Pure Appl. Chem., Vol. 75, No. 10, pp. 1443–1451, 2003.

Birch reduction and its application in the total synthesis of natural products*

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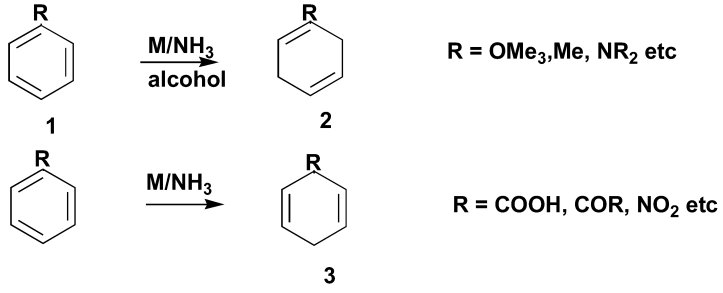
Abstract: The unique availability of substituted cyclohexa-1,4- and 1,3-dienes, notably enol ethers, from Birch reduction of anisoles, permits many novel synthetic reactions of general utility. The total synthesis of several natural products derived from polyketides have been accomplished using a Diels–Alder and Alder–Rickert process. The strategies of the synthesis are discussed.

INTRODUCTION

The reduction [1] of aromatic substrates with alkali metal, alcohol in liquid ammonia, known as "Birch reduction", has greatly increased the utility of benzenoid compounds in alicyclic synthesis [2]. It has had a less profound effect on heterocyclic synthesis [3]. It provides steric control is one of the most highly used synthetic reactions in organic chemistry [2,4,5].

Our understanding of the reduction process as applied to benzenoid substrates is summarized in Scheme 1. As a general rule, the reduction of aromatic substrates (**1**) with electron-donating substituents such as OMe, Me, NR_2, and $SiMe_3$ provides the corresponding 2,5-dihydroderivatives (**2**), while those having electron-withdrawing substituents such as COOH, COR, and NO_2 yield the corresponding 1,4-dihydro compounds (**3**) as shown below (Scheme 1).



Scheme 1

The methoxycyclohexadienes (**2**) obtained from the metal-ammonia and alcohol reduction of anisoles are synthetically useful because of their unique structural features, which comprise (i) the directed enol-ether double bond and (ii) the diene system and its reactions in the form of unconjugated, and conjugated with the effects of alkoxyl group on transformations of products. The reactions of the dienes as unconjugated include the ability to form a regiospecific carbanion formation without the presence of anion-stabilizing groups such as CO_2R and Ph, while the conjugated dienes are useful in the Diels–Alder

*Lecture presented at the 4th Florida Heterocyclic Conference, Gainesville, FL, USA, 10–12 March 2003. Other presentations are published in this issue, pp. 1403–1475.

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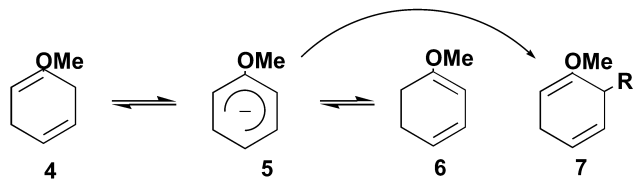
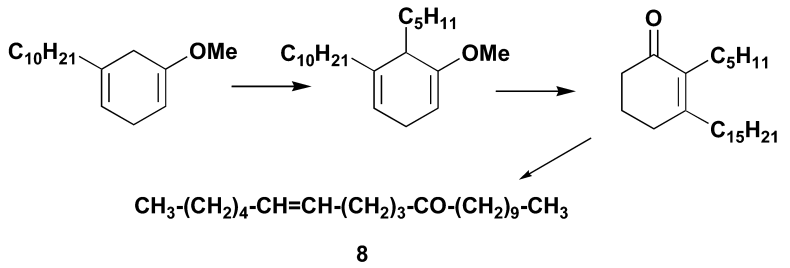
and Alder–Rickert reactions. Because of their structural versatility and easy availability, the methoxycyclohexadienes have been a favorite choice as starting materials in organic synthesis. We have extensively used these dienes for the total synthesis of polyketides [6–11], terpenoids [12–16], and other natural products of biological interest. Some of our work in the area of oxygen heterocycles is presented here.

An important property of 1-methoxycyclohexa-1,4-dienes, holding great synthetic potential, is their ability to loose a doubly allylic proton on treatment with a base to give a regionally defined mesomeric C-5 anion. The structure of this anion is mainly determined by the position as well as the nature of substituents present in the aromatic precursor. The presence of 1-methoxy, and especially 1,5-dimethoxy group, has an acidifying effect [17] and determines that the proton lost is from the carbon adjacent to the carbon bearing the OMe group only. Kinetically controlled protonation or alkylation of U-shaped anions takes place principally or entirely at the central carbon to give **7** (Scheme 2). This was the first method of making an equilibrium mixture of the 1,3-diene (75 %) and 1,4-diene (25 %) using a base catalyst [17].



Scheme 2

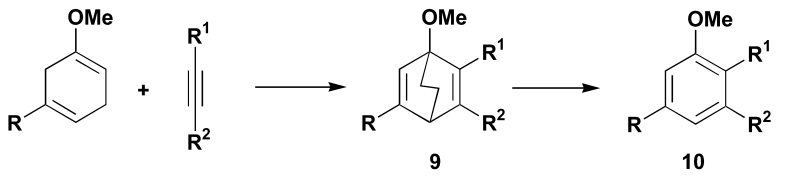
The formation of C–C bond at the central position by alkylation leads to a new set of dienes that are otherwise difficult to obtain by other methods. An example of application of this method is illustrated by the synthesis of the insect pheromone, henicosa-6-ene-11-one, **8** developed earlier as shown in Scheme 3.



Scheme 3

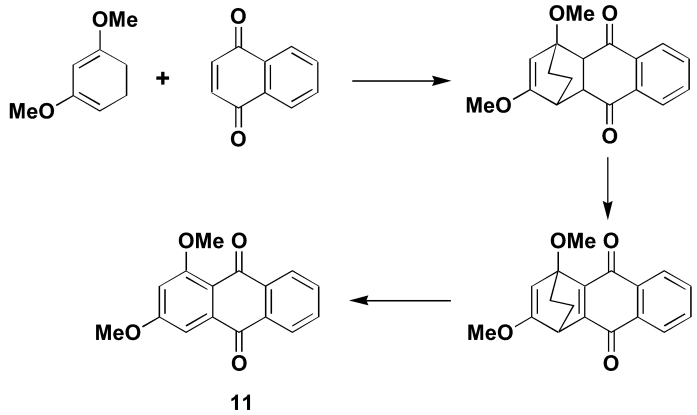
ALDER–RICKERT REACTION FOR THE SYNTHESIS OF AROMATIC COMPOUNDS

A typical Alder–Rickert reaction is shown in Scheme 4. The structural requirement for this reaction is a 2,5-C_2-bridge across a cyclohexa-1,4-diene (**9**). Pyrolysis of **9** affords the aromatic ring **10** through the elimination of the ethano bridge. The nature of the bridge is unimportant because it is lost during the retro reaction. The methodology is unique because the unsaturated bridged ring structures can be obtained by the addition of activated acetylenes to cyclohexadienes as shown in the Scheme 4.



Scheme 4

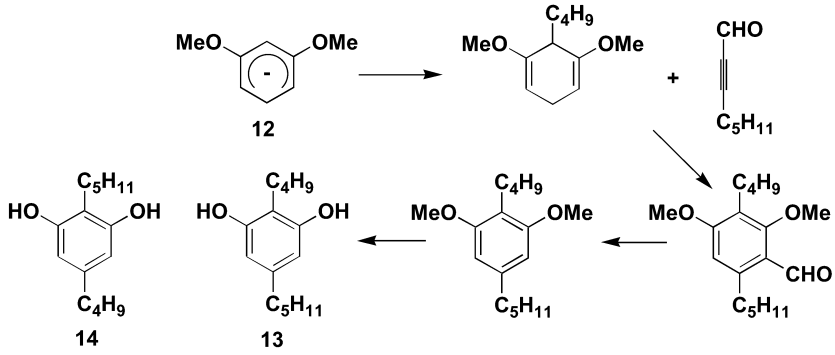
In cases of quinones as the dienophiles, addition of naphthoquinone to the 1,3-dimethoxycyclohexa-1,3-diene results in the adduct which on oxidation followed by aromatization gives [18] the 1,3-dimethoxyanthraquinone (**11**) in good yield as indicated in Scheme 5. The Alder–Rickert process had initially given [19–21] several polyketide derivatives. We have thoroughly investigated this reaction and synthesized several natural oxygen heterocycles of polyketide origin, which included the orsellinic acid derivatives, phthalides, and the complex xanthone, morellin, having the oxatricyclo[4.3.1.0]decan-2-one moiety [3,7]. These results are presented here.



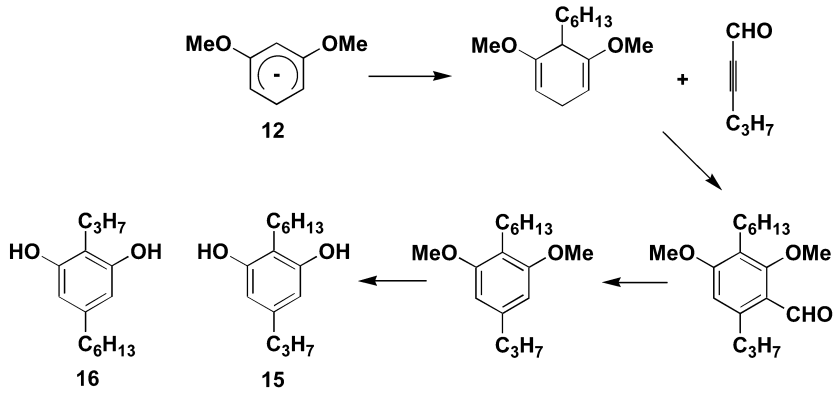
Scheme 5

Stemphol (13) and DB-2073 (15)

The structures of the metabolites, stemphol **13**, isolated from *Stemphilium majusculum*, and the antibiotic DB-2073 (**15**), isolated from *Pseudomonas sp. B-9004*, have been deduced from their spectral data. These structures were confirmed [7] by synthesis by using the Alder–Rickert reaction strategy from the appropriate dienes and the acetyleneic dienophiles. The isomeric compounds **14** and **16** have also been prepared by this methodology as indicated in Schemes 6 and 7.



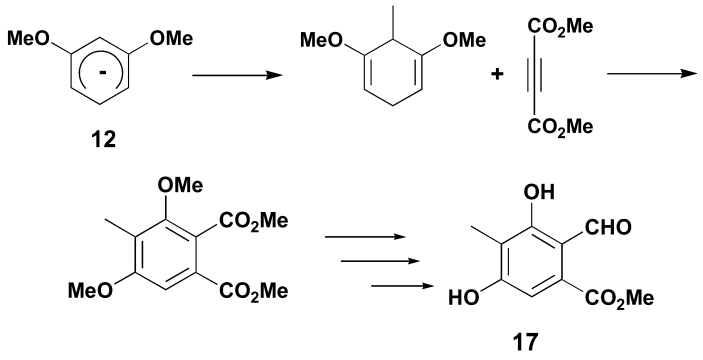
Scheme 6



Scheme 7

Methyl 3,5-dihydroxy-2-formyl-4-methylbenzoate (17)

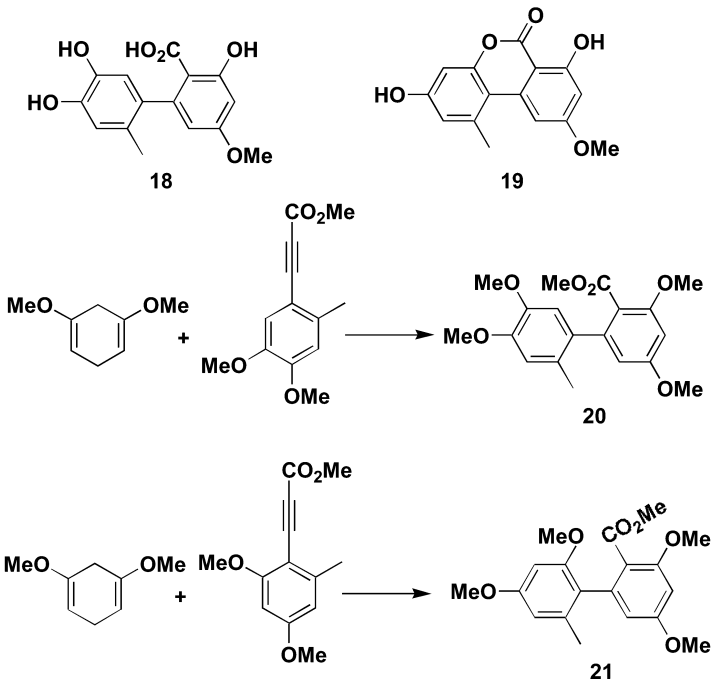
This root growth stimulant has been synthesized by the strategy involving a reductive alkylation of the diene and addition to a dienophile using Alder–Rickert reaction (Scheme 8).



Scheme 8

Altenusin (18) and alternariol (19)

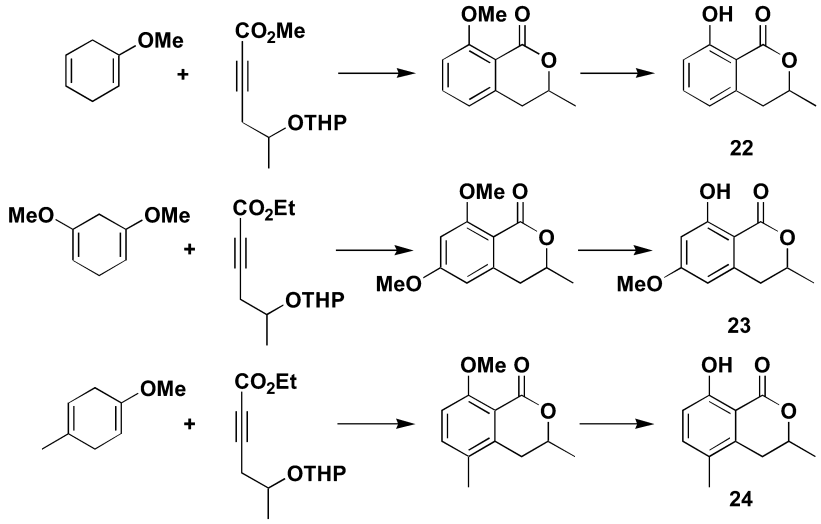
These are fungal metabolites having 6-arylresorcilate skeleton and are known to possess antibacterial activity. The structures of these metabolites were initially deduced from their spectral data. They are now confirmed by synthesis [8] using the Diels–Alder and Alder–Rickert strategy as shown in Scheme 9.



Scheme 9

Synthesis of mellein (22), 6-methoxymellein (23), and 5-methoxymellein (24)

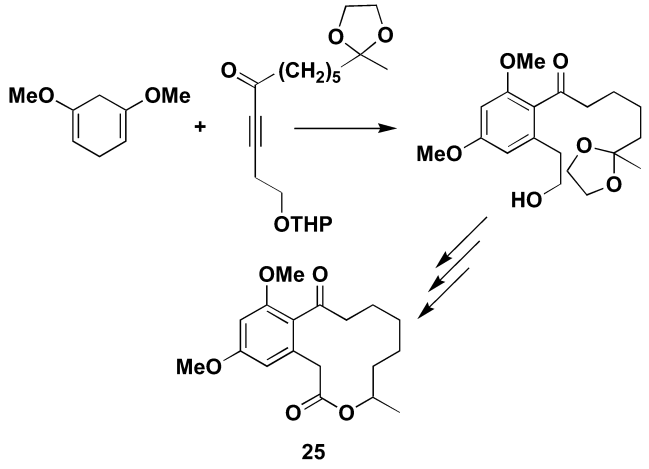
Based on the Alder–Rickert strategy, the isocoumarin natural products mellein (**22**), 6-methoxy mellein (**23**), and 5-methoxy mellein (**24**) have been synthesized [7] (Scheme 10).



Scheme 10

Curvularin (25)

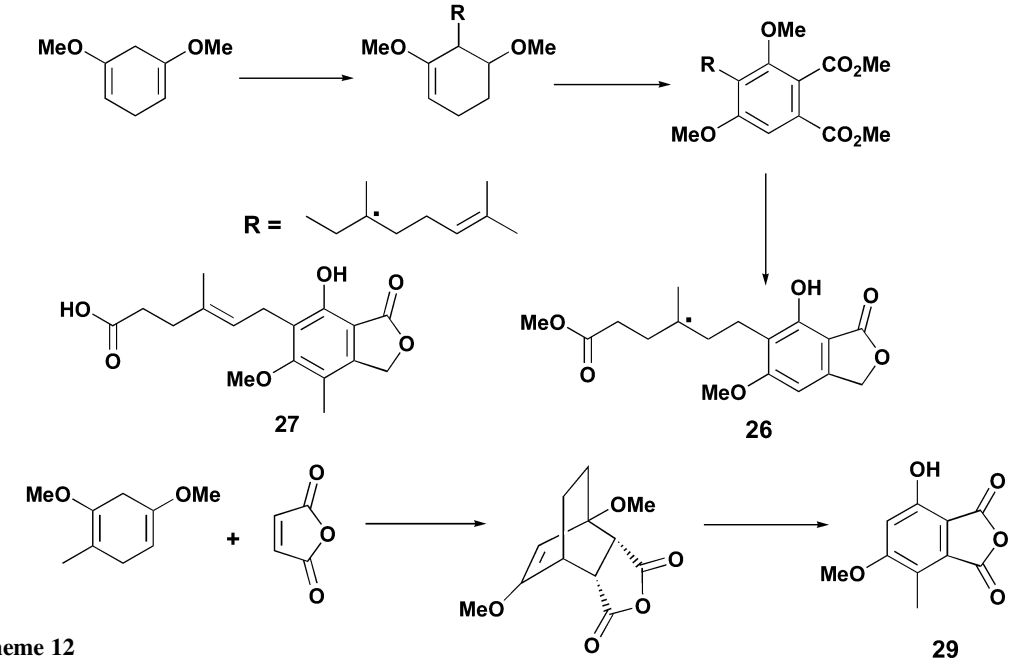
The naturally occurring macrolide, curvularin (**25**) is notable for its antifungal and antibiotic activities. This 12-member macrocycle fused to aromatic ring has been synthesized [9] based on the Alder–Rickert strategy (Scheme 11).



Scheme 11

Synthetic studies toward mycophenolic acid

Mycophenolic acid (**27**), a metabolite of *Penicillium brevi compactum*, has been well recognized for its immunosuppressant, antiviral, and antimiotic activities. A chiral analog of mycophenolic acid **26** has been synthesized [22] based on the alkylation of the diene followed by an Alder–Rickert reaction as indicated below (Scheme 12). Further, the synthesis of the key intermediate **29** was accomplished [22] by

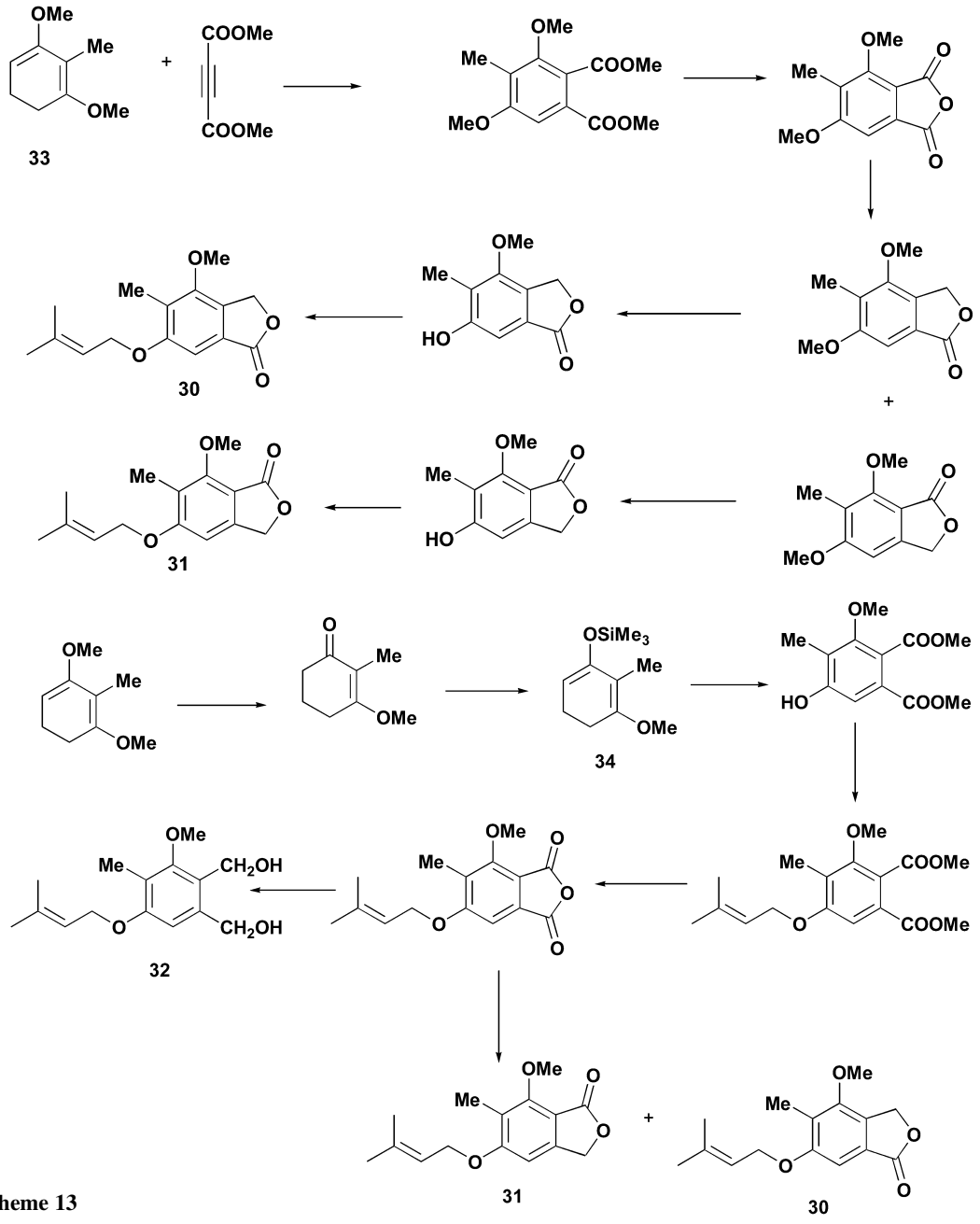


Scheme 12

making use of the Diels–Alder reaction of the diene with maleic anhydride followed by dehydrogenation of the resulting adduct and an Alder–Rickert reaction.

Naturally occurring phytotoxic phthalides

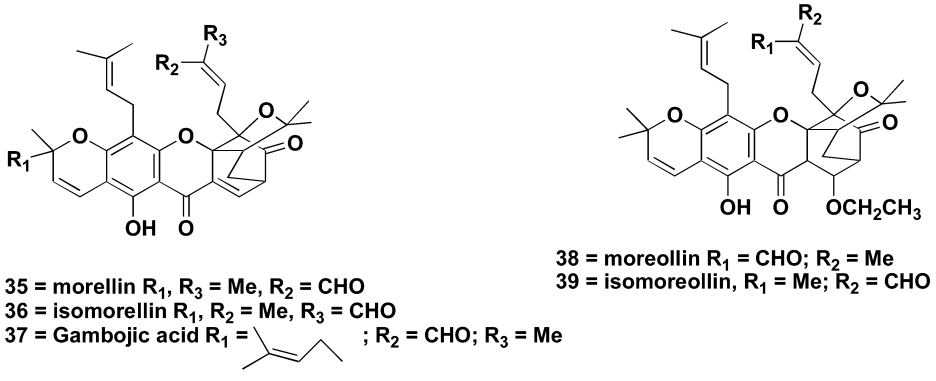
The phytoalexin phthalides **30** and **31** were isolated from the *Alternaria* species, and their synthesis was accomplished [10] using the Diels–Alder and Alder–Rickert process from the dienes **33** and **34** as shown in the Scheme 13.

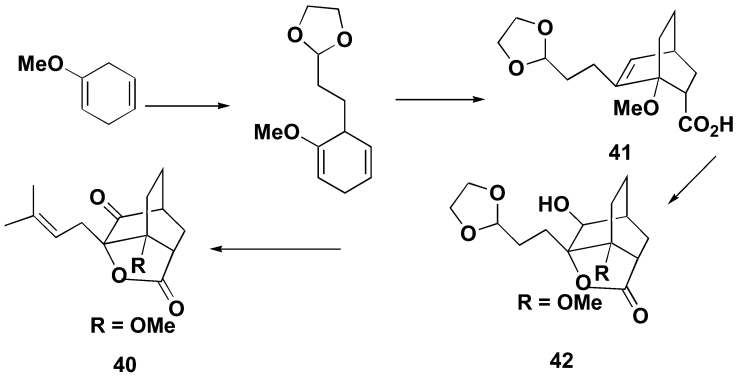


Scheme 13

Synthetic studies toward morellin

The complex xanthones, morellin (**35**), isomorellin (**36**), moreollin (**38**), isomoreollin (**39**), and gambogic acid (**37**), were isolated from *Garcinia* species, and they possess a novel oxatricyclo[4.3.1.0]decane moiety. Recently, a general strategy for the synthesis of 5,5-dimethyl-methoxy-4-oxatricyclo[4.3.1.0]decan-2-one **40** was reported [23] from our laboratory. The key step in the synthesis is the oxidative cyclization of the acid **41** to the lactone **42**, which was further elaborated to **40** (Scheme 14).





Scheme 14

ACKNOWLEDGMENTS

I would like to thank my able coworkers, whose names are given in the list of references for their hard work, skill, and enthusiasm. This work was supported by the Council of Scientific and Industrial Research and Department of Science and Technology, New Delhi, India. I thank CSIR for financial assistance (Emeritus Scientist). I also thank INSA for the award of Senior Scientist position.

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