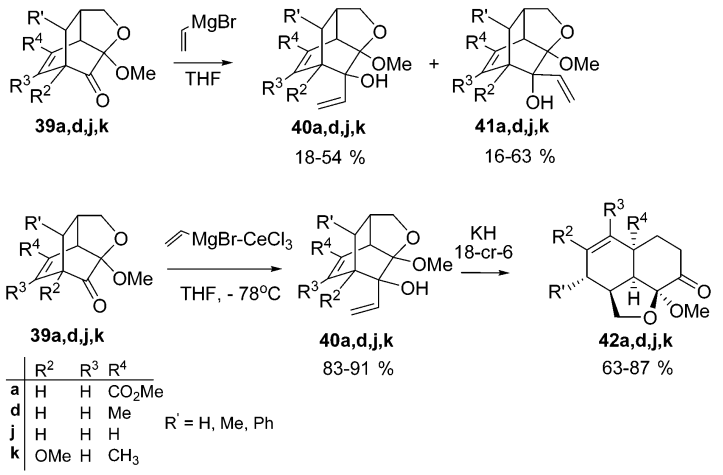
The cyclohexadienone moiety of MOB can either act as a diene or dienophile, and it occurred to us that if the allylic alcohol is replaced with a 2,4-dienol, it might give rise to *cis*-decalins of type **31–34** and/or tricyclic compounds of type **35–38** (Scheme 7) [21]. Accordingly, initial investigations were conducted on the MOB generated in situ from methyl vanillate (**1a**) in the presence of *trans*-penta-2,4-dienol (**23**) using BTIB in THF. At room temperature, the intramolecular cycloaddition underwent smoothly to provide the tricyclic compound **35a** and *cis*-decalin **31a** each in 31 % isolated yields, exhibiting the dual behavior of MOB **27a**, as a diene and a dienophile. Subsequently, this reaction was extended to other 2,4-dienols **24–26**. A wide variety of 2-methoxyphenols **1d–i** bearing electron-donating and electron-withdrawing substituents along with unsubstituted parent 2-methoxyphenol (**1j**) were used as starting materials for the IMDA reactions. The majority of the oxatricyclic compounds obtained from IMDA reactions underwent Cope rearrangement smoothly when heated to 200–250 °C in mesitylene (Scheme 7). To make the whole transformation simple, the crude Diels–Alder reaction mixtures were concentrated using rotavapor after the usual work-up, and the residues were dissolved in mesitylene and heated to 200–250 °C to obtain decalins as sole products in high yields.



Scheme 7 IMDA reactions for the synthesis of *cis*-decalins.

Anionic oxy-Cope rearrangement of *syn*-2-vinylbicyclo[2.2.2]octenols

The broad applicability of anionic oxy-Cope rearrangement has received considerable attention in the syntheses of the polycyclic and medium ring systems present in natural products. Upon treatment with vinylmagnesium bromide, tricyclic β,γ-enones, which were prepared from 2-methoxyphenols via oxidation with DAIB and the IMDA reaction, provided the diastereomeric alcohols **40** and **41** (Scheme 8). However, when vinylmagnesium bromide-$CeCl_3$ was used following Imamoto's protocol [22a], exclusive formation of *syn*-diastereomers **40** was observed (Scheme 8). Treatment of *syn*-diastereomers **40** with KH at appropriate temperatures provided [3,3]sigmatropic rearrangement products *cis*-decalins **42** in good yields (Scheme 8) [22b].

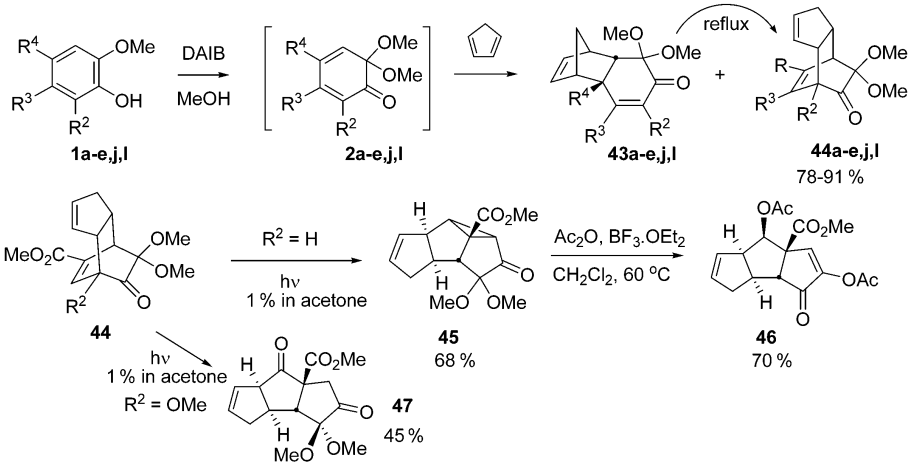


Scheme 8 Grignard addition followed by anionic oxy-Cope rearrangements for the synthesis of *cis*-decalins.

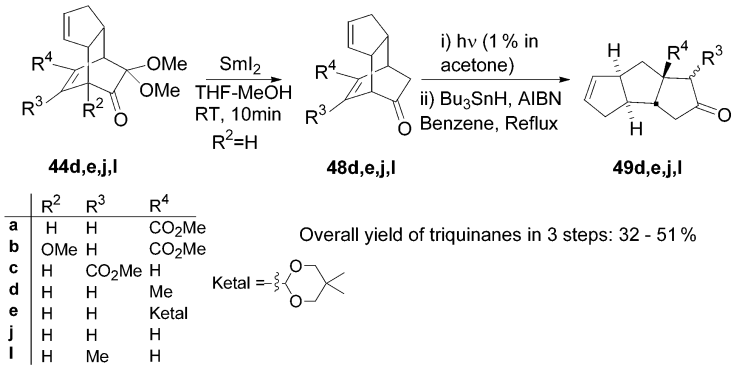
SYNTHESIS OF LINEAR TRIQUINANES

Extensive efforts by synthetic organic chemists during the past two decades toward the synthesis of polyquinane natural products have resulted in the development of several elegant approaches [23]. Recent synthetic efforts in our laboratories directed at the utilization of MOBs resulted in the successful acquisition of linear [24] and angular triquinanes [25], which are pivotal subunits in the construction of several natural products. Accordingly, the cycloadducts **44a** and **44b**, obtained from the

Diels–Alder reactions between the corresponding MOBs and cyclopentadiene, were irradiated in acetone using light of wavelength centered at 300 nm in a Rayonet reactor to furnish the triquinanes **46** and **47**, respectively, in good yields (Scheme 9). Here, R^4 is a methoxycarbonyl that can stabilize the biradical intermediates, thus facilitating the oxa-di-π-methane (ODPM) rearrangements, whereas, in contrast, compounds **44c–f** led to complex mixtures under the same irradiation condition. Thus, SmI_2-mediated reductive removal of the ketal group (which stabilizes the free radical intermediates, and thus increases the possibility of side reactions) furnished demethoxylated compounds **48** (Scheme 10), which, upon irradiation in acetone followed by reductive cleavage of the cyclopropane ring, provided the desired triquinanes **49** in good yields [24].



Scheme 9 Synthesis of linear triquinanes.



	R^2	R^3	R^4
a	H	H	CO_2Me
b	OMe	H	CO_2Me
c	H	CO_2Me	H
d	H	H	Me
e	H	H	Ketal
j	H	H	H
l	H	Me	H

Scheme 10 Transformation of tricyclic compounds **48** into linear triquinanes.

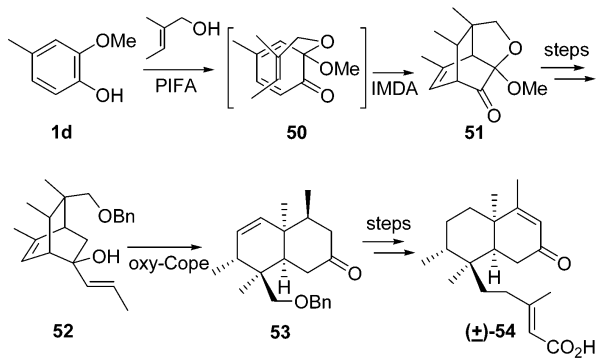
SYNTHETIC APPLICATIONS OF MOBs

The MOB Diels–Alder chemistry is a very valuable method for the synthesis of a wide variety of structurally diverse compounds, and was subsequently employed for the total syntheses of several natural products. This section deals with a number of natural products based on *cis*-decalin skeleta and linear triquinanes, and only the key steps in each synthesis will be described.

Total syntheses of natural products based on *cis*-decalin skeleton

*(±)-(13E)-2-Oxo-5α-cis-17α,20α-cleroda-3,13-dien-15-oic acid, an alleged cis-clerodane diterpenic acid (**54**)*

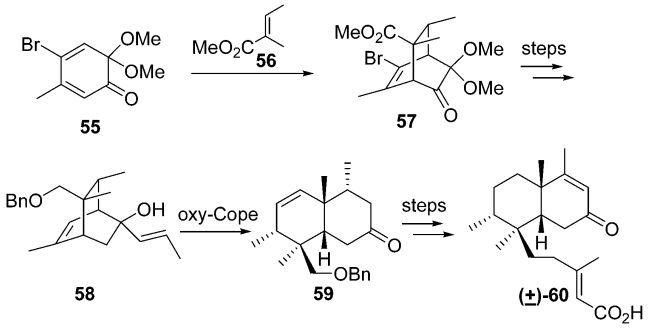
Clerodanes are an important family of diterpenoids [26], some of them possessing interesting biological properties such as antifeedant, antiviral, antitumor, etc. [26b]. A diterpenic acid was isolated from the seed-pods of *Eperua purpurea* Bentham by Avila's group and assigned as (13*E*)-2-oxo-5α-*cis*-17α,20α-cleroda-3,13-dien-15-oic acid [27]. We synthesized this compound using IMDA reactions of an MOB and anionic oxy-Cope rearrangement as the key steps (Scheme 11) [28a]. Thus, the tricyclic β,γ-enone **51** with the desired three methyl groups and four stereogenic centers was obtained via IMDA reaction of MOB **50** and was converted in three steps to compound **52**, which was transformed via anionic oxy-Cope rearrangement into *cis*-decalin **53** having the core structure of the desired natural product. The total synthesis of **54** was then accomplished via sequential transformations. The X-ray diffraction study confirmed the stereochemistry of ethyl ester of **57**. However, the ^{1}H and ^{13}C NMR spectra of synthetic **53** are quite different from those of the natural product.



Scheme 11 Synthesis of a *cis*-clerodane diterpene using IMDA reaction as a key step.

*(±)-cis-Clerodane diterpenic acid (**60**)*

The acid **60** was isolated from methylated petrol extract of *Aristolochia brasiliensis* by Lopes et al. in the form of its methyl ester [29a]. In our design of its total synthesis, the bromo MOB **55** reacted with methyl tiglate (**56**) via IMDA reaction yielded bicyclo[2.2.2]octenone **57**, which was transformed to **58** via a series of steps including debromination, reduction of ester group followed by protection of the thus-formed primary alcohol, the α-transposition of the carbonyl group, and the addition of 1-propenyllithium-$CeCl_3$ to the newly generated carbonyl group following Imamoto's protocol [22a]. The anionic oxy-Cope rearrangement of **58** furnished *cis*-decalin **59**, which provided the natural product **60** whose stereochemistry was confirmed by X-ray diffraction study of its methyl ester (Scheme 12) [29b]. Thus, this approach makes use of readily available starting materials and relies on the intermolecular Diels–Alder reaction of an MOB and anionic oxy-Cope rearrangement of vinylbicyclo[2.2.2]octenol to effectively fix the stereochemistry at all the stereogenic centers.

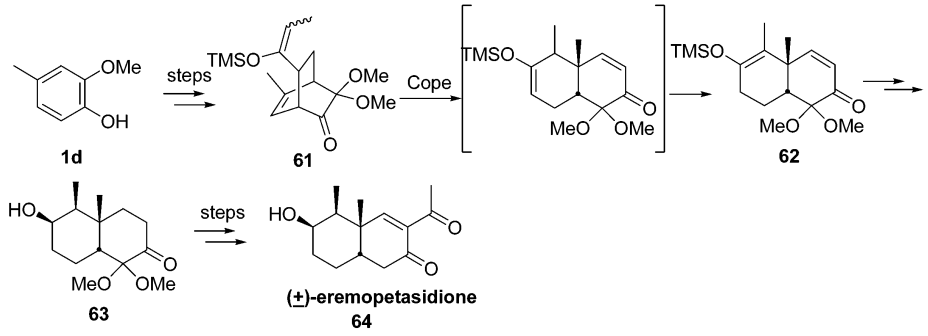


Scheme 12 Synthesis of a *cis*-clerodane diterpene using intermolecular DA reaction as a key step.

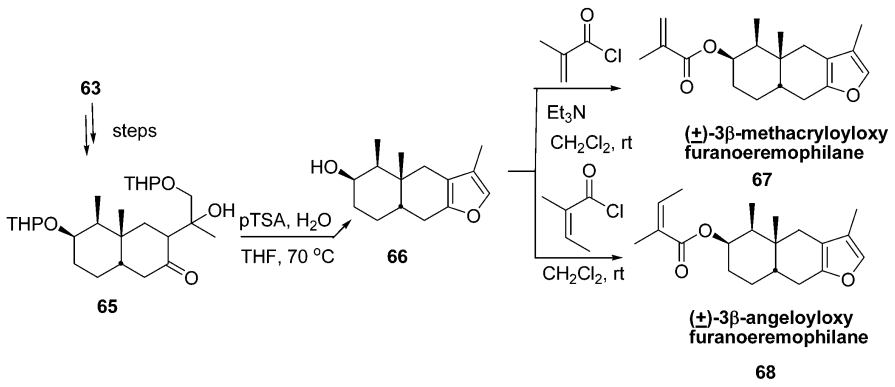
*(±)-Eremopetasidione (**64**), (±)-3β-methacryloyloxyfuranoeremophilane (**67**) and (±)-3β-angeloyloxyfuranoeremophilane (**68**)*

(±)-Eremopetasidione, a norsesquiterpenoid, was isolated [30a] recently from rhizomes of *Petasites japonicus* MAXIM, having interesting medicinal properties [30b]. The total syntheses of the natural products **64**, **67**, and **68** were designed to share the common intermediate **63**.

The regio- and stereocontrolled intermolecular Diels–Alder reaction of the MOB generated from **1d** and ethyl vinyl ketone followed by the transformation of the carbonyl group into the corresponding silyl enol ether provided bicyclo[2.2.2]octenone **61**. Cope rearrangement of this 1,5-diene followed by migration of a double bond under the reaction condition furnished *cis*-decalin **62**, which upon desilylation and reduction of the thus-generated carbonyl group and the conjugated double bond gave **63**. The stereochemical outcome of **63** was assigned from ^{1}H NMR nuclear Overhauser effect (NOE) experiments and was further confirmed by X-ray diffraction studies. Compound **63** led to natural product (±)-eremopetasidion (**64**) after a few simple transformations [31] (Scheme 13). The common intermediate **63** was converted to **65**, which on treatment with acid gave a furan-fused *cis*-decalin **66**. Treating **66** independently with methacryloyl chloride and angeloyl chloride in the presence of Et_3N provided (±)-3β-methacryloyloxyfuranoeremophilane (**67**) and (±)-3β-angeloyloxyfuranoeremophilane (**68**), respectively [36] (Scheme 14).



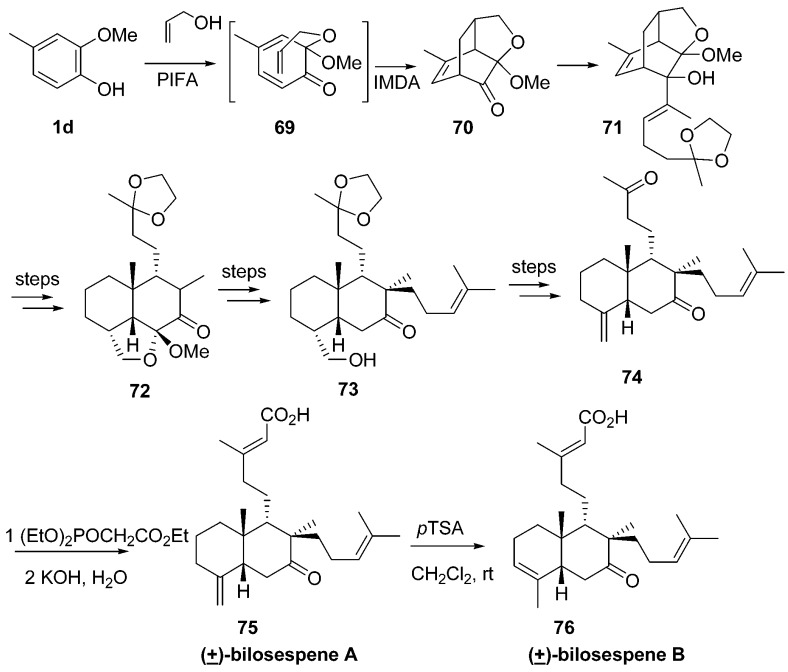
Scheme 13 Synthesis of (±)-eremopetasidione using Cope rearrangement of a silyloxy-1,5-diene as a key step.



Scheme 14 Synthesis of furanoeremophilanes.

*Refuted (±)-bilosespenes A (**75**) and B (**76**)*

Bilosespenes A and B were isolated [33] recently from the Red Sea sponge *Dysidea cinerea* as an unstable and inseparable mixture having cytotoxicity against several cancer cells. The access to tricyclic compound **70** was achieved from creosol (**1d**) and allyl alcohol via the IMDA reaction of MOB **69**. Compound **71**, produced from addition of Imamoto's vinylcerium reagent [22a] to the carbonyl group of **70**, underwent anionic oxy-Cope rearrangement followed by hydrogenation of the double bond providing **72**. α-Alkylation of **72** followed by reductive cleavage of the ketal functionality with SmI_2 furnished **73**. The exocyclic double bond was introduced by taking the advantage of the formed primary alcohol. The carbonyl group in **74**, generated from hydrolysis of the protective ethylene ketal, was converted to (*E*)-α,β-unsaturated acid by the use of Horner–Emmons reaction followed by saponification to provide **75**, which on treatment with *p*-toluenesulfonic acid gave **76** (Scheme 15). The structures of these synthetic acids were elucidated by ^{1}H-^{13}C COSY and ^{1}H NMR NOE experiments. However, the ^{1}H and ^{13}C NMR spectra of synthetic compounds **75** and **76** were quite different from those reported for the natural products (±)-bilosespenes A and B [34].

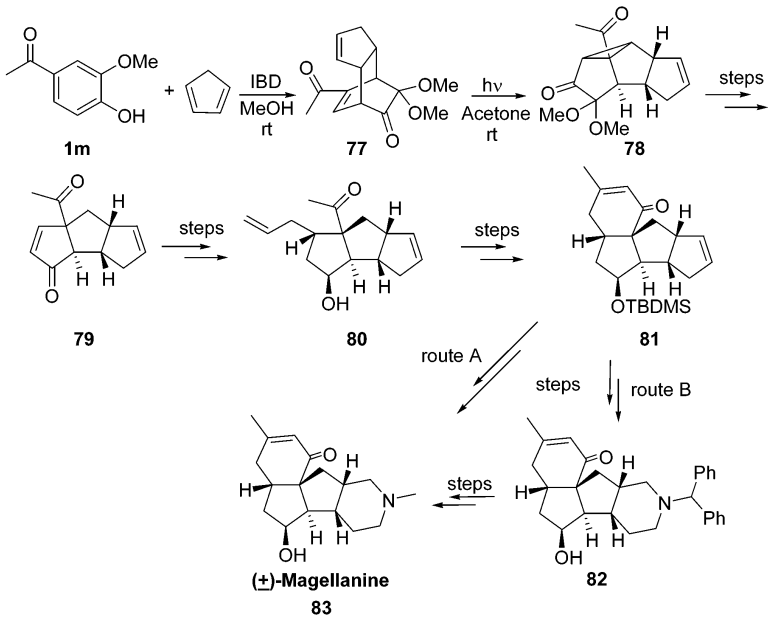


Scheme 15 Synthesis of alleged (±)-bilosespenes A and B.

Total syntheses of natural products based on linear triquinanes

*(±)-Magellanine (**83**)*

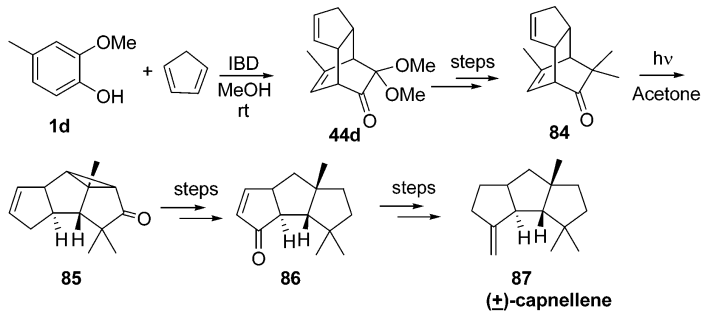
Magellanine, possessing a tetracyclic framework with six contiguous stereogenic centers, was isolated from the club mosses of the genus *Lycopodium* [35], and its structure has been a challenge for synthetic chemists. Triquinane **79**, a key intermediate for our synthesis, was obtained via sequential reactions including the key steps, the intermolecular Diels–Alder reaction of the MOB generated from acetovanillone (**1m**) with cyclopentadiene, photochemical ODPM rearrangement, and reductive cleavage of cyclopropane ring. Diallylcyanocuprate-mediated 1,4-addition onto the enone followed by the chemoselective reduction of diketone generated the desired compound **80**, which was transformed via Ito's method into **81**, a precursor for (±)-magellanine (**83**). The conversion of a cyclopenetene ring in **81** to *N*-methylpiperidine moiety in (±)-magellanine (**83**) was accomplished directly via route A or indirectly via route B (Scheme 16) in which the structure of **82** was determined by X-ray diffraction method [36].



Scheme 16 Synthesis of (±)-magellanine.

*(±)-Capnellene (**87**)*

(–)-$\Delta^{9(12)}$-Capnellene (**87**), produced by a soft coral known as *Capnella imbricate* and demonstrating antitumor and antibacterial activity, was first isolated in 1974 [37]. Our formal synthesis of (±)-capnellene is shown in Scheme 17. The Diels–Alder reaction of cyclopentadiene and the MOB generated in situ from creosol (**1d**) provided cycloadduct (**44d**), which on reductive removal of the ketal functionality and dialkylation at the α-position of the carbonyl group furnished compound **84**. Triplet sensitization of **84** in acetone via ODPM rearrangement gave the tetracyclic compound **85**, which gave a known compound **86** via sequential reactions including the key steps, reductive cleavage of the cyclopropane ring, Wolf–Kishner reduction, and allylic oxidation. Hydrogenation of **86** followed by Wittig reaction afforded (±)-capnellene (**87**) [38].



Scheme 17 Synthesis of (±)-capnellene.

CONCLUSIONS

Here we have demonstrated how MOB chemistry has been developed into a versatile strategy for the preparation of a wide variety of *cis*-decalin and triquinane systems. Their applicability has been extended to the total syntheses of several natural products. Readily available inexpensive starting materi-

als, broad and elegant synthetic methodologies, and elaborated experimental techniques allow their applicability in the synthesis of complex molecular frameworks.

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