Spiroepoxycyclohexa-2,4-dienones in Organic Synthesis

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Cyclohexa-2,4-dienones have been known for many years.[1] However, their chemistry has been limited to dimerization and rearrangement[1] until recently.[2−5] This is presumably because of their instability and high reactivity toward themselves and their propensity to aromatization and rearrangement.[1] In context with a research program to develop a unified strategy for the synthesis of polyquinanes and protoilludanes which has generated considerable interest,[6,7] cycloaddition of in situ generated spiroepoxycyclohexa-2,4-dienones of type **1** was explored[4,5] and a route to a variety of annulated bicyclo[2.2.2]octenones of type **2** and **3** was developed. Chemical and photochemical reactions of the annulated bicyclo[2.2.2]octenones thus obtained were also investigated. This led to the development of routes to various carbocyclic structures of contemporary interest[6,7] such as linearly fused *cis*−*anti*−*cis* triquinanes **4**, *cis*−*syn*−*cis* triquinanes **5,** tetraquinanes **6** and **7**, protoilludanes **8**, and the oxa-sterpurane framework **9** (Figure 1). In this Account, we summarize developments in this area wherein the spiroepoxycyclohexa-2,4-dienones have played a very important and crucial role, in conjunction with the chemical and photochemical reactions of the resulting tricyclic frameworks.

Generation of Spiroepoxycyclohexa-2,4-dienones In Situ and Intermolecular $\pi^{4s} + \pi^{2s}$ Cycloaddition with Cyclic Dienes. (a) Synthesis of *endo* Tricyclo[5.2.2.0^{2,6}]-undecanes. Conceptually, the tricyclo[5.2.2.0^{2,6}]undecanes of type 2 should be directly accessible in a single step via cycloaddition of cyclohexa-2,4-dienones such as 10 or 11 (Scheme 1) with appropriate olefins. Although the parent cyclohexa-2,4-dienone **10** (the keto tautomer of phenol) is unknown, only a few methods are known[8−10] for the preparation of 6,6-dialkyl derivatives **11** such as alkylation of substituted phenols[8] and rearrangement[9] of the exo-

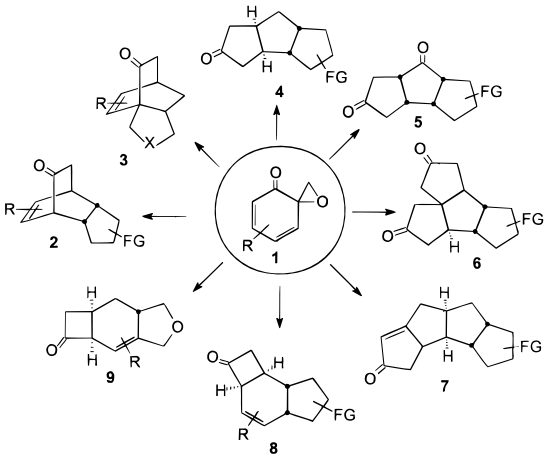


FIGURE 1. Types of carbocyclic frameworks synthesized from spiroepoxycyclohexa-2,4-dienones of type 1.

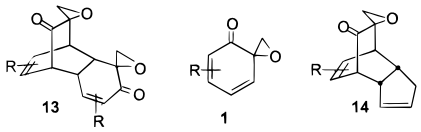
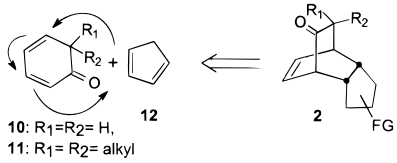


FIGURE 2. Potential precursors for generation of **1** and tricycloundecadienones.

Scheme 1



cyclic epoxide derived from dimethylfulvene. However, these methods appeared to be unsuitable for the above purpose. Therefore, a new indirect sequence for the synthesis of tricyclo[5.2.2.0^{2,6}]undecanes of type **2** employing epoxycyclohexa-2,4-dienones of type **1** was developed. It was envisaged that cycloaddition of **1** with cyclopentadiene would furnish adducts of type **14** (Figure 2) whose epoxyketone moiety and olefinic bond present in the five-membered ring would be readily manipulated to give a variety of tricyclo[5.2.2.0^{2,6}]undecanes of type **2**. However, spiroepoxycyclohexadienones of type **1** have only a fleeting existence during the oxidation of o-hydroxymethyl phenols and instantaneously dimerize.[11] Therefore, it was thought to generate the spiroepoxycyclohexa-2,4-dienones via a retro Diels−Alder reaction of the readily obtainable[11] epoxydimers **13,** and intercept them with a suitable diene/olefin.

Unfortunately, pyrolysis of dimers of type **13** in the presence of dienes/olefins failed to yield adducts of type **14** and gave the corresponding aldehyde instead (Scheme 2). This is apparently due to the thermal rearrangement of the oxirane followed by a retro Diels−Alder reaction and aromatization. At this juncture, spiroepoxycyclohexa-2,4-dienone **1** was generated and intercepted with a suitable olefin/diene during the oxidation of hydroxymethylphenol itself.

Vishwakarma Singh received his Ph.D. degree in 1976 from the University of Gorakhpur after which he joined the Indian Institute of Technology, Kanpur, and University of Hyderabad to work with Professor Goverdhan Mehta. He was awarded a Monbusho Fellowship from the Ministry of Education, Government of Japan, to work with Prof. E. Osawa at Hokkaido University, Sapporo, Japan (1979−1980). He then moved to the United States and worked with Prof. A. R. Martin and Dr. V. V. Kane as a Research Associate at the University of Arizona, Tucson. Vishwakarma Singh also worked with Prof. J. B. Hendrickson at Brandeis University, Waltham, MA (1981−1992). Dr. Vishwakarma Singh returned to India and after working at the Malti-Chem Research Center Nandesari, Baroda, and the M. S. University of Baroda, he joined the Indian Institute of Technology, Bombay, in October 1989, and currently he is Professor. His research interests are in the area of organic synthesis and photochemistry.

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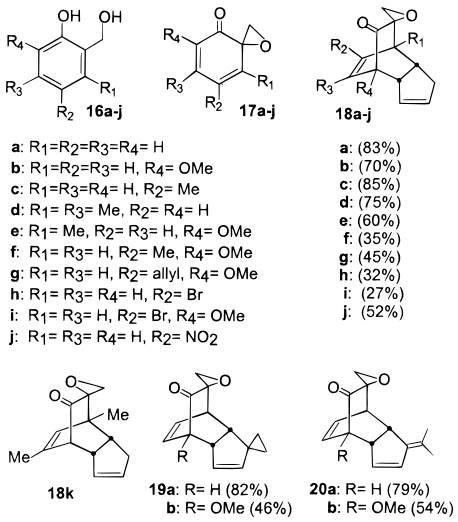
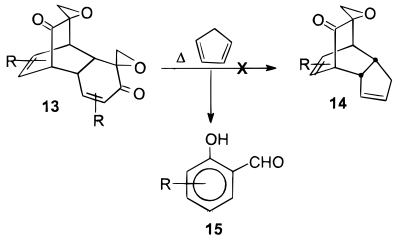
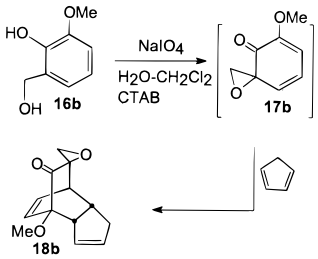


FIGURE 3. A list of the tricyclic adducts prepared by cycloaddition of various spiroepoxycyclohexa-2,4-dienones with dienes.

Scheme 2



Scheme 3



Thus, oxidation of *o*-vanillyl alcohol with aqueous sodium *meta* periodate at 0 °C in the presence of cyclopentadiene in a biphasic ($CH_2Cl_2-H_2O$) medium containing cetyltrimethylammonium bromide as a phase transfer catalyst, furnished the adduct **18b** in excellent yield (70%) (Scheme 3).[4] Similar oxidation of *o*-vanillyl alcohol in the presence of spiro[4,2]hepta-1,3-diene[12] and dimethyl fulvene[13] gave the adducts **19b** and **20b** respectively in good yields (Figure 3). Following the above method and a modification thereof,[5a] a large number of annulated bicyclo[2.2.2]octenones **18**−**20** were prepared in a single step by oxidation of a variety of phenols in the presence of a suitable diene (Figure 3). The generation of structural complexity in a single step from simple starting materials, one of the desirable features in organic synthesis,[14] may be noted. The structures of all the adducts were deduced through detailed analysis of the spectral data. The above cycloadditions proceeded with a high degree of regio- and stereoselectivity because all of the reactions gave single *endo* adducts in each case wherein cyclopentadiene

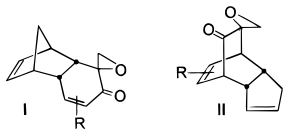
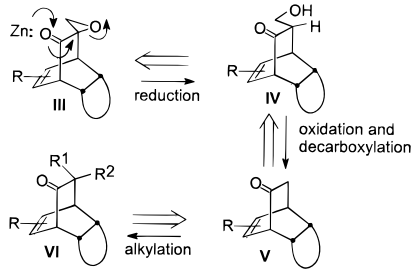


FIGURE 4. Some other possibile adducts during cycloaddition of spiroepoxycyclohexa-2,4-dienones.

Scheme 4

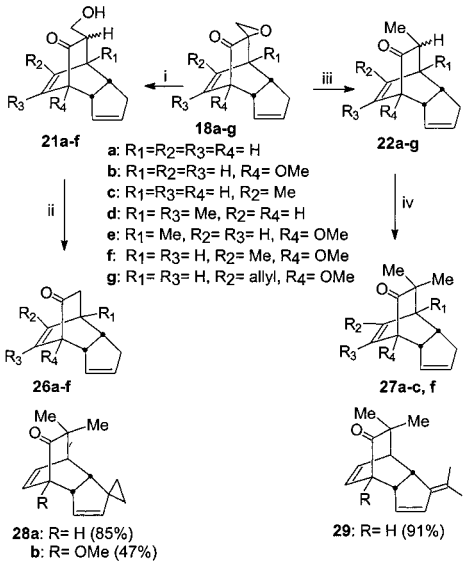


apparently behaved as a 2π partner. In principle, the reaction of the cyclohexa-2,4-dienone with dienes could give rise to a number of products such as **I** via an alternate pericyclic mode,[15,16] or adducts of type **II** (Figure 4) having the opposite orientation of the oxirane ring. Adducts of type **II** were not obtained in any case except during oxidation of **16d** which gave **18k** in minor amounts (3%) in addition to **18d**.[5e] There exists a mechanistic dichotomy [17,18] regarding the formation of the adducts and pericyclic modes during cycloaddition of cyclohexa-2,4-dienones with dienes. For instance, the adducts **18**−**20** could be obtained either via a direct primary mode of addition wherein the cyclohexa-2,4-dienones behave as a 4π partner and the diene as a 2π partner or via a 3,3-shift in the adducts of type **I** which may initially form during the cycloaddition as a result of $\pi^{4s}_{(\text{diene})} + \pi^{2s}_{(\text{dienone})}$ addition.[17,18] However, the adducts of type **I** were not obtained in the above experimental conditions.

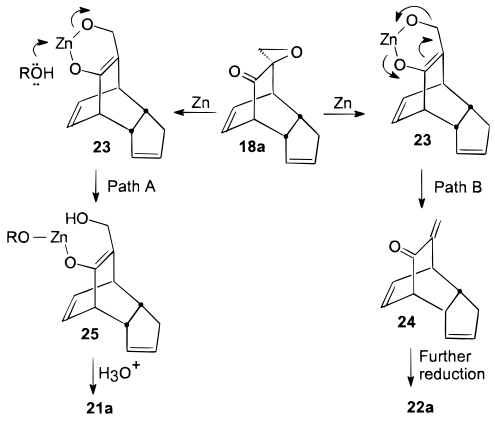
Transformation of the adducts 18−20. The cycloadducts obtained via the reaction of spiroepoxycyclohexa-2,4-dienones and dienes provided a unique opportunity for further manipulation because of the presence of a contiguous keto-epoxide functionality and a double bond in the annulated five-membered ring. It was considered that reduction of keto-epoxide would give a β-keto-alcohol (**IV**) which could then easily be converted into the parent tricyclic systems (**V**) as well as the substituted analogues (**VI**) (Scheme 4).

In view of the above, the adduct **18a** was treated with activated zinc in dry methanol containing ammonium chloride at 60 °C for 8 h. However, the deoxygenated product **22a** was also obtained in addition to the desired keto-alcohol **21a**. It was observed[19] that the above reduction in aqueous methanol at ambient temperature (~30 °C) gives the keto-alcohol **21a** (mixture of syn−anti isomers) selectively as a major product (77%), whereas reduction in dry dioxane at reflux furnishes the deoxygenated product **22a** as a major product (76%) in a selective manner (Scheme 5). A plausible mechanism, origin of selectivity, and stereochemical outcome of this reduction are briefly presented below.

Scheme 5



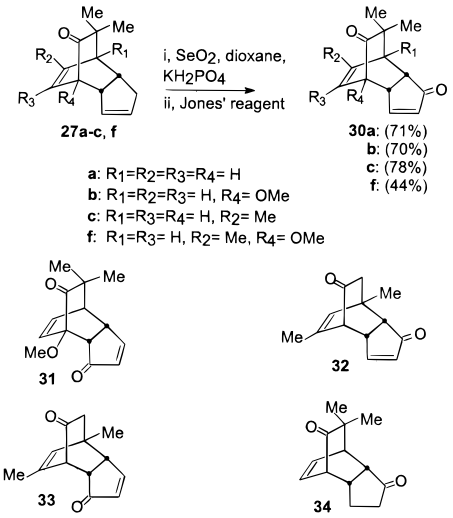
Scheme 6



The above reduction apparently proceeds through the formation of a six-membered organozinc intermediate such as **23**, which after solvolytic cleavage (path A) followed by protonation of the resulting enol (or its zinc equivalent), gives the keto-alcohol **21a** (as a syn−anti mixture) as shown in Scheme 6. Alternatively the intermediate **23** may collapse to give the trienone **24**, especially in non-nucleophilic solvent, which may undergo further reduction with zinc to furnish the ketone **22a** (Scheme 6). This mechanism is supported from the following observations.

When the above reduction was terminated after 3 h, the trienone **24** was also obtained along with keto-alcohol **21a** and the ketone **22a.** Moreover, it became immediately clear that the ketone **22a** is formed via further reduction of enone **24** because a mixture of **22a** and **24** was transformed solely into **21a** upon further treatment with zinc. Initially, it was thought that the enone **24** might arise by dehydration of the β-hydroxyketone **21a**. However, treatment of **21a** with zinc and ammonium chloride under similar experimental conditions did not yield the trienone

Scheme 7



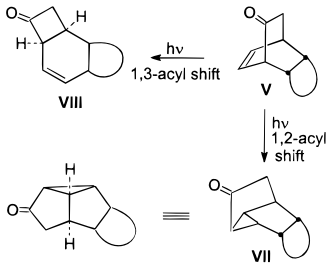
24. These observations suggested that the keto-alcohol **21a**, and trienone **24** (and hence the ketone **22a**), arises from a common intermediate such as **23**. The selective formation of the keto-alcohol **21a** and **22a** from **18a** on reduction in aqueous methanol and dry dioxane, respectively, clearly supported the aforementioned views.[19]

Although zinc has been used on innumerable occasions for the reductive elimination of various functionalities α- to carbonyl groups,[20] the deoxygenation of α,β-epoxyketones under such mild conditions has not been recorded.

The aforementioned solvent-dependent reduction proved to be advantageous because it provided a simple method to obtain both the products **21a** and **22a** selectively, in good yields, for further transformation. Thus, the hydroxymethyl ketone **21a** was easily converted to the parent system **26a** via Jones' oxidation[21] and decarboxylation of the resulting keto-acid. Furthermore, the monomethyl ketone **22a** was alkylated[22] with methyl iodide to give the dimethyl ketone **27a** in good yield (95%). Following the above methods, other adducts were also transformed into a variety of *endo* tricyclo[5.2.2.0^{2,6}]-undecane systems **26**−**29** (Scheme 5) having a β,γ-unsaturated carbonyl chromophore.

To introduce functional groups in the five-membered ring of tricyclic systems, some of the compounds obtained after manipulation of the epoxide group were subjected to allylic oxidation.[23] Thus, compound **27a** was first oxidized with selenium dioxide to give a mixture of allylic alcohols which upon further oxidation with Jones' reagent furnished the enone **30a** in major amounts (∼70%) (Scheme 7). The structure of the enone was deduced through a detailed analysis of high field ^{1}H NMR, carbon magnetic resonance (^{13}CMR), and correlation spectroscopy (COSY)/decoupling experiments.[5c] Similarly, the substrates **27b**, **c**, **f,** and **26d** were converted into the enones **30b**,[5d]**c**, **f,**[5a] and **32,**[5e] respectively. The enones **31** and **33** were also obtained in small amounts (∼30%) during the oxidation of **27b** and **26d**, respectively.[5d,5e] Enone **30a** was further transformed into the dione **34** by reduction with Zn−NH_4Cl in refluxing dioxane.[5c] Thus, a

Scheme 8



number of *endo* tricyclo[5.2.2.0^{2,6}]undecanes were prepared from simple *o*-hydroxymethyl phenols via their oxidation to corresponding spiroepoxycyclohexa-2,4-dienones, interception with suitable dienes, and transformation of the resulting adducts.

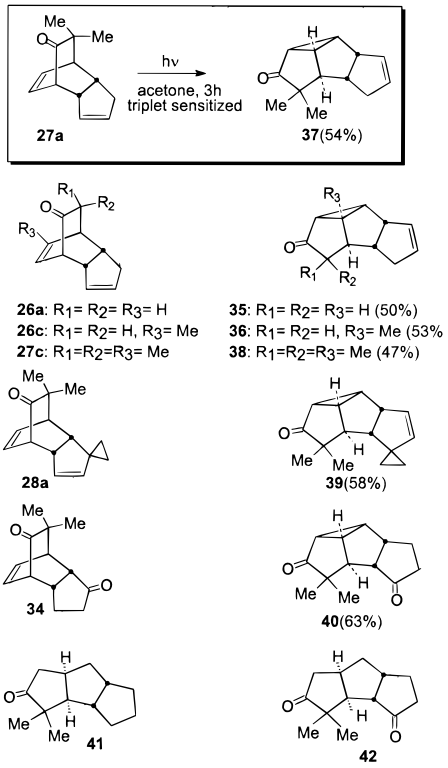
(b) Chemical Reactions of the *endo* Tricyclo[5.2.2.0^{2,6}]-undecanes in Excited States: A Novel Route to Polyquinanes and Protoilludanes. The tricyclic systems **26**−**34** offered a unique opportunity for us to explore their photochemical reactions because they are endowed with a β,γ-unsaturated carbonyl group which is an unusually reactive chromophore. Photochemical reactions of β,γ-enones have stimulated great interest in the past[24] which was enhanced recently[25] because of their synthetic potential. Rigid β,γ enones undergo two unusual reactions, namely a 1,2-acyl shift or oxa-di-π-methane rearrangement to form a cyclopropyl conjugated ketone upon triplet sensitization, and a stereospecific 1,3-acyl shift to form cyclobutanones upon singlet excitation.[24,25]

Some time ago[26,27] it was considered that 1,2-acyl and 1,3-acyl shifts in *endo* tricyclic systems of type **V** would lead to novel and stereospecific routes to polyquinanes of type **VII** and the protoilludane framework **VIII** (Scheme 8). In view of this, photoreactions of some of the tricyclic systems were explored.

Although photochemical reactions of β,γ-enones have been studied in detail, earlier investigations mainly were focused on the mechanistic aspect and singlet and triplet dichotomy.[24a,28−31] Although the application of the oxa-di-π-methane rearrangement in the synthesis of simple bicyclic systems was realized,[25b] the photochemical rearrangements in complex tricyclic β,γ-enones and their synthetic potential were not explored until recently.[4,26]

(i) Photochemical Reaction of the Tricyclic Chromophoric Systems upon Triplet Sensitization: Synthesis of Polyquinanes. The photoreactions of β,γ-enones are quite characteristic of the respective excited states; often a mixture of products is obtained because of the population of singlet and triplet excited states. Moreover, the photoreactions also depend on the structure of the chromophoric system and substituents in a subtle fashion.[24,28−30,32] In view of the above, the photochemical behavior of tricycloundecadienones **26**−**34** upon triplet sensitization was investigated. First, a solution of compound **27a** in dry acetone (solvent as well as sensitizer) was irradiated in a Pyrex immersion well (Hg vapor lamp, Hanovia) under nitrogen and the rearranged product **37** was furnished smoothly in good yield (54%) (Scheme 9).

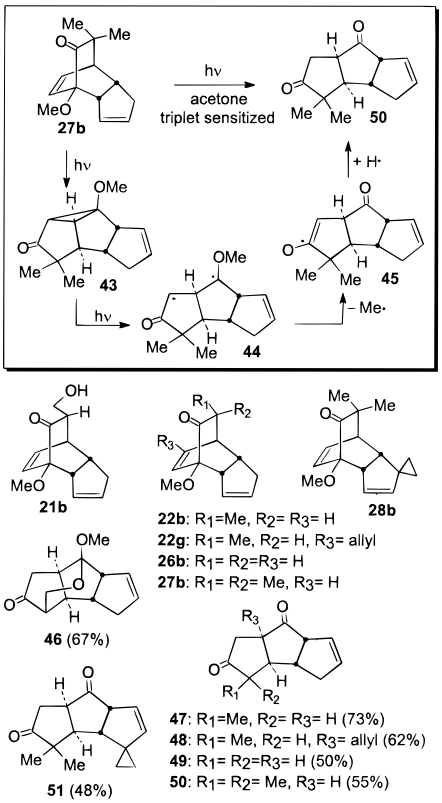
Scheme 9



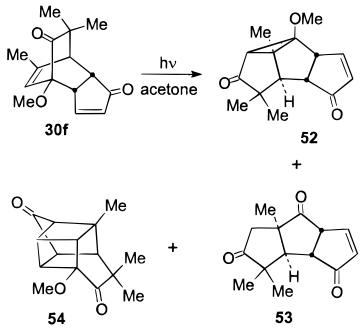
Similarly, irradiation of **26a**,**c** and **27c**, **28a**, **34** in acetone gave oxa-di-π-methane products **35**, **36**, and **38**−**40**, respectively, in good yields (Scheme 9).[5c] Structures of all the photoproducts were established through spectral and analytical data. Irradiation of the chromophoric system **34** containing an additional reactive carbonyl chromophore in the five-membered ring also gave the tetracyclic compound **40** in good yield. However, compound **29** did not undergo oxa-di-π-methane rearrangement upon sensitized irradiation presumably because of the quenching effect of the diene moiety.[24a,33] The tetracyclic photoproducts **37** and **40** were further converted into *cis*−*anti*−*cis* triquinanes **41** and **42**, respectively, upon reductive cleavage of the cyclopropane ring.[5c]

The sensitized irradiation of the *endo* tricyclic compounds **22b**, **g**, **26b**, **27b**, and **28b** containing an α-methoxy-β,γ-enone chromophore produced a more remarkable result because irradiation of all the compounds in acetone furnished directly the *cis*−*anti*−*cis* triquinane diones **47**−**51**, respectively (Scheme 10), and the usual oxa-di-π-methane products were not observed.[4a,5d] This type of photoreaction appears to be unique for rigid systems having α-methoxy-β,γ-enone chromophore and has also been observed[34] earlier in a simple bicyclic system. The above photochemical reaction may proceed through an initial oxa-di-π-methane rearrangement to give a tetracyclic compound of type **43** which upon cleavage of the cyclopropane ring leads to the diradical **44**. Subsequent loss of a methyl radical in **44** may give the intermediate **45** which abstracts a hydrogen to furnish the final product.[4a,34] Although the loss of a methyl radical in the above photoreaction is unexpected, a similar mechanism

Scheme 10



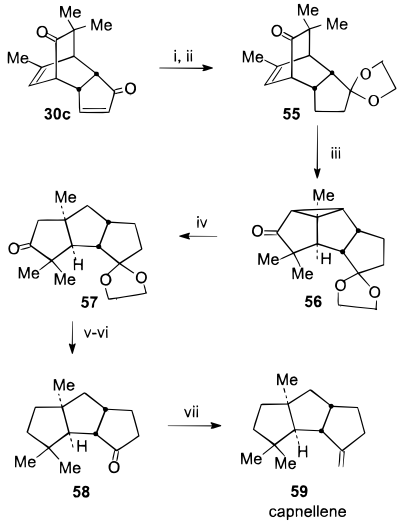
Scheme 11



invoking expulsion of methyl radical was suggested to explain the formation of products.[34] Irradiation of the keto-alcohol **21b** furnished an interesting tetracyclic product **46** presumably arising through participation of the hydroxyl group in the photoreaction.[5d] The photoreaction of the enones **30** was only briefly investigated and gave a mixture of products as expected. Thus, irradiation of **30f** in acetone gave **53**, the cage product **54** formed as a result of intramolecular $\pi^{2s} + \pi^{2s}$ cycloadditon, and a very small amount of **52** (Scheme 11). Further irradiation of 1,2-acyl shift product **52** was found to give **53**, thus strengthening these views on the mechanism of the photoreaction of α-methoxy-β,γ-enones.[5a,34]

Thus, the photoreaction of *endo* tricyclic compounds provided two efficient, general, and stereoselective routes to linearly fused *cis*−*anti*−*cis* triquinanes. Application of this cycloaddition−photochemical strategy toward syntheses of triquinane natural products, capnellene and coriolin, is briefly outlined below.

Scheme 12

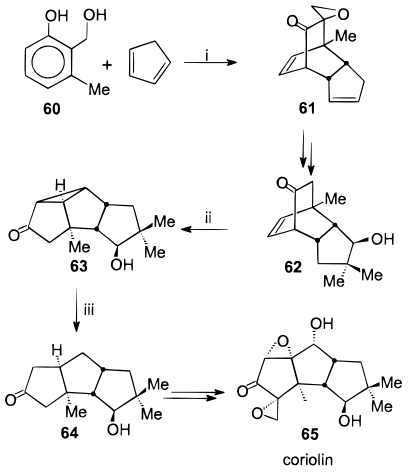


Reagents/conditions: i, (a) $NaBH_4$, MeOH, 0-10ºC, (b) Jones oxidation, 68%; ii p-TSA, ethyleneglycol, benzene, Δ, 64% ; iii, hν, acetone,1.5h, 64%; iv, H_2, Pd-C, MeOH, 85%; v, (a) $NaBH_4$, MeOH, r.t., 90%, (b) NaH, CS_2, imidazole, MeI, 90%, (c) $(Bu)_3SnH$, AIBN, toluene, Δ, 76% ; vi H_3O^+; vii, $PPh_3{=}CH_2$, toluene, Δ, 72%.

Total Synthesis of Capnellene. Capnellene (**59**), a triquinane sesquiterpene isolated from marine soft coral *Capnella imbricata*, is a popular target for synthesis[35,36] presumably because of its molecular architecture and its role in the defense mechanism and biosynthesis.[37] However, most syntheses of capnellene generate its tricyclic framework iteratively after a multistep sequence, often in a non-stereoselective fashion. Cycloaddition−photochemical strategy led to synthesis of capnellene from adduct **18c** which contains 13 out of 15 carbons required. Thus, the enone **30c** readily available from **18c** (vide supra) was elaborated to the keto-ketal **55**. The ketal **55** contains 14 carbons (out of 15) of capnellene, with appropriate connectivity and substituents at desired centers. Irradiation of **55** in acetone furnished the key tetracyclic precursor **56**. Reductive cleavage of the cyclopropane ring in **56** gave the triquinane **57**. Reduction of the carbonyl group followed by Barton deoxygenation and hydrolysis of the ketal group yielded the known[36c] precursor **58**. Wittig reaction on **58** gave capnellene, **59** (Scheme 12).[35a,b]

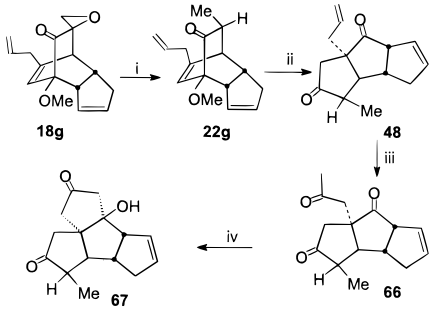
In a similar fashion, Funk's[37] intermediate **64** for coriolin **65**, a metabolite of microorganism *Coriolus consors*,[38a] was synthesized from aromatic precursor **60**. Thus, the oxidation of **60** with sodium *meta* periodate in aqueous acetonitrile containing cyclopentadiene furnished in good yield the key *endo* tricyclic adduct **61** which was transformed into the tricyclic precursor **62.** Triplet-sensitized irradiation of **62** furnished the tetracyclic precursor **63.** Reductive cleavage of the cyclopropane ring in **63** gave the intermediate **64** (Scheme 13)[38b] which has already been elaborated to coriolin, **65**. A large number of methods have been developed previously for the synthesis of triquinane natural products, but a majority of the methods are target oriented, lack adaptability, and generate the triquinane framework often in a nonselective manner.[6,7]

Scheme 13



Reagents/ conditions: i, $NaIO_4$, CH_3CN-H_2O, 45%; ii, hν, acetone, 65%; iii H_2, Pd-C, MeOH, 55%

Scheme 14



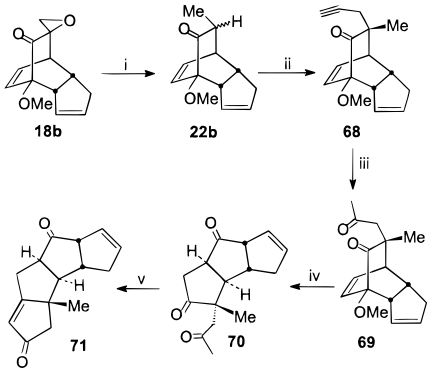
Reagents/ conditions: i, Zn, NH_4Cl, dioxane, Δ, 73%; ii, hν, acetone, 62%; iii,$PdCl_2$, CuCl, O_2, DMF, 63%; iv, KO^{t}Bu-^{t}BuOH, r.t. ,74%.

Synthesis of Tetraquinanes. The synthetic versatility of the adducts obtained by the reaction of 2-methoxy-6-spiroepoxycyclohexa-2,4-dienones is further demonstrated through the syntheses of angular and linear tetraquinanes.

The *endo* tricyclic compound **22g**, which is readily available from the adduct **18g**, provided an efficient route to angular tetraquinane **67** as presented in Scheme 14.[39] Thus, triplet-sensitized photoreaction of **22g** gave functionalized triquinane **48**. The dione **48** was readily converted into the trione **66** by Wacker oxidation,[40] which upon aldol condensation gave the tetraquinanedione **67** in good yield (Scheme 14). In analogous fashion the compound **22b** obtained from the adduct **18b** was readily elaborated to linear tetraquinane **71** as presented in Scheme 15.[39] Thus, the monomethyl ketone **22b** was propargylated to give **68** with the propargyl group syn to the double bond in the bicyclo[2.2.2]octane framework as a major product. Hydration of the alkyne moiety gave the dione **69**, which upon photochemical rearrangement furnished the trione **70**. Subsequent aldol condensation in **70** gave the linearly fused tetraquinane **71** (Scheme 15).

(ii) Sigmatropic 1, 3-Acyl Shift in the Singlet Excited State: Another Facet of the Photochemistry of *endo* Tricyclo[5.2.2.0^{2,6}]undecanes. A Novel and Stereoselective Route to Protoilludanes. In the preceding section,

Scheme 15



Reagents/conditions: i, Zn, NH_4Cl, dioxane, Δ, 65%; ii, NaH, THF, propargyl bromide, 62%; iii, HgO, H_2SO_4-H_2O, 80%; iv, hν, acetone, 78%; v, KO^{t}Bu-^{t}BuOH, r.t. ,65%.

application of *endo* tricyclo[5.2.2.0^{2,6}]undecanes obtained from cycloadducts of various spiroepoxycyclohexa-2,4-dienones toward tri- and tetraquinanes were described. These tricyclic compounds provided yet another opportunity for the development of a novel and stereoselective route to protoilludanes, a class of sesquiterpenoids obtained along the humulene cyclization cascade.[41,42] Protoilludanes have a unique carbocyclic framework consisting of four-, six-, and five-membered rings fused in an angular *cis*−*anti*−*cis* fashion. There has been a resurgence in the chemistry and biology of protoilludanes and related sesquiterpenes recently.[41,42] Although there have been no attempts to develop routes to recently isolated protoilludanes,[41] only a few routes are known[43] for the earlier members of this class of compounds. To develop a novel and stereoselective route to protoilludanes, the photochemical 1,3-acyl shift in *endo* tricyclo[5.2.2.0^{2,6}]undecanes **26c, d**, **27a**−**29** was studied.

Initially a solution of **27a** in benzene was irradiated in a quartz immersion well. However, a mixture of products containing only a small amount of the desired 1,3-acyl shift product (IR), was obtained. Therefore, a solution of **27a** in benzene was irradiated in a Pyrex immersion well, which furnished the desired product **81** (Scheme 16) in reasonably good yield. Other tricyclic systems **26c**,**d**, **28a**, **29** were also subjected to singlet excitation and gave the corresponding protoilludanes **79**, **80**, **82**, **83**, respectively (Scheme 16). Irradiation of more functionalized tricyclic systems **72**−**78**, which are readily prepared following the methodology presented earlier, also furnished embellished protoilludane frameworks **84**−**90** (Figure 5).[5c,e] The substrate **29**, which did not undergo the triplet-sensitized 1,2-acyl shift or oxa-di-π-methane rearrangement (vide supra), readily underwent 1,3-acyl shift upon singlet excitation to give the corresponding product **83**.[5c] This observation further supports the understanding[24−28] that the oxa-di-π-methane rearrangement occurs through the triplet excited state, whereas the 1,3-acyl shift is a reaction of the excited singlet state. Irradiation of the enone **74**, which contains an additional highly reactive α,β-epoxy ketone chromophore, also underwent a smooth 1,3-acyl shift upon irradiation in benzene to furnish the product **86** in good yields.[5c]

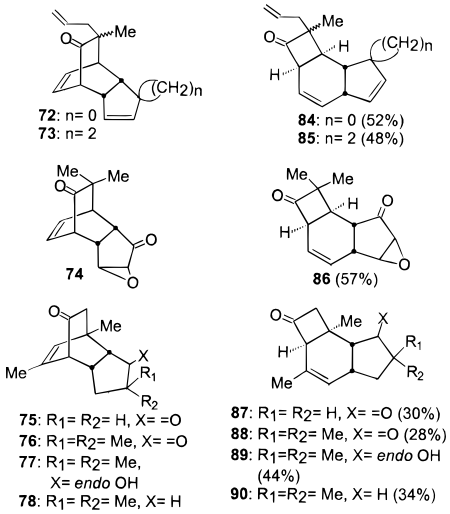
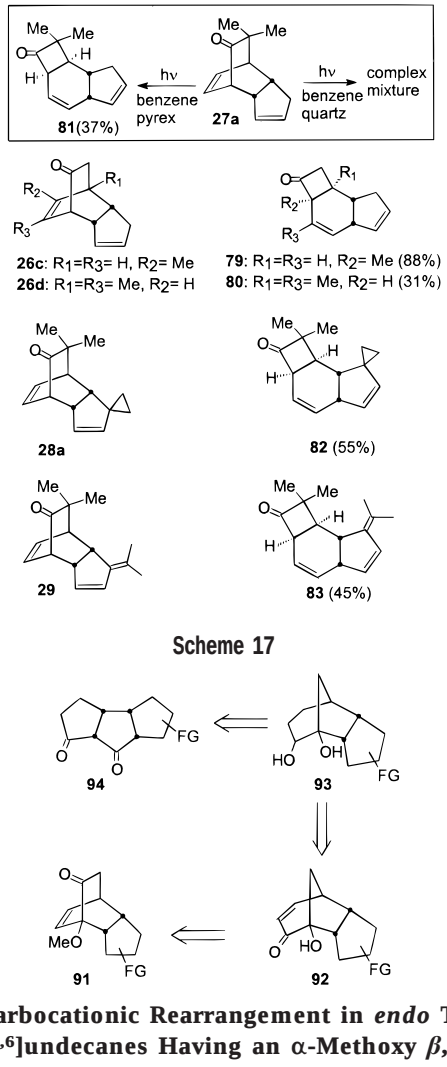


FIGURE 5. A list of tricyclic chromophoric systems and photoproducts obtained after singlet excitation.

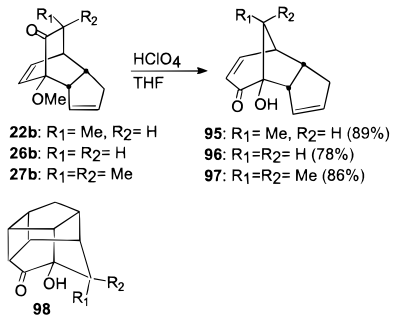
Scheme 16



Scheme 17

(c) Carbocationic Rearrangement in *endo* Tricyclo-[5.2.2.0^{2,6}]undecanes Having an α-Methoxy *β,γ*-enone Group: A Route to Folded *cis*−*syn*−*cis* Triquinanes. Folded tricyclopentanoids having *cis*−*syn*−*cis* geometry of type 94 (Scheme 17) have also generated significant interest because of their role in the synthesis of asthetic higher polyhedra[44] and because of their potential in the synthesis of concave, preorganized molecular hosts.[45] The *endo* tricyclic compounds of type **91** having an α-methoxy-*β,γ*-enone group provided further opportunity to develop a new and efficient method for the synthesis of *cis*−*syn*−*cis* tricyclopentanoids, thus exhibiting yet another facet of chemistry of the adducts derived from cycloaddition of 2-methoxy-6,6-spiroepoxycyclohexa-2,4-dienones. The cornerstone of strategy for the elaboration of the tricyclic systems of type **91** to folded *cis*−*syn*−*cis* triquinanes such as **94** is the recognition of the structural and functional relationship between **91** and the *endo* tricyclic diol **93** with an annulated bicyclo[3.2.1]framework. It was realized that the tricyclic diol **93** is endowed with two of the three cyclopentane rings needed for the synthesis of triquinane and that the elements of the third cyclopentane ring are also present in latent form. Furthermore, it was considered that the *endo* tricyclic diol **93** could be obtained from the ketone **91** *via* a regioselective carbocationic rearrangement followed by reduction of the resulting keto alcohol **92** (Scheme 17). There are no direct routes to tricyclo[5.3.1.0^{2,6}] ring systems of type **92**, although this ring system constitutes the carbocyclic core of gymnomitrol, a representative of an important class of sesquiterpene.

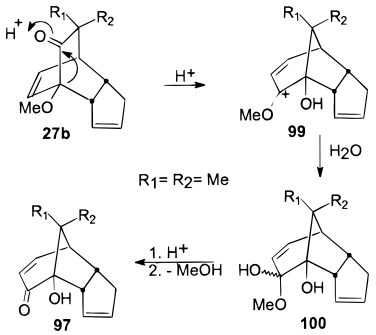
Scheme 18



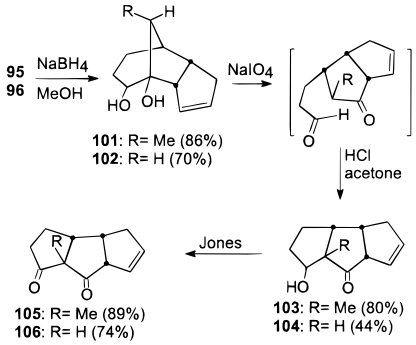
In view of the above, the compound **27b** was treated with *p*-toluenesulfonic acid in refluxing benzene following a procedure by Rogers and co-workers.[46] However, this reaction gave a complex mixture of products. Treatment of ketone **27b** with BF_3·OEt_2 in dry methanol at ∼50 °C furnished the rearranged product, although the rearrangement was slow and incomplete. Aqueous perchloric acid (70%) in tetrahydrofuran was found to be the most suitable reagent for the desired rearrangement.[47,48] Thus, a brief treatment of ketone **27b** with $HClO_4$ gave the keto-alcohol **97** in excellent yield (86%). The structure of the rearranged product **97** was deduced from its spectral data and the *endo* stereochemistry at the ring junction was proved through its photoconversion to a novel trishomocubane derivative **98** (Scheme 18). This skeletal rearrangement proceeds through protonation of the carbonyl group in **27b** and regioselective migration of the C1−C2 bond to give the stabilized carbocation **99**. Nucleophilic capture of the cation by water gives the hemiacetal **100** and subsequent loss of methanol finally furnishes the product as shown in Scheme 19.

Following the above observation, other compounds **22b** and **26b** were also rearranged to **95** and **96**, respectively.

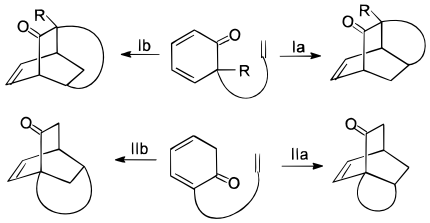
Scheme 19



Scheme 20



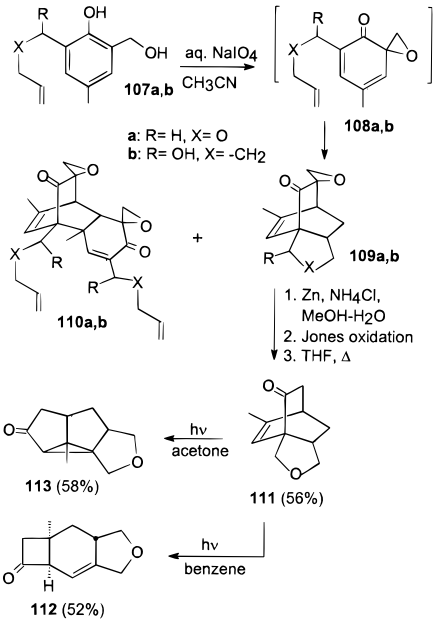
Scheme 21



Reduction of the rearranged products **95** and **96** with sodium borohydride furnished the corresponding diols **101** and **102** which were readily converted to *cis*−*syn*−*cis* tricyclopentanoids **105** and **106**, respectively, as shown in Scheme 20.[47]

Intramolecular Cycloaddition of Cyclohexa-2,4-dienones. Intramolecular Diels−Alder reactions[48a] of cyclohexa-2,4-dienones offer myriad possibilities for rapid creation of a variety of complex carbocyclic frameworks depending upon the place of attachment of the tether containing the dienophilic moiety. Some possibilities are shown in Scheme 21. A few cycloadditions of type Ia, b are known.[48,49] In connection with a project on synthesis of sterpurane sesquiterpenes, the cycloaddition of type II wherein the tether is attached at C-2 of the cyclohexadienone was studied. Thus, the spiroepoxycyclohexa-2,4-dienones **108a**,**b** were generated by oxidation of the corresponding aromatic precursors **107a**,**b** which gave the adducts **109a**,**b**, respectively, along with some amounts of the dimers **110**. The adduct **109a** was then transformed into tricyclic ketone **111** following the methodology presented in an earlier section and its photochemical reaction was explored. Thus, triplet-sensitized irradiation of **111** gave the tetracyclic compound **113**, whereas direct irradiation of **111** in benzene furnished the oxa-sterpurane framework **112** efficiently (Scheme 22).[50] Studies on chemical and photochemical reactions of **109b** are in progress.

Scheme 22



Conclusion

Cycloaddition of spiroepoxycyclohexa-2,4-dienones and the transformation of resulting adducts were explored. This chemistry led to synthesis of a variety of complex tricyclic systems having a β,γ-unsaturated carbonyl chromophore not readily accessible otherwise. The chemical and photochemical reactions of the resulting adducts provided novel, efficient, and general strategies to a variety of complex frameworks of natural products in a highly stereoselective and efficient fashion. The methodologies presented in this account provide stereoselective routes to linearly fused *cis*−*anti*−*cis* triquinanes, tetraquinanes, protoilludanes, and oxa-sterpurane framework and *cis*−*syn*−*cis* triquinanes from simple aromatic precursors. Application of cyclohexa-2,4-dienones toward synthesis of phorbol esters, taxol, and sterpuranes is in progress.

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