

Masked *o*-Benzoquinones in Organic Synthesis

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ABSTRACT

An account of the synthetic utility of masked *o*-benzoquinones is provided. The inter- and intramolecular Diels–Alder reactions of in situ generated masked *o*-benzoquinones produced cycloadducts in excellent selectivities. New synthetic methodologies have been developed for the synthesis of highly substituted ring systems including bicyclo[2.2.2]octenones, oxatricycles, triquinanes, polysubstituted cyclohexanes, and bicyclo[4.2.2]decenones with complete stereocontrol from easily accessible 2-methoxyphenols via the Diels–Alder reaction of masked *o*-benzoquinones. Other reactions of adducts derived from masked *o*-benzoquinones are also described. The efficacy of our methodology is demonstrated by several examples of the total synthesis of natural products.

Introduction

The development of simple methods for the rapid construction of complex molecules with defined stereochemistry from easily accessible starting materials remains an exciting challenge in contemporary organic synthesis. In this context, *o*-benzoquinones and their derivatives sustain vast synthetic potential for the creation of molecular complexity.¹ Simple *o*-benzoquinones are usually unstable, and they undergo notorious reactions in addition to dimerization. On the other hand, *o*-benzoquinones that are protected at one of the carbonyl functionalities (types I–III, Figure 1), which were named as masked *o*-benzoquinones (MOBs) by us,² are relatively stable compared to the corresponding unprotected *o*-benzoquinones.

MOBs, which are linearly conjugated cyclohexadienones, can potentially participate in cycloaddition and nucleophilic addition reactions. The double bonds of the

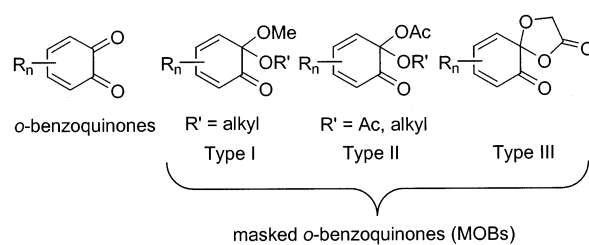
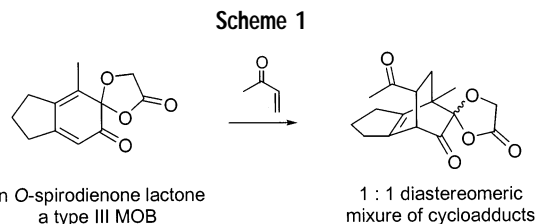


FIGURE 1. Structures of *o*-benzoquinones and masked *o*-benzoquinones.



diene moiety, being positioned between a carbonyl and an acetal functions, are electronically differentiated and can be elaborated regioselectively in various reactions. In addition, the acetal moiety serves as monoprotection for the vicinal carbonyl system. Despite their remarkable synthetic potential, MOBs are relatively underexploited in organic synthesis as compared to their counterparts derived from *p*-benzoquinones.³ This dearth of MOB chemistry may be attributed to their high reactivity, resulting in great propensity toward dimerization. Furthermore, lack of efficient methods for the preparation of MOBs appears to be another main deterrent to their use in organic synthesis. Intrigued by the unexploited synthetic potential of this class of synthons, we have embarked on a research program on “chemistry of masked *o*-benzoquinones” with the main aim of evolving new synthetic methodologies, especially based on the Diels–Alder reactivity of MOBs. It is worth mentioning that Deslongchamps opened the field in 1969 by reporting the first example⁴ (shown in Scheme 1), which led later on the total synthesis of (+)-ryanodol.⁵

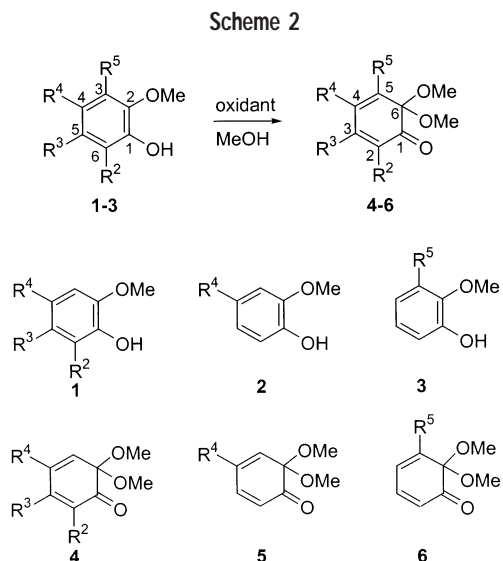
This Account is limited to the chemistry of MOBs of type I where the mask is a genuine acetal functionality. We present herewith the developments of MOB chemistry, the Diels–Alder reactions and their applications in particular, that have taken place in recent years with a focus principally on the advances made in our laboratories, but the contributions of other research groups are also included.

Intermolecular Diels–Alder Reactions

The Diels–Alder reaction appears to be the most widely used protocol to synthesize simple and complex ring systems due to its ability of creating up to four contiguous stereogenic centers in a highly stereoselective and predictable manner in a single laboratory operation. MOBs, by virtue of their structure, can react as either a diene or a dienophile in the Diels–Alder reaction. MOBs 4–6 are most frequently generated by chemical oxidation of

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2-methoxyphenols **1–3** (Scheme 2); these general structures are given on the basis of the substitution pattern to facilitate the discussion throughout this Account. Owing to their advantages over the traditional oxidants, the hypervalent iodine reagents⁶ such as diacetoxyiodobenzene (DAIB) and phenyliodonium(III) bis(trifluoroacetate) (PIFA) are often used. This oxidation is a two-electron process.⁷ Simple MOBs are found to be highly reactive and dimerize rapidly to produce dimers **7** in high yields (Figure 2). The dimerization occurs in a highly site-, regio-, and stereoselective manner via the Diels–Alder reaction. It results from the cycloaddition of a molecule of MOB as the diene and C₄=C₅ double bond of the other as the dienophile. The dimers of MOBs possess ortho-regiochemistry and anti-stereochemistry (the C₃=C₂ bond is adjacent and anti to the C₁ carbonyl group in **7**).

As the dimerization of MOB and the Diels–Alder reaction between MOB and an external dienophile are competitive reactions, a high-dilution technique was employed to prevent/minimize the formation of dimers by generating MOB in situ at low concentration in the presence of large excess of dienophile.⁸ The low concentration of transiently generated MOB was maintained by the slow addition of 2-methoxyphenols using a syringe pump to a mixture of oxidant and dienophile in methanol at appropriate temperature. With this technique, the MOB were trapped by various dienophiles via the Diels–Alder reactions.

Several MOB **4** bearing diverse functionalities, as shown in Scheme 3, have been generated in situ from the oxidative methoxylation of inexpensive and readily available 2-methoxyphenols **1**. The cycloaddition reaction of

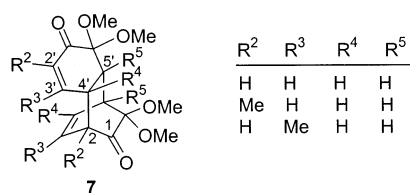
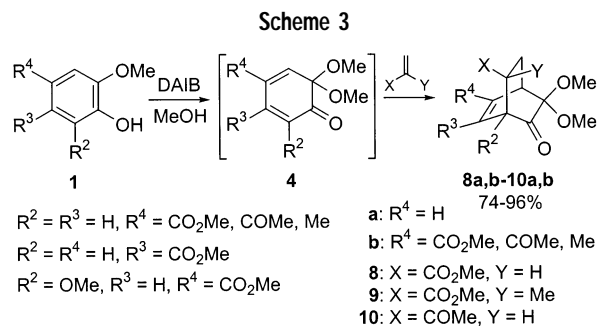


FIGURE 2. Examples of dimers of MOB.



these MOB with electron-deficient dienophiles such as methyl acrylate (MA), methyl methacrylate (MMA), and methyl vinyl ketone (MVK) afforded the bicyclo[2.2.2]-octenone derivatives **8a,b–10a,b** via endo addition in good to excellent yields^{8,9} (Scheme 3).

The reaction of the MOB derived from creosol (2-methoxy-4-methylphenol) with acrolein under usual conditions produced the Diels–Alder adduct **11** (R² = H, R⁴ = Me) in rather low yields, apparently due to the undesired side reaction of DAIB with acrolein. However, the yield was enhanced when DAIB in methanol was added slowly to a mixture of creosol and acrolein in methanol. In a parallel fashion, acrolein and methacrolein could undergo cycloaddition with MOB derived from creosol, methyl vanillate, and methyl isovanillate to provide the corresponding adducts **11** and **12** in 80–87% yields¹⁰ (Figure 3).

The Diels–Alder reactions of the parent MOB and its 2-Me and 3-Me derivatives with MA, MMA, and MVK provided the corresponding cycloadducts **8a–10a** in low to moderate yields along with substantial amounts of dimers **7** (Scheme 4).¹¹

Though in principle, there are four possible modes of [4 + 2] cycloaddition, ortho,anti-adduct (the electron-withdrawing group X is adjacent and anti to the carbonyl function of the bicyclo[2.2.2]octenone moiety) was obtained as the sole product in each case indicating that the

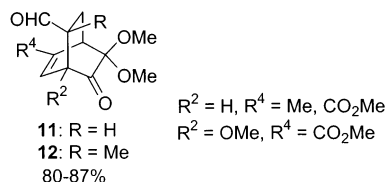
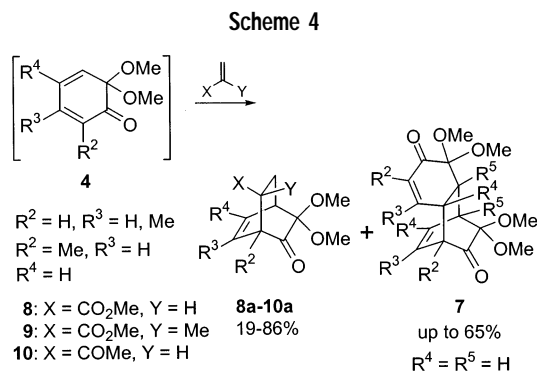


FIGURE 3. Diels–Alder adducts of MOB with acrolein and methacrolein.



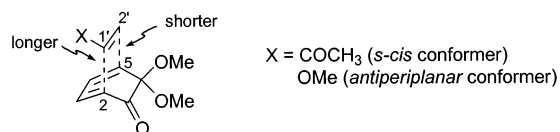


FIGURE 4. Simplified transition state for the reactions of parent MOB with methyl vinyl ketone and methyl vinyl ether.

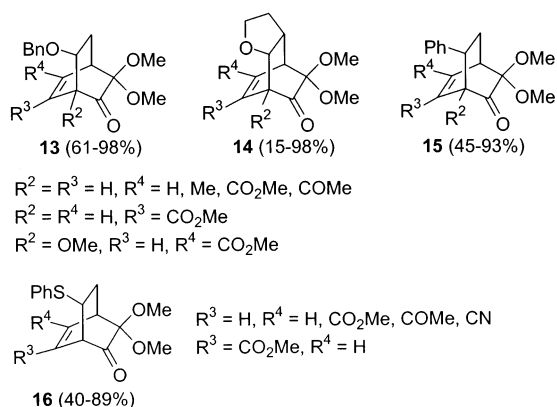
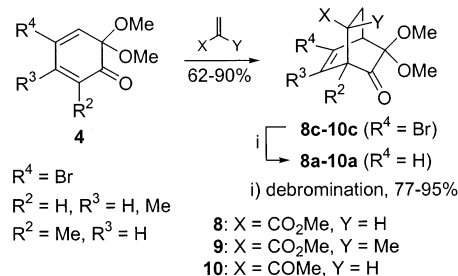


FIGURE 5. Diels–Alder adducts of MOBs with electron-rich dienophiles.

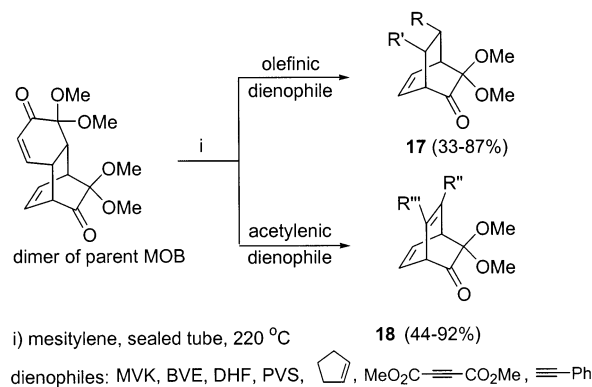
Diels–Alder reaction is highly regio- and stereoselective. To rationalize the observed selectivities on the basis of the frontier molecular orbital (FMO) theory, we have carried out theoretical calculations. However, the results obtained from these calculations are not enough to explain the experimentally observed selectivities.⁹ Consequently, calculations on the transition-state structures for the reaction between parent MOB and methyl vinyl ketone based on the *ab initio* RHF/3-21G method have been performed.¹² Among the eight possible transition-state structures (four each for *s-cisoid* and *s-transoid* conformers of MVK), the one leading to the adduct shown in Figure 4 has the lowest energy. The calculations have also suggested that this cycloaddition is a nonsynchronous concerted reaction and the formation of the C₅–C_{2'} bond is faster than that of the C₂–C_{1'} bond.

The Diels–Alder reactions of various MOBs with electron-rich dienophiles such as benzyl vinyl ether (BVE), dihydrofuran (DHF), styrene, and phenyl vinyl sulfide (PVS) were investigated.¹³ These cycloadditions were both regio- and stereoselective and furnished ortho,anti-adducts **13**–**16** (Figure 5) as in the cases of electron-deficient dienophiles. Styrene exhibited excellent reactivity in almost all the cases studied. The MOBs derived from 2-methoxyphenols such as methyl vanillate, methyl isovanillate, and acetovanillone bearing EWGs displayed excellent reactivities in general with BVE and DHF. The reactions of the MOBs derived from guaiacol and creosol are slower than those of other 2-methoxyphenols bearing EWGs. Unlike the above electron-rich dienophiles, the reactions of vinyl acetate with MOBs were found to be inefficient and nonstereoselective.⁸ On the basis of FMO theory, the theoretical calculations suggested that these are inverse-electron demand processes and also supported the observed selectivities in most cases.^{13b} The calculations (RHF/3-21G) for the reaction between parent MOB and

Scheme 5



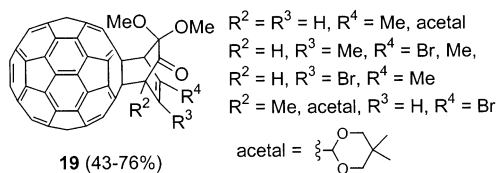
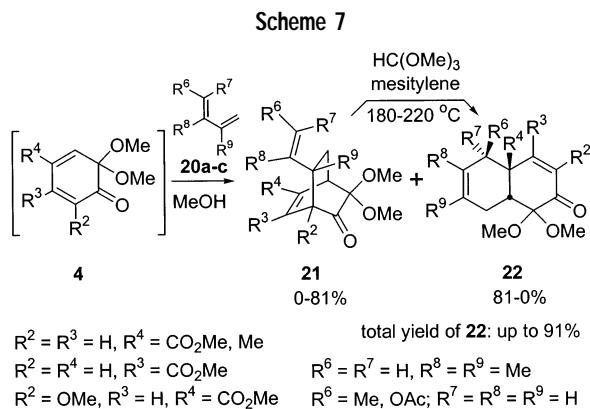
Scheme 6



methyl vinyl ether (MVE) indicate that among the eight transition-state structures (four each for synperiplanar and antiperiplanar conformers of MVE), the one shown in Figure 4 (X = OMe) has the lowest energy.¹²

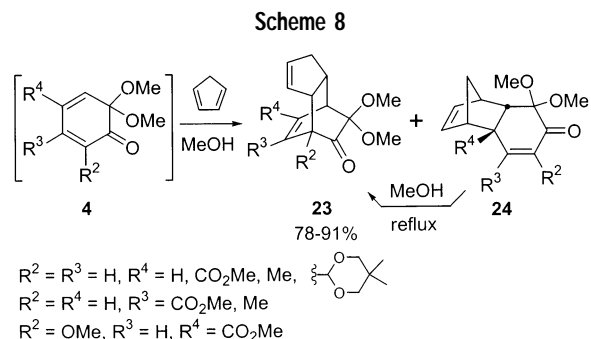
To overcome the dimerization event in the cases of MOBs of guaiacol and its 5- and 6-methyl derivatives, a bromine atom was introduced as an additional removable substituent at position-4 of MOB, assuming that 4-bromo MOBs would gain stability by retarding the dimerization pathway. As anticipated, the reactions of MOBs derived from 4-bromo-2-methoxyphenols with electron-deficient dienophiles, in stoichiometric quantities or slight excess, proceeded efficiently to produce the adducts **8c**–**10c** in good to excellent yields as the single stereoisomer in each case (Scheme 5). Thus this alternative method,¹¹ albeit with two additional simple synthetic operations (bromination and debromination), offered bicyclo[2.2.2]octenones **8a**–**10a** in 20–40% higher yields in comparison with those obtained directly in single step.

The domino retro-Diels–Alder/Diels–Alder strategy has been utilized in MOB chemistry to produce bicyclo[2.2.2]octenones from the parent dimer,¹⁴ as an alternative to the aforementioned detour method involving bromination and debromination. The required dimer, obtained in quantitative yield from guaiacol by the oxidation with DAIB at room temperature, underwent retro-Diels–Alder reaction at 220 °C in mesitylene in sealed tubes to generate *in situ* the parent MOB, which reacted with various olefinic and acetylenic dienophiles to furnish the requisite adducts **17** and **18** as shown in Scheme 6. While the reactions of benzyl vinyl ether and phenyl vinyl sulfide were found to be less stereoselective (endo/exo = 9/1 and 10/1, respectively) at this elevated temperature, all the other olefinic dienophiles produced exclusively ortho,anti-adducts.

FIGURE 6. Diels–Alder adducts of MOBs with C_{60} .

The reaction of MOBs with spherical allotrope of carbon C_{60} was also tested.¹⁵ The [4 + 2] cycloaddition of MOB having 4- CO_2Me group with this electron-poor polyene at various temperatures resulted in the formation of fullerene derivative in poor yield together with dimer. Nevertheless, 4-Me and 3-Br-4-Me MOBs exhibited improved Diels–Alder reactivity with C_{60} . Subsequently, a series of stable and isolated MOBs **4** were allowed to react with [60]fullerene to produce cycloadducts **19** in good yields (Figure 6). The 5-substituted MOBs **6** (5-Me, 5-OMe, 5- CO_2Me) did not participate in the cycloaddition apparently due to the steric encumbrance at position-5 that prevents the approach of the bulky buckyball. This suggests that as in the earlier cases (Figure 4), the cycloaddition follows a nonsynchronous concerted pathway and the formation of bond at C_5 occurs prior to that at C_2 of MOB.

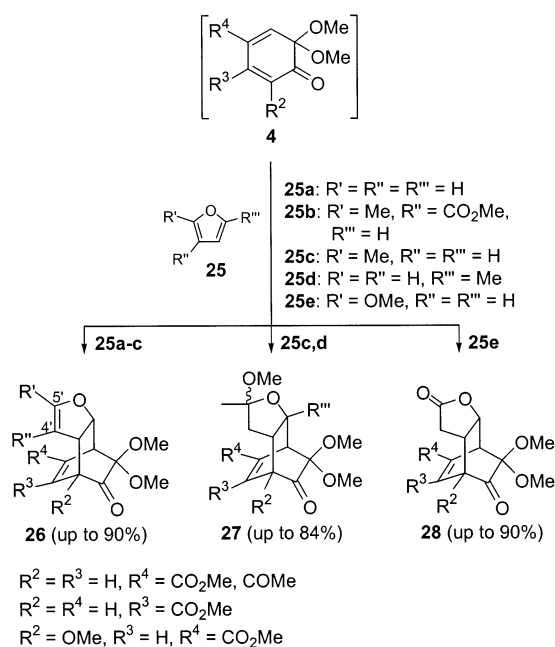
The dienophilic behavior of MOBs in their reactions with unactivated 1,3-butadienes was found for the first time in our laboratories.¹⁶ The MOBs, derived from creosol, methyl vanillate, methyl isovanillate, and methyl syringate, upon reaction with 1,3-butadienes **20a–c** provided Diels–Alder adducts **21** and **22** (Scheme 7). The ratio of adducts **21** and **22** depends on the nature and position of the substituents on both the MOBs and the dienes. All the reactions except the case of creosol proceeded in a highly regio- and stereoselective manner. The formation of **21** and **22** indicates the dual character of MOB as a diene and a dienophile. When some of the adducts **21** were separately heated in methanol in the presence of acetic acid and the corresponding 1,3-diene, no appreciable change was noticed. This indicates that **21** and **22** are generally primary products. Furthermore, the transformation of adducts **21** into **22** was effected at 180–220 °C via Cope rearrangement, which renders this approach an efficient methodology to synthesize *cis*-decalins from 2-methoxyphenols in three steps.



Cyclopentadiene, a widely used diene in the Diels–Alder reactions, was also employed as a cycloaddition partner in the reactions with in situ generated MOBs **4**.¹⁷ The reaction of guaiacol and its 3-methyl derivative in the presence of DAIB in refluxing methanol provided **23** and **24**, whereas at higher temperature it afforded solely adducts **23**. In contrary, the MOBs derived from other 2-methoxyphenols reacted with cyclopentadiene in refluxing methanol to produce exclusively adducts **23** in high yields (Scheme 8). However, controlled experiments carried out at 0 °C revealed that two competitive Diels–Alder reactions were taking place to produce **23** and **24** as a result of dual (dienic and dienophilic) behavior displayed by MOBs. It is interesting to note that while the adducts **22** formed via the dienophilic MOBs and 1,3-butadienes are more stable, the adducts **23** formed via the dienic MOBs and dienophilic cyclopentadiene are more stable, presumably due to the difference in strain energies.

Despite their aromaticity, furans participate in the Diels–Alder cycloaddition essentially as 4π partners. Nevertheless, MOBs compelled furans to act as dienophiles in the Diels–Alder reactions.¹⁸ In situ generated MOBs **4** reacted with a variety of furans **25a–e** at appropriate temperatures in methanol to afford the corresponding cycloadducts with a high degree of regio- and stereoselectivity (Scheme 9). The products **27** were formed by the addition of methanol to the resulting enol ether moiety of the corresponding adducts. Owing to the highly reactive nature of the MOBs, furan **25b** bearing EWG took part in the cycloaddition. It should be noted that all the reactions between MOBs and furans produced ortho,anti-adducts **26** (the $C_4=C_5$ bond of the five-membered heterocyclic moiety is adjacent and anti to bicyclooctenone carbonyl function). Interestingly, the regiochemistry of the reactions of furans is opposite to that of the reactions of dihydrofuran (Figure 5). Unlike other furans, 2-methoxyfuran (**25e**) reacted efficiently even with the other MOBs bearing ERG(s) at room temperature to produce γ -lactones **28** in 78–95% yields after the hydrolysis of cyclic ketene acetals in the adducts.^{18b} Theoretical calculations (RHF/3-21G) on the transition-state structures of the reaction between parent MOB and furan supported the observed selectivities.^{12,19} Among the four possible transition-state structures, the one leading to the adduct as shown in Figure 7 ($X = O$) has the lowest energy. The calculations have also suggested that this cycloaddition proceeds through a nonsynchronous concerted pathway and the formation of C_5-C_2 bond is faster than that of

Scheme 9



the C_2 – C_3' bond. Very recently, density functional theory study of the cycloaddition reaction between MOB **5** ($R^4 = CO_2Me$) and furan **25c** was reported.²⁰

The cycloadditions of pyrroles are generally less efficient than those of furans due to the higher resonance energy of the former. In addition, pyrroles undergo Michael additions. Despite these obstacles, *N*-acyl pyrroles **29a–e**, in their capacity as dienophiles, underwent extremely facile Diels–Alder reaction with 4-EWG substituted MOBs **5** ($R^4 = CO_2Me, COMe, CN$) in high selectivity²¹ (Figure 8). While the *N*-acylated parent and methylpyrroles **29a–d** provided adducts **30a–d** in good to excellent yields, *N*-acetylated pyrrole **29e** bearing EWG in the ring exhibited less reactivity. It is pertinent to note that the mildness of the reaction (0 °C or room temperature) with considerable generality and exquisite selectivities of the products are unprecedented in the cycloaddition chemistry of pyrroles. The observed selectivities from these reactions were supported by the calculations (RHF/3-21G), and the simplified structure of the lowest energy transition state is depicted in Figure 7 ($X = NCOMe$).

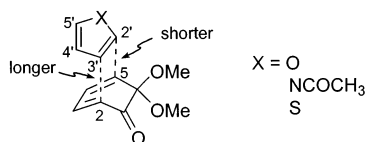


FIGURE 7. Simplified transition state for the reactions of parent MOB with five-membered heteroaromatics.

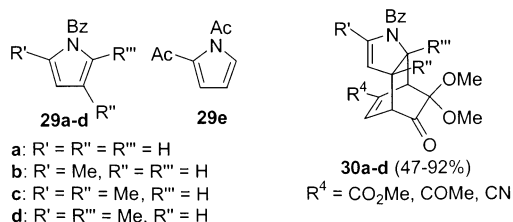
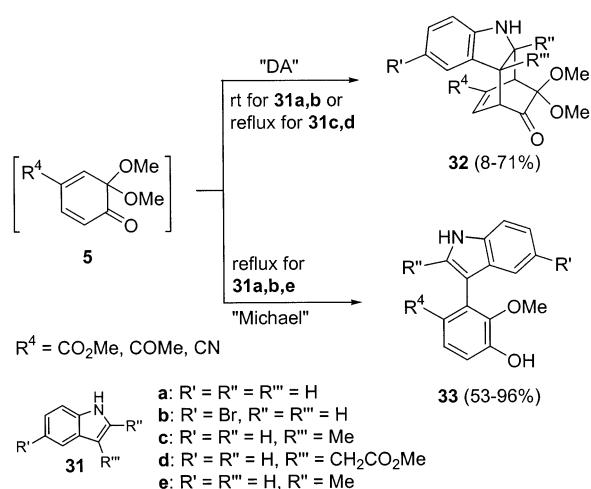


FIGURE 8. Diels–Alder adducts of MOBs with *N*-acyl pyrroles.

Scheme 10



Interestingly, MOBs **5** in their reactions with indoles behaved as both dienes and Michael acceptors depending on the reaction temperature and the substitution pattern on indoles and produced hydrocarbazoles and 3-arylindoles, respectively (Scheme 10).²² The parent indole (**31a**) and 5-bromoindole (**31b**) on reacting with MOBs **5** produced Diels–Alder adducts **32a,b** at room temperature and aromatized Michael adducts **33a,b** in refluxing methanol. As position-3 was substituted in indoles **31c,d**, they underwent only Diels–Alder reaction with **5** in refluxing methanol to afford **32c,d**. 2-Methylindole (**31e**) provided aromatized Michael adducts **33e** as the sole products under reflux.

The overwhelming results achieved in the cycloadditions of MOBs with furans and pyrroles have prompted us to investigate the Diels–Alder reactions of thiophenes despite their higher aromaticity. Thus, the reactions between thiophenes **34a–e** and MOBs **5** ($R^4 = EWG$) were studied (Figure 9).²³ The parent thiophene (**34a**) furnished bis-adducts **35**, although in low yields. While 2-methyl and 3-methylthiophenes (**34b,c**) yielded cycloadducts **36b,c**, 2-methoxythiophene (**34e**) gave thiolactones **37** in acceptable yields. On the other hand, 2,4-dimethylthiophene (**34d**) provided other products in addition to adducts **36d**. In these reactions, MOBs cycloaddition to thiophenes in a highly regio- and stereoselective manner, and the latter apparently played the role of dienophiles. The observed selectivities in these reactions were supported by theoretical calculations (RHF/3-21G) (Figure 7, $X = S$).

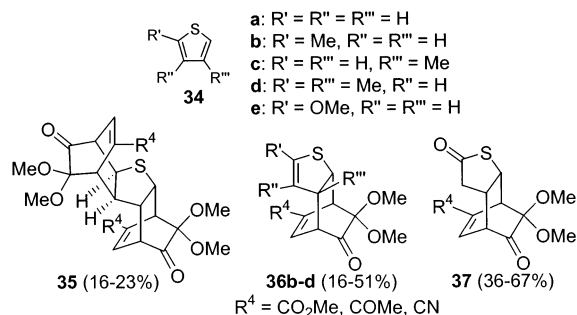
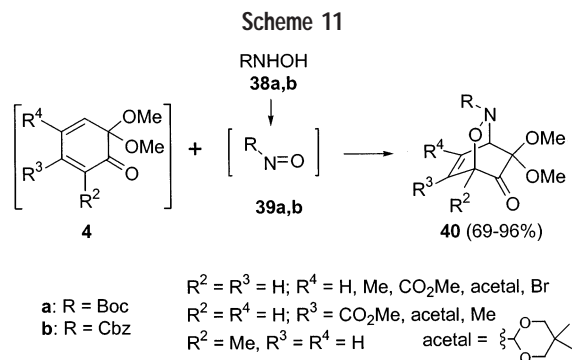


FIGURE 9. Diels–Alder adducts of MOBs with thiophenes.

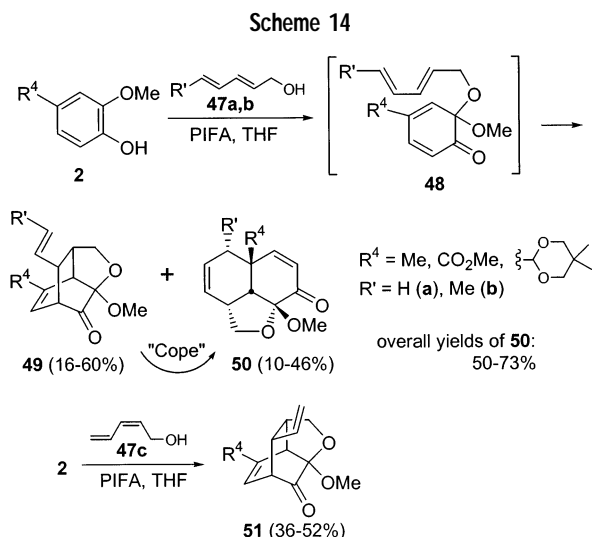
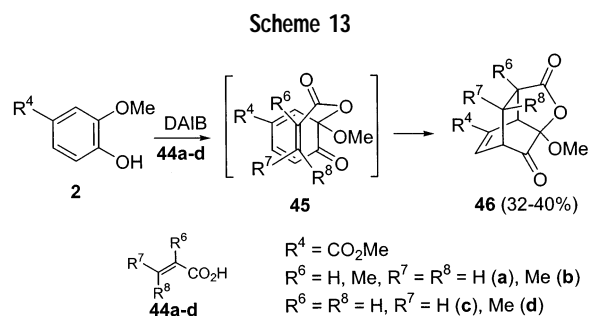
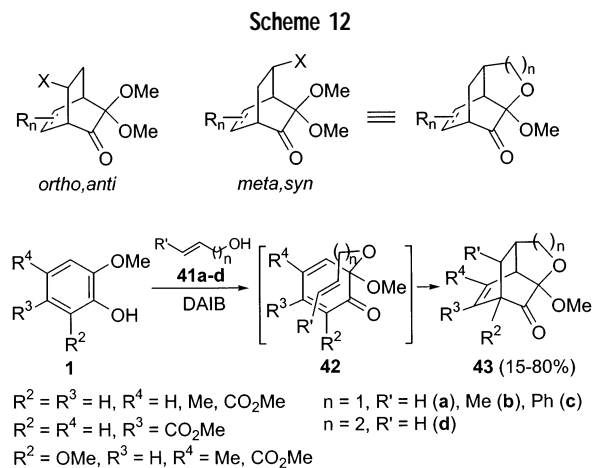


An obvious extension to the carbo-Diels–Alder reaction is the hetero-Diels–Alder reaction. The MOBs derived from guaiacol and several of its derivatives (EWGs, ERGs) were treated with nitroso compounds **39a,b** derived from *N*-hydroxycarbamates **38a,b** to produce highly functionalized heterocycles **40** in good to excellent yields via facile hetero-Diels–Alder reactions of transiently generated MOBs **4** and nitroso dienophiles **39a,b** (Scheme 11).²⁴ While the relatively stable MOBs bearing ERGs at C₄ required moderate temperatures (50 °C) to achieve optimum results, all other MOBs reacted efficiently at 0 °C. This reaction provides rapid access to bicyclo[2.2.2]-octenones embedded with heteroatoms that are potential precursors for the synthesis of naturally occurring alkaloids from 2-methoxyphenols.

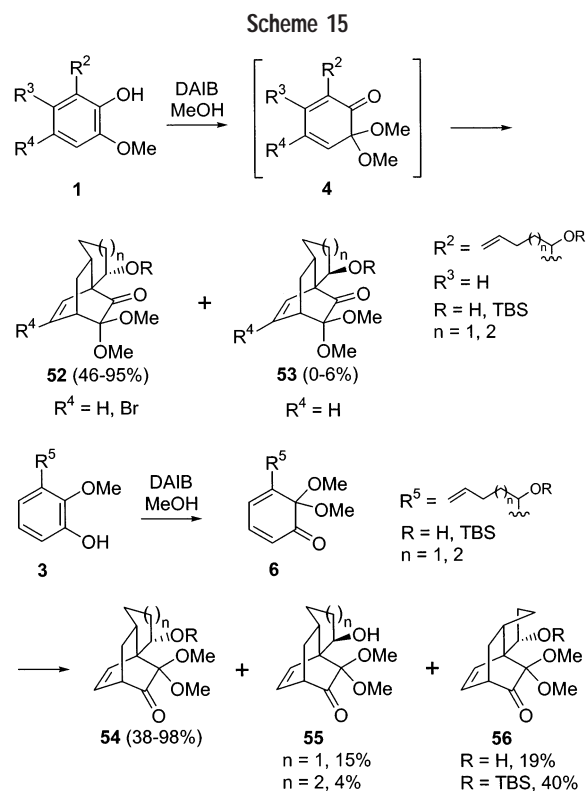
Intramolecular Diels–Alder Reactions

The intramolecular Diels–Alder (IMDA) reaction is a powerful tool for the rapid construction of highly substituted polycyclic carbon skeletons. When methanol is replaced by an alkenol or a dienol during the oxidation of 2-methoxyphenols, thus formed MOBs (or the MOBs bearing alkene moiety attached through a carbon tether) can undergo IMDA reaction to furnish tricyclic ring systems. We have developed an unprecedented IMDA reaction via *in situ* tethering of an alkene to a diene system through acetal formation.^{8,25} Several commercially available 2-methoxyphenols **1** were oxidized by DAIB in the presence of alkenols **41a–d** to generate MOBs **42**, which underwent IMDA reaction smoothly to furnish highly functionalized oxatricycles **43** in moderate to high yields (Scheme 12). It is worth mentioning that in contrast to the intermolecular Diels–Alder reaction (*ortho,anti*-adducts), these adducts obtained via domino oxidative acetalization–IMDA process can be considered as equivalents of *meta,syn*-adducts (with respect to the carbonyl group). The reactivity of a particular MOB appears to depend on the substituents on alkene terminus and the position of substitution(s) on the dienone moiety. The alkenoic acids **44a–d** were employed in the place of alkenols in the above process with methyl vanillate to afford tricyclic lactones **46** in 32–40% yields (Scheme 13).

When the alkenols were replaced by 2,4-dienols in the above process, the cyclohexa-2,4-dienone moiety of MOB displayed dual behavior, i.e., both dienic and dienophilic character resulting in mixtures of adducts, bicyclo[2.2.2]-



octenones **49** and *cis*-decalins **50**, following the endo rule.²⁶ The 4-substituted 2-methoxyphenols **2** and dienols **47a,b** were used for these studies to furnish the two types of adducts of varying ratios in combined yields of 62–76% (Scheme 14). While the 4-Me or 4-acetal group of MOBs **48** enhances their dienic behavior, 4-CO₂Me increases dienophilicity. The adducts **49** can be easily transformed into *cis*-decalins **50** in excellent yields via Cope rearrangement (mesitylene, 200 °C). Alternatively, the crude Diels–Alder adducts were subjected to Cope rearrangement to furnish *cis*-decalins **50** in 50–73% yields, thus making this approach a short route to *cis*-decalins with total stereocontrol. *cis*-Penta-2,4-dienol (**47c**) provided tricyclic compounds **51** as sole products; as predicted, they did not undergo Cope rearrangement. Inde-

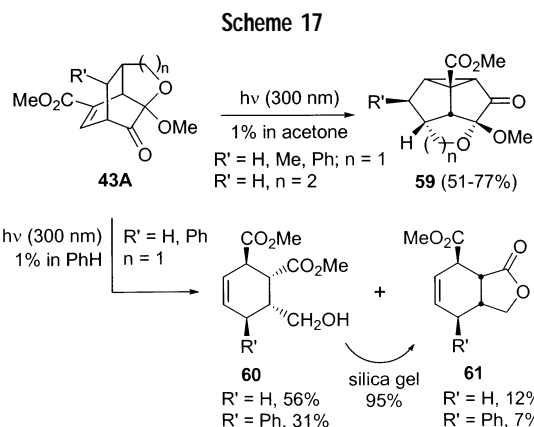
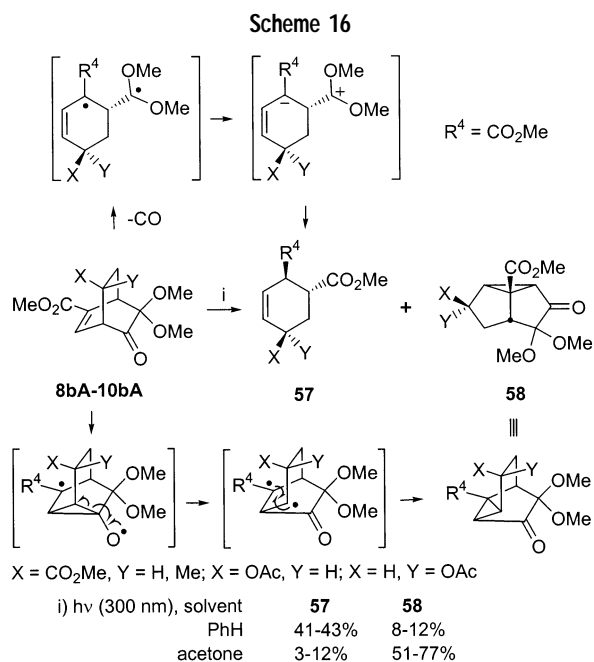


pendently, Rodrigo and co-workers have reported²⁷ IMDA reactions of MOBs generated from dienol **47a** and 2-methoxyphenols.

Very recently, we have reported²⁸ diastereoselective IMDA reactions of various MOBs **4** and **6** bearing a chiral center in the alkenyl carbon tether to provide densely substituted tricyclic [*m*.2.2.0] ring systems. The alkene was tethered at either C₂ position of the MOBs, an OH or OTBS group was placed at the chiral center, and the IMDA reaction of the MOBs **4** furnished tricycles **52** as predominant or major adducts and **53** as minor adducts (Scheme 15). The MOBs **6** having a tether at C₅ afforded **54** as predominant or major adducts and **55** and **56** as minor adducts. The less reactive 5-substituted MOBs **6** required relatively high temperatures and longer reaction times in comparison with 2-substituted MOBs **4**. Unlike five- and six-membered annulations ($n = 1, 2$), seven-membered annulations ($n = 3$) were not efficient (yields: 0–15%). The tricyclic adducts obtained from this protocol may serve as precursors for linear and angular tricyclic skeletons.

Synthetic Applications: Construction of Various Skeletons from 2-Methoxyphenols

Bicyclo[2.2.2]octenones embedded with β,γ -unsaturated carbonyl chromophore are rich with photochemistry.²⁹ Thus, intermolecular and intramolecular Diels–Alder adducts of MOBs offered us a unique opportunity to explore their photochemical reactions. The adducts **8bA–10bA**, upon direct irradiation in benzene furnished cyclohexenes **57** in 41–43% and the oxa-di- π -methane (ODPM) rearrangement products **58** in minor amounts, whereas irradiation in acetone provided **58** as the major products.

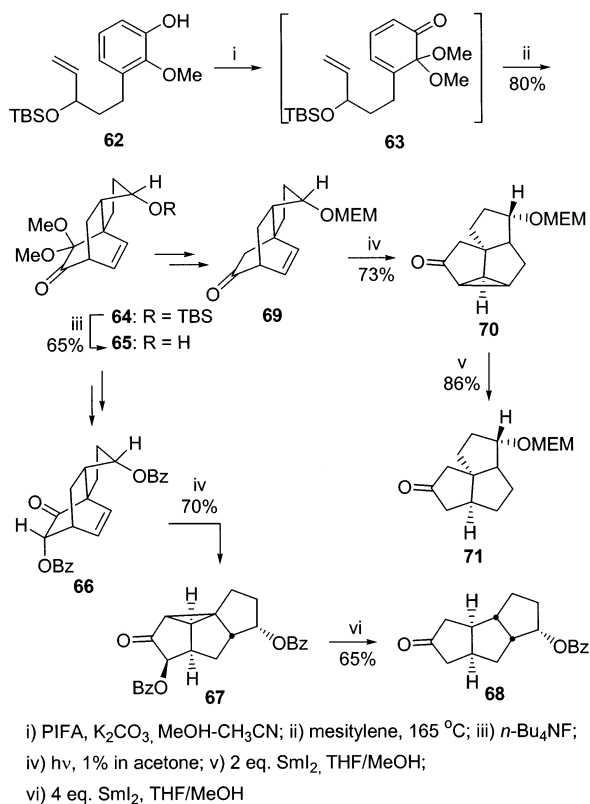


The plausible pathways of these photochemical transformations are depicted in Scheme 16. On the other hand, the IMDA adducts **43A** ($\text{R}' = \text{H, Ph}; n = 1$) upon irradiation in benzene, afforded decarbonylated products, cyclohexenes **60** and lactones **61**, and provided ODPM rearrangement products **59** by irradiating in acetone solution³⁰ (Scheme 17). The compounds **60** could be transformed into lactones **61** by treatment with silica gel in ethyl acetate.

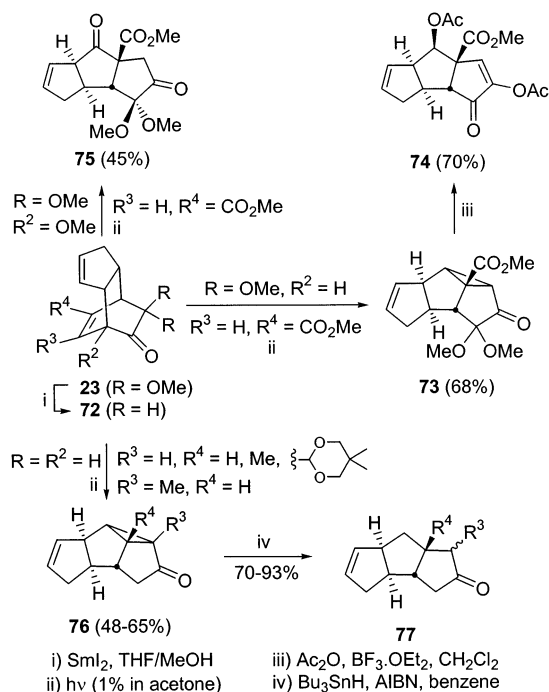
Numerous methods have been developed for the synthesis of triquinanes due to their synthetic potential toward higher polyhedra of fundamental importance. In our laboratories, linearly and angularly fused triquinanes **68** and **71** were synthesized³¹ from a common intermediate **65**, which was obtained from IMDA reaction of MOB **63**. Photochemical ODPM rearrangement of **66/69** and reductive ring opening of the cyclopropyl ketone intermediates **67/70** are the other key steps in this strategy (Scheme 18).

The intermolecular Diels–Alder adducts **23** and their demethoxylated analogues **72** were transformed into linear triquinanes **74** and **75** and **77**, respectively, via ODPM rearrangement in acetone¹⁷ and cyclopropane ring

Scheme 18



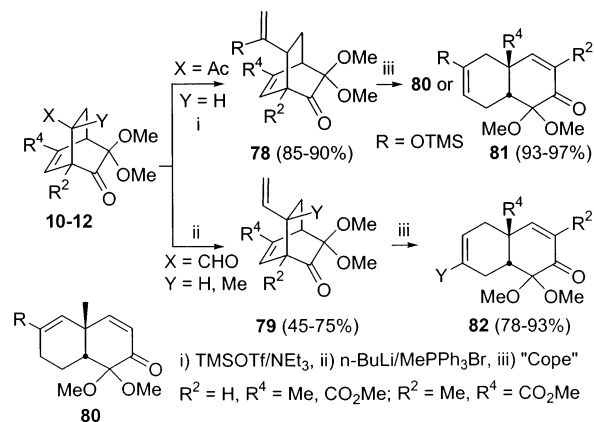
Scheme 19



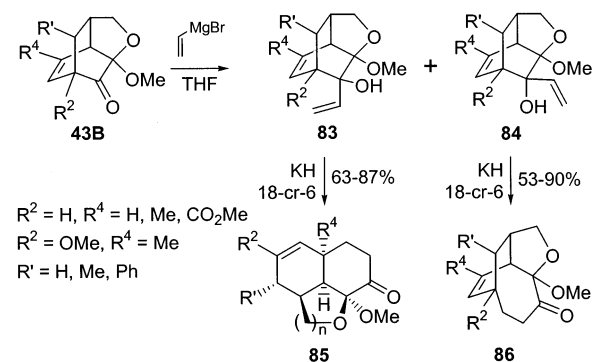
opening (Scheme 19). Thus, a new methodology was developed to synthesize appropriately oxygenated and variously substituted linear triquinanes bearing *cis*:*anti*:*cis* stereochemistry of naturally occurring triquinane skeletons efficiently in 3–4 steps from inexpensive and easily accessible 2-methoxyphenols **1**.

From the preceding sections, it is quite clear that the Diels–Alder protocol of MOBs serves as a powerful

Scheme 20



Scheme 21



strategy to generate complex molecular structures with defined stereochemistry. In addition to bicyclo[2.2.2]-octenones, various substituted oxatricycles^{8,25–27} and *cis*-decalins^{16,26,27} were constructed rapidly from simple 2-methoxyphenols. The 1,5-dienes **78** and **79** derived from cycloadducts **10–12** underwent Cope rearrangement efficiently to provide highly substituted and oxygenated *cis*-decalins **80–82** in excellent yields¹⁰ (Scheme 20).

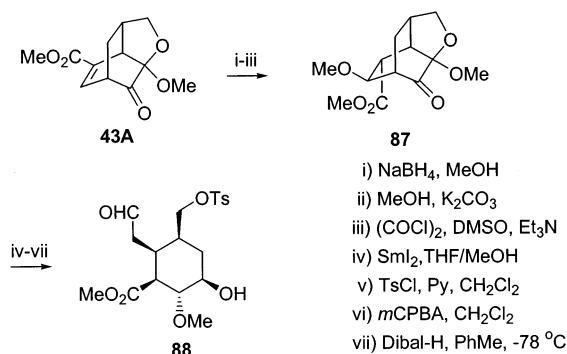
A novel and efficient four-step methodology has been developed for the stereocontrolled synthesis of bicyclo[4.2.2]decanones from 2-methoxyphenols.³² The IMDA adducts **43B**, upon addition of vinylmagnesium bromide, furnished diastereomeric alcohols **83** and **84** of varying ratio, and either one can be stereoselectively prepared by use of various Lewis acids.³³ The *syn* alcohols **83** when exposed to KH in the presence of 18-crown-6 produced *cis*-decalins **85** in very good yields via anionic oxy-Cope rearrangement, whereas *anti* alcohols **84** afforded ring enlarged bicyclo[4.2.2]dec-7-en-4-ones **86** in high yields (Scheme 21).

Synthetic Applications: Formal/Total Syntheses of Natural Products

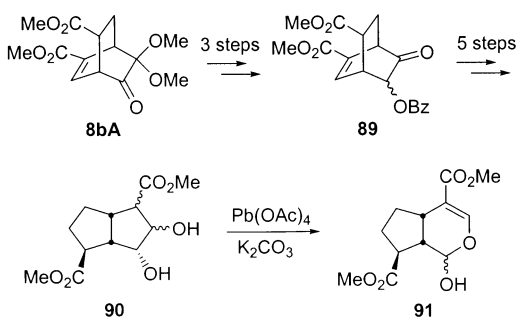
The synthesis of (+)-ryanodol by Deslongchamps' group is the earliest elegant example involving the Diels–Alder reaction of a type-III MOB.⁵ The efficacy of our Diels–Alder strategy of MOBs has been exemplified on several occasions in the synthesis of natural products.

A key intermediate **88** in Stork's synthesis of (±)-reserpine³⁴ was achieved in 8 steps from methyl vanillate

Scheme 22



Scheme 23



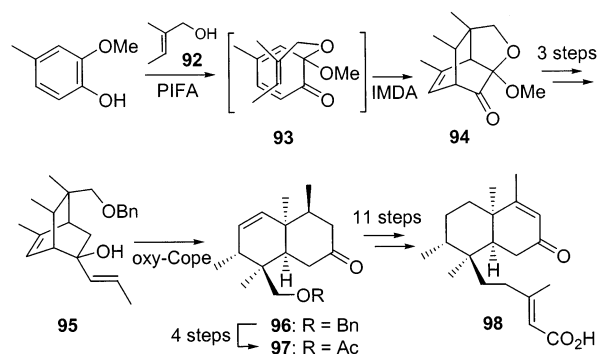
in our research group (Scheme 22). The IMDA adduct **43A** ($n = 1$, $\text{R}' = \text{H}$) was transformed into tricyclic ketone **87** by means of sequential carbonyl reduction, 1,4-addition of methanol to α,β -unsaturated ester, and Swern oxidation. A set of reactions involving the cleavage of acetal function of oxatricycle **87** followed by tosylation, regioselective Baeyer–Villiger lactonization, and Dibal-H reduction afforded cyclohexane derivative **88** possessing five stereocenters, thus leading to the formal synthesis of (\pm)-reserpine.³⁵

The synthesis of iridoid (\pm)-forsythide aglucone dimethyl ester (**91**) was accomplished via MOB Diels–Alder strategy³⁶ as shown in Scheme 23. It may be noted that all the carbon atoms required were introduced in a single operation. The Diels–Alder adduct **8bA** was transformed into **89** in three steps by the transposition of carbonyl functionality. The ODPM rearrangement of **89** is another key step in this route. The conversion of **89** into a mixture of two diastereomers of diquinane **90** was achieved in five steps, although four isomers are possible. Oxidation of **90** provided a 2:1 epimeric mixture of the target molecule **91**.

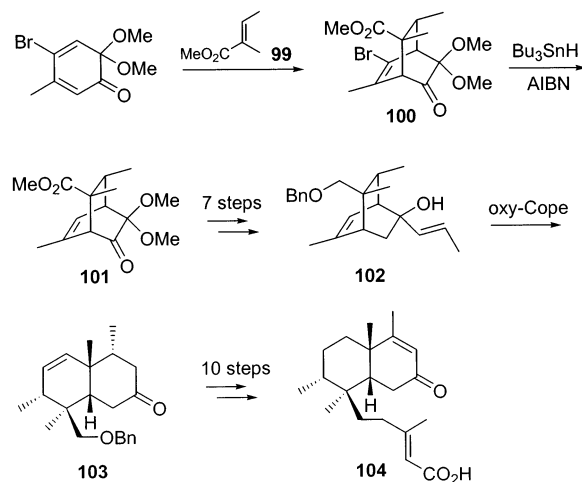
The synthesis of *cis*-clerodane diterpenic acid **98** in racemic form in 19 steps from creosol is depicted in Scheme 24.³⁷ In the key step, IMDA reaction of MOB **93** derived from creosol and **92** provided tricyclic β,γ -enone **94** bearing the desired three methyl groups and four stereogenic centers. Transformation of **94** into dienol **95** in three steps followed by another key step, anionic oxy-Cope rearrangement, gave the *cis*-decalin **96**. The target **98** was reached by the further elaboration of **96** in several steps.

Another *cis*-clerodane diterpenic acid **104**, a diastereomer of **98**, was synthesized utilizing intermolecular

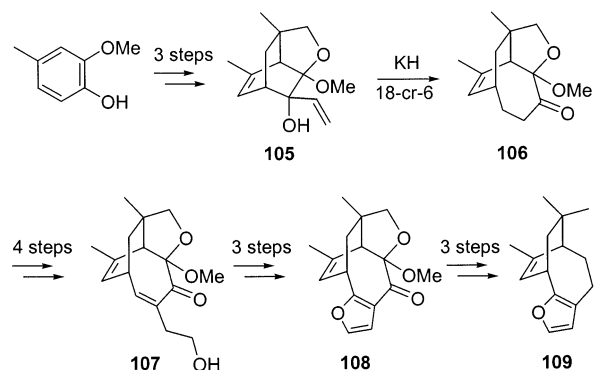
Scheme 24



Scheme 25

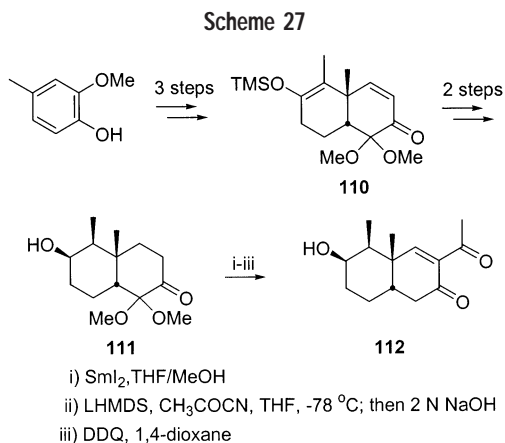


Scheme 26



Diels–Alder strategy.³⁸ The cycloadduct **101** was obtained via the detour method involving bromination and debromination developed by us. The compound **101** was transformed into dienol **102** in 7 steps for subsequent stereocontrolled anionic oxy-Cope rearrangement into *cis*-decalin **103**. This was further elaborated into **104** in 10 steps (Scheme 25). It may be noted that the NMR data for **98** and **104** were not quite identical with those of the corresponding natural products, whose structures await further investigation.

The four-step methodology developed³² for the stereocontrolled synthesis of bicyclo[4.2.2]decenones has been utilized for the synthesis of (\pm)-palescensin B (**109**)³⁹ (Scheme 26). The bicyclo[4.2.2]decenone **106** was subjected to furan ring construction to furnish **108** in seven



steps via intramolecular Michael addition of hydroxy-enone **107**. Then the deoxygenation of **108** was achieved to accomplish the total synthesis of (\pm)-pallascensin B.

The total synthesis of (\pm)-eremopetasidone (**112**) was accomplished⁴⁰ by using the four-step stereocontrolled synthesis of *cis*-decalins¹⁰ (Scheme 27). The *cis*-decalin **110** was converted into ketone **111** in two steps. Demethoxylation of **111** followed by C-acetylation and dehydrogenation afforded **112**.

In addition to our efforts, the versatility of MOBs was also exemplified by other research groups in the syntheses of the following: (\pm)-calicheamicinone aglycon (**113**);⁴¹ (\pm)-kadsurenone (**114**), (\pm)-denudatin B (**115**), (\pm)-liliflolanone (**116**), (\pm)-*O*-methylfliflodione (**117**);⁴² asatone (**118**);⁴³

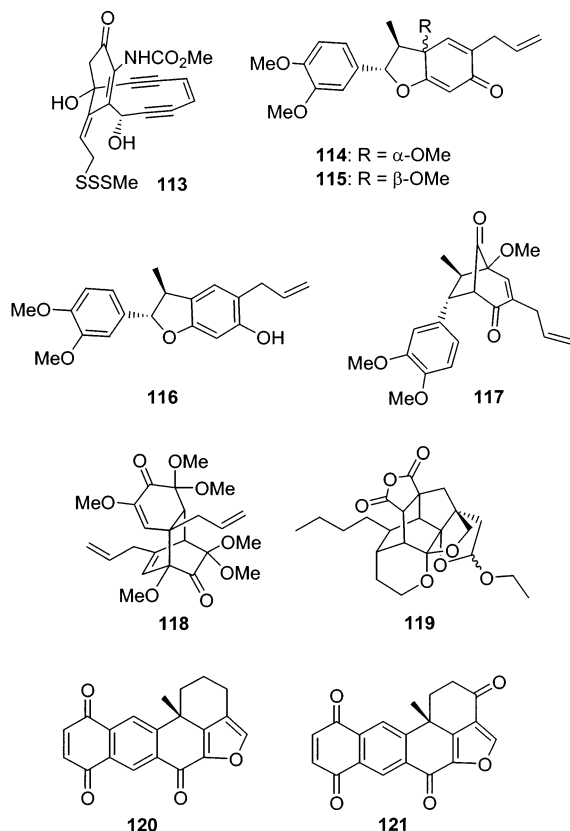


FIGURE 10. Syntheses of other natural products and related molecules from MOBs.

carbocyclic core **119** of CP-263,114;⁴⁴ (\pm)-xestoquinone (**120**),^{27a,c} (\pm)-halenoquinone (**121**)⁴⁵ (Figure 10).

Perspective

During our investigations we have learned more about reactivity and stability of these MOBs. The MOBs are indeed highly reactive and versatile building blocks. We have shown that MOBs react with a wide range of dienophiles under mild conditions in a highly site-, regio-, and stereoselective manner enabling rapid access to a variety of bicyclic and tricyclic ring systems from readily available 2-methoxyphenols. Furthermore, the adducts obtained from the MOB Diels–Alder strategy have been utilized in the syntheses of several natural products. Other reactions such as Michael addition and epoxidation of MOBs have just commenced. The scope of the MOB Diels–Alder chemistry can be extended to the pool of heterodienophiles for the generation of useful heterocycles. As the general trend on the stability of MOBs has already been suggested, in the future, MOBs can be subjected to several novel reactions, including other cycloadditions, aziridination, dihydroxylation, and aminohydroxylation. Asymmetric variation of the Diels–Alder reaction of MOBs is another potential area of research, which is underway in our laboratories.

The work reported in this account would not have been possible without the excellent efforts by the co-workers whose names appear in the references. This research was generously supported by National Science Council and Ministry of Education, Republic of China. We thank Professors Hsing-Jang Liu and Biing-Jiun Uang for stimulating discussions. R.K.P. thanks the NSC for a postdoctoral fellowship.

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