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NEW APPROACHES TO THE TOTAL SYNTHESIS OF BIOLOGICALLY ACTIVE NATURAL PRODUCTS

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Abstract - New concepts will be presented which employ intra- and intermolecular Diels-Alder reactions and electrocyclic rearrangements in the synthesis of several biologically active natural products of great structural diversity. Among the various target molecules are the steroids (cortisone and estrone), the anthracyclines and their analogues (aclacinomycin, collinemycin, etc.), and terpenes such as β-cuparenone and coronafacic acid. In particular, a new approach to estrone and cortisone via an intramolecular Diels-Alder reaction is described.

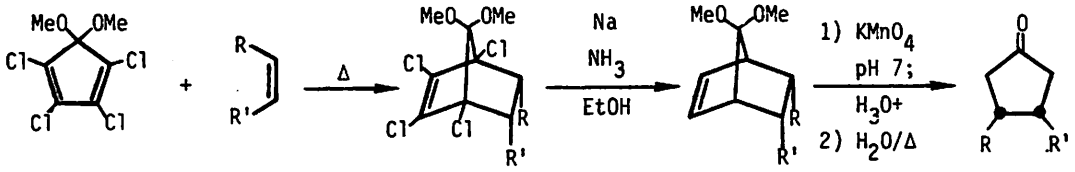
INTRODUCTION

Of all of the varied ways to construct organic molecules, few methods of carbon-carbon bond formation can match cycloadditions and electrocyclic rearrangements for their efficiency and their regiochemical and stereochemical control in the formation of new relative asymmetric centers in the molecule. For example, the Diels-Alder reaction not only results in the formation of two new carbon-carbon bonds, but also allows one the opportunity to control the stereochemistry of all of the new asymmetric centers. The Cope and Claisen rearrangements and their variants offer the possibility of new carbon-carbon bond formation with transfer of asymmetry at one center to another. The inherent elegance of these basic methods led us about five years ago to initiate a program concerned with the development of new general methodology for the facile construction of natural products of wide structural diversity utilizing as the key step both inter- and, in particular, intramolecular cycloadditions and facile electrocyclic rearrangements. As a special goal, we hoped to develop new dienes for the Diels-Alder reactions which would have higher reactivity or offer better regiochemical control than those available.

PERCHLORINATED DIENES

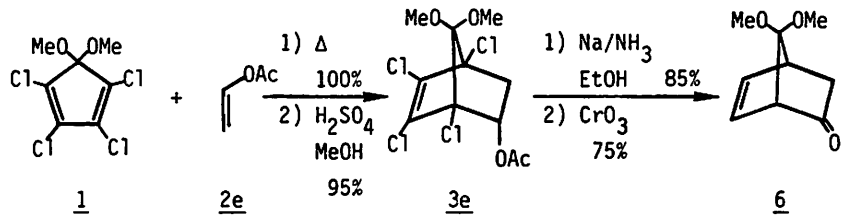
One of our initial goals in this broad program was the development of a general method for a process we termed functionalized three-carbon annulation (1), namely the attachment of a three-carbon unit to two adjacent carbons of a cyclic or acyclic precursor to form a functionalized cyclopentane ring. No good general method existed for this transformation, although the two corresponding ones - [2 + 2→4] (photochemical cycloaddition of two olefins) and [2 + 4→6] (Diels-Alder reaction) - were quite well known and of great synthetic utility. To give the greatest generality to the method, we desired to place as few restrictions as possible on the nature of the olefinic substrate so that not only electron-rich and electron-poor olefins but even simple unsubstituted olefins would afford good yields of the final cyclopentanone products. This problem was solved admirably by the use of the very highly reactive compound dimethoxytetrachlorocyclopentadiene 1 (2) as the diene component. Cycloaddition of 1 with representative olefins 2 afforded the adducts 3 in very good yields. Replacement of all of the chlorine atoms by hydrogen was smoothly effected by reduction with sodium in liquid ammonia / ethanol to furnish 4 in good yield. These are the products of a formal Diels-Alder reaction of dimethoxycyclopentadiene with the simple olefins, a reaction that is quite unlikely to produce especially in the case of the simple olefins. This technique of using a perchlorinated diene as the very reactive diene component, i.e., capable of cycloadding to "unreactive" dienophiles, followed by a high-yielding reductive dechlorination should permit the preparation of many Diels-Alder adducts that are unavailable at present. Final oxidation, hydrolysis, and decarboxylation of 4 produced the desired cyclopentanones 5 in moderate overall yields (34-40%).

This new synthetic approach allowed the facile preparation of other small highly functionalized molecules which are of great value in synthesis and are unavailable or available only with difficulty today. For example, the four step sequence shown for the preparation of the enone ketal 6 can be carried out on large scale in good overall yield (~60%) and is now an undergraduate laboratory preparation at UCLA. The dechlorination of 3e is an exciting reaction to run since as one adds each drop of the ethereal solution of 3e and ethanol to

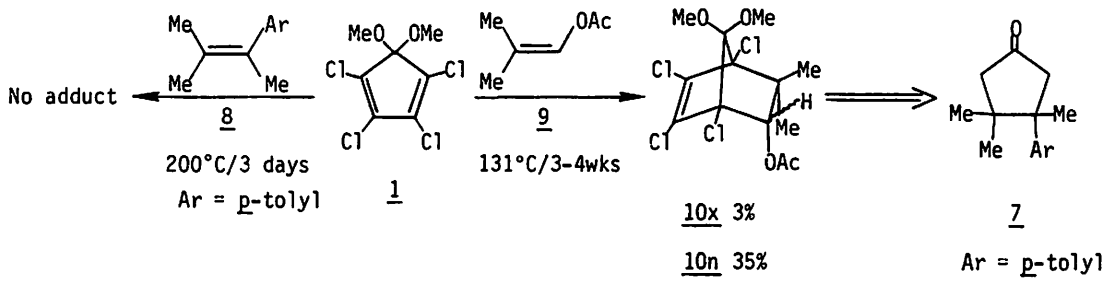


a R = R' = $(CH_2)_4$	77%	87%	56%	37% overall
b R = R' = $(CH_2)_5$	75%	86%	60%	38% overall
c R = Ph R' = H	97%	76%	54%	40% overall
d R = COOMe R' = H	95%	74%	50%	34% overall

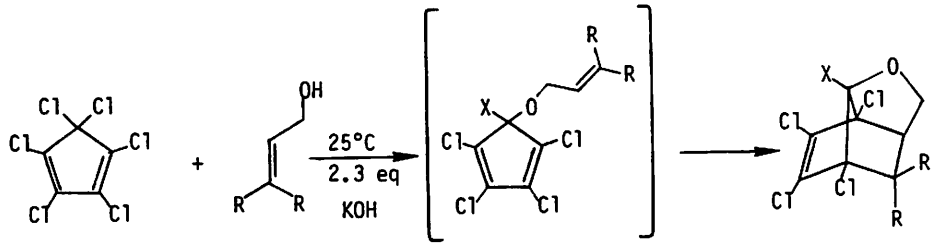
the solution of sodium in ammonia at -78°C, a bright green light is produced! This occurs only for the endo alcohol 3e and not for any of the other tetrachloronorbornene derivatives 3a-d. We have no definite explanation for this unusual chemiluminescence. The enone ketal 6 proved to be a very valuable compound for natural products synthesis as described below in the section on anionic oxy-Cope rearrangements.



We have utilized this new concept of the use of perchlorinated dienes followed by dechlorination in the synthesis of the natural product β-cuparenone 7 and have begun an investigation of its use in heterocyclic systems. Whenever a new synthetic method is developed, a responsibility falls on the developer to determine its drawbacks as well as its advantages. We decided to do this for the diene 1 and have found that it is quite sensitive to steric hindrance. Therefore, although disubstituted olefins react quite well with 1, tri- and tetrasubstituted olefins react very slowly, if at all. This was illustrated in a total synthesis of the sesquiterpene β-cuparenone 7 (3). The tetrasubstituted olefin 8 did not react with 1 under forcing conditions while the trisubstituted olefin isobutenyl acetate 9 required very vigorous conditions to give a fair yield of a mixture of the exo and endo adducts 10xn. These adducts were then converted by a straightforward route into the natural product 7.



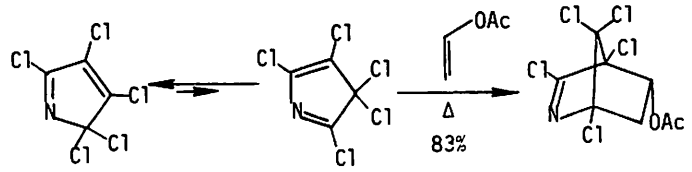
This steric impediment to intermolecular Diels-Alder reactions of 1 with trisubstituted olefins could be readily overcome by making the cycloaddition intramolecular (4). Thus, when a solution of hexachlorocyclopentadiene 11 in dimethylallyl alcohol 12b was treated with 2.3 equiv of potassium hydroxide at 25°C for 9h, the two intramolecular Diels-Alder adducts 15b and 16b were produced in yields of 12% and 31% respectively, along with 15% of the uncyclized dialkoxycyclopentadiene 14b. It is interesting that this enormous difference in reaction rates between the intramolecular cycloaddition of 11 and 12 (9h, 25°C, 43%) and the intermolecular cycloaddition of 1 and 9 (3-4 wks., 131°C, 38%) is observed even though there is considerable ring strain in the products of the intramolecular case.



11 12a R = H 12b R = Me 13a R = H X = Cl 14a R = H X = OR' 13b R = Me X = Cl 14b R = Me X = OR' (15%) 15a 44.5% 16a 15% 15b 12% 16b 31%

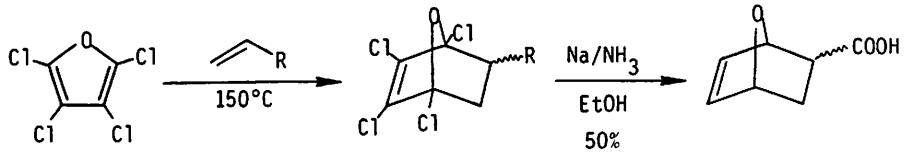
A similar reaction of 11 with allyl alcohol 12a produces the analogous products 15a and 16a in good yield.

We have begun investigating the extension of this methodology to heterocyclic systems. The 1-azapentachlorocyclopentadiene 17 rearranges to the 2-aza isomer 18 before undergoing cycloaddition with vinyl acetate to give 19 (5), in agreement with Wong's work (6). More exciting are our preliminary results with tetrachlorofuran 20 as a diene in Diels-Alder



17 18 19

reactions (7). Reaction of 20 with acrylic acid and a small amount of hydroquinone at 150°C for 15 sec produced a 90% yield of a mixture of exo and endo isomers, 21xn. This is to be contrasted with the cycloaddition of furan with methyl acrylate which requires several weeks at room temperature. Reductive dechlorination of 21 afforded the reduced products in fair yield (~50%). We also have preliminary results which show that 20 reacts with "unreactive" dienophiles such as allyl alcohol 12a, i.e., reaction of 12a and 20 at 150°C for 1d gave after chromatography a 75% yield of a mixture of products whose spectral characteristics are consistent with the isomeric Diels-Alder adducts 22xn.



20

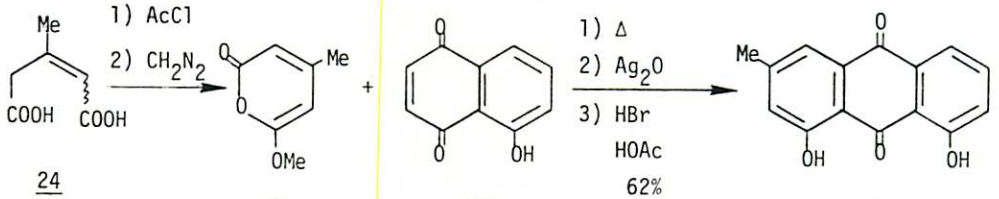
R = COOH 15sec 90% 21xn R = COOH

12a R = CH_2OH 1day 75% 22xn R = CH_2OH

We are presently attempting to extend this general methodology of perchlorodiene cycloaddition-dechlorination to other systems where the Diels-Alder reaction of the unchlorinated diene does not occur or is troublesome.

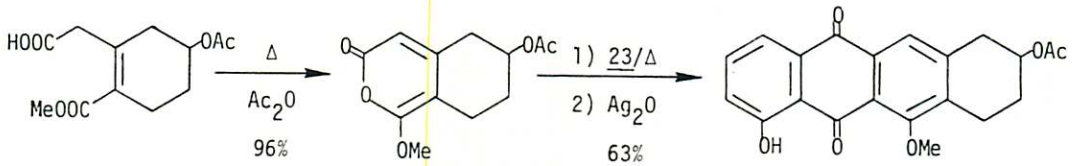
SUBSTITUTED 2-PYRONES

As a new general approach to the synthesis of anthracyclines and other anthraquinone natural products, we have investigated the use of substituted 2-pyrones as dienes in Diels-Alder cycloadditions. Although 3-methoxy- and 3-hydroxy-2-pyrone (8) had been used in Diels-Alder cycloadditions, no reports on the use of 6-alkoxy-2-pyrones had been published. We reasoned that the reaction of 6-alkoxy-2-pyrones with substituted naphthoquinones such as juglone 23 would proceed with loss of carbon dioxide to give after oxidation a 1,8-dialkoxyanthraquinone, the integral structural unit of the aclacinomycin class of anthracycline antitumor agents (9). The necessary pyrone 25 was readily available from β-methylglutaconic acid 24 in two steps, dehydrative cyclization and methylation (10). Reaction of 6-methoxy-4-methyl-2-pyrone 25 with juglone 23 followed by oxidation and demethylation furnished the natural anthraquinone chrysophanol 26 regiospecifically in 62% overall yield (10). This new methodology has been extended to the preparation of tetracyclic intermediates for anthracycline synthesis (11). For this application, a new method of regiospecific pyrone formation was developed, which involved directed cyclization of a specific glutaconic



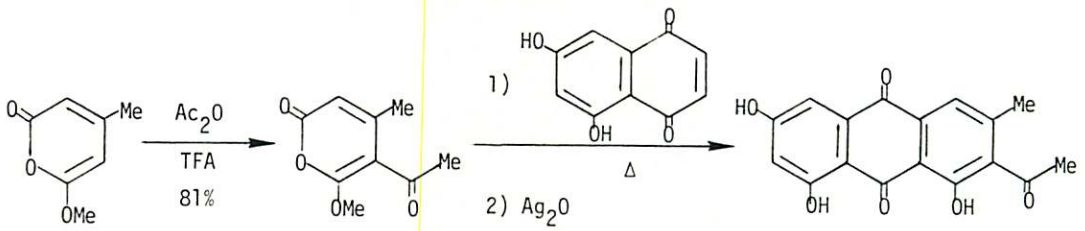
24 25 23 26

half ester. Thus, the acid ester 27 cyclized to the desired pyrone 28 on treatment with acetic anhydride in 96% yield. Cycloaddition of 28 with juglone 23 followed by oxidation produced the tetracyclic material 29 in 63% yield.



27 28 29

Other extensions of this method involved the regiospecific acetylation of 6-methoxy-4-alkyl-2-pyrones with acetic anhydride in trifluoroacetic acid (12). In this manner, 25 was converted regiospecifically into the 5-acetylpyrone 30 which could be reacted with 5,7-dihydroxynaphthoquinone to give the natural product 2-acetylemodin 31.



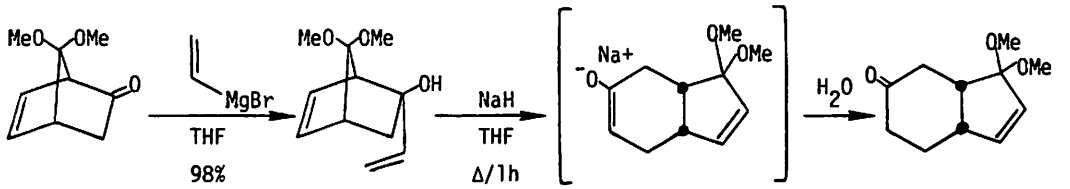
25 30 31

Further extensions using 2-benzopyran-3-ones and 2-pyrone-5-carboxylates are also under investigation currently in our laboratories (13).

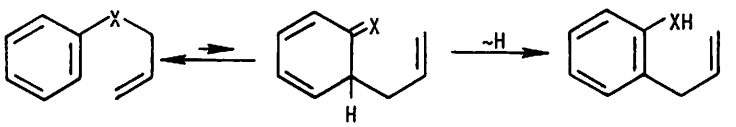
ANIONIC OXY-COPE REARRANGEMENTS

Evans' discovery that the rate of the oxy-Cope rearrangement (14) was enhanced by up to a factor of 10^{17} by reaction of the anion of the allylic alcohol rather than the neutral compound (15) has greatly increased the usefulness of this process. We reasoned that an application of this reaction to organometallic adducts of the bicyclic enone ketal 6 would permit a rapid access to substituted cis-hydrindenones. This proved to be the case.

Addition of vinylmagnesium bromide to 6 occurred exclusively from the endo face, due to the steric hindrance of the syn-7-methoxy group toward exo attack, to give the exo alcohol 32 (16). Treatment of 32 with NaH in THF at 66°C for 1h produced a 72% yield of the hydrindenone 33. With the demonstration of the feasibility of this type of anionic rearrangement



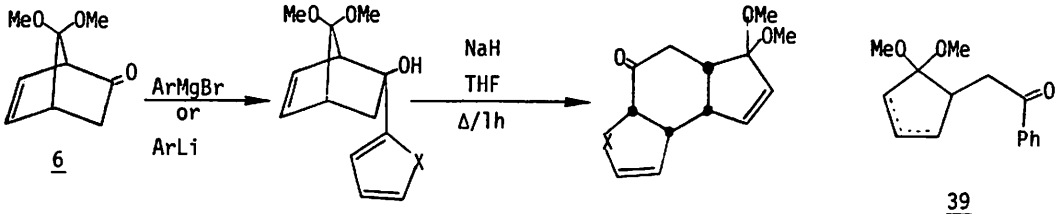
in simple norbornenyl systems, attention was then directed to the possibility of utilizing aromatic rings as the olefinic components. At the outset of this research, there was only one example of the Cope rearrangement on an aromatic system, namely the pioneering work of Doering (17), i.e., 34a → 36a, which has recently been claimed to be in error (18). The difference in the reactivities of the two analogous systems toward [3,3]sigmatropic rearrangements, namely, the unreactivity of 4-phenyl-1-butene 34a toward Cope rearrangement under vigorous conditions (18) versus the high reactivity of allyl phenyl ether 34b toward Claisen rearrangement, has never been adequately explained. Lambert has shown that it is the first step of the Cope rearrangement that is the highly unfavorable step (19). We believe that the reasons for this can be easily understood by an examination of the overall thermodynamic changes of the two systems in the first step. For 34a, the loss of aromatic resonance energy is not compensated for in any way and thus the activation energy for this step should be very high. However, for 34b the loss of resonance energy is greatly compensated for by the thermodynamic driving force of forming a carbonyl group and two



34a X = CH_2 35a X = CH_2 36a X = CH_2

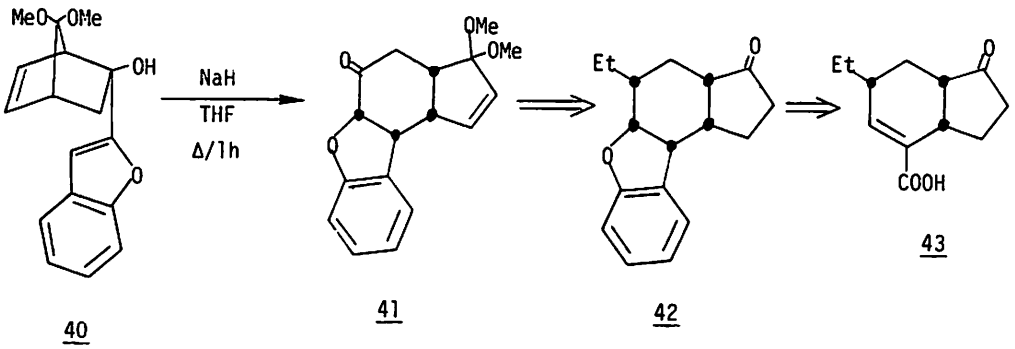
34b X = O 35b X = O 36b X = O

C-C bonds at the expense of a C=C bond and 2 C-O bonds. Thus, the starting material and product are of more nearly equal energy and one might expect a corresponding lowering of the activation energy of the pathway connecting them. In any event, we reasoned that by using the great rate enhancements offered by the anionic variation of the oxy-Cope rearrangement (15), one might be able to overcome the activation energy barrier and effect the Cope rearrangement on aromatic substrates. The substrates 37abc were prepared by addition of the corresponding aryl organometallic reagents to the enone 6. Rearrangement of the naphthyl and furyl adducts, 37ab, occurred quite readily (NaH, THF, 66°C, 1h) to give the rearranged products 38ab in high yields (75% and 72%, respectively) (16). However, the phenyl adduct 38c could not be induced to undergo [3,3]sigmatropic rearrangement, but rather underwent carbon-carbon bond cleavage to 39 instead (20). Thus, the driving force of the anionic oxy-Cope rearrangement does not seem to compensate for the loss of aromaticity of the phenyl system but does for the less stabilized naphthyl and furyl systems. The naphthyl systems could be taken on to steroid analogues by reduction of the two non-aromatic olefins and epimerization of the C9 hydrogen to the α-epimer.



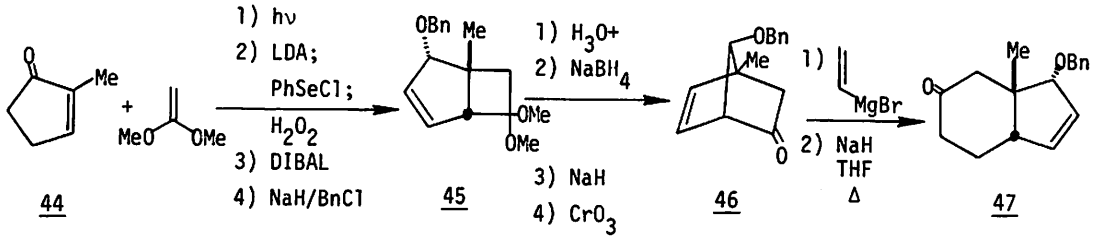
90%	37a X = C_6H_4	75%	38a X = C_6H_4
94%	37b X = O	72%	38b X = O
92%	37c X = CH=CH		

This new synthetic concept of an anionic oxy-Cope rearrangement on an aromatic substrate has been used for the synthesis of the natural product coronafacic acid 43 (21). The benzofuryl adduct of the enone 40 was cleanly rearranged to 41 which was converted into the natural product 43 via the intermediate 42 (22).



40 41 42 43

Recently we have extended this work to a synthesis of the angularly methyl-substituted hydrindenones necessary for the synthesis of natural steroids. The bicyclic enone 46 could be prepared in 8% overall yield in an 8-step synthesis starting from 2-methylcyclopentenone 44 via 45 as shown. Addition of vinylmagnesium bromide and rearrangement afforded a good yield of the desired methylhydrindenone 47 (23). The addition of groups other than vinyl and the conversion of these intermediates into steroids and other natural products, i.e., tricothecanes, is currently under investigation.



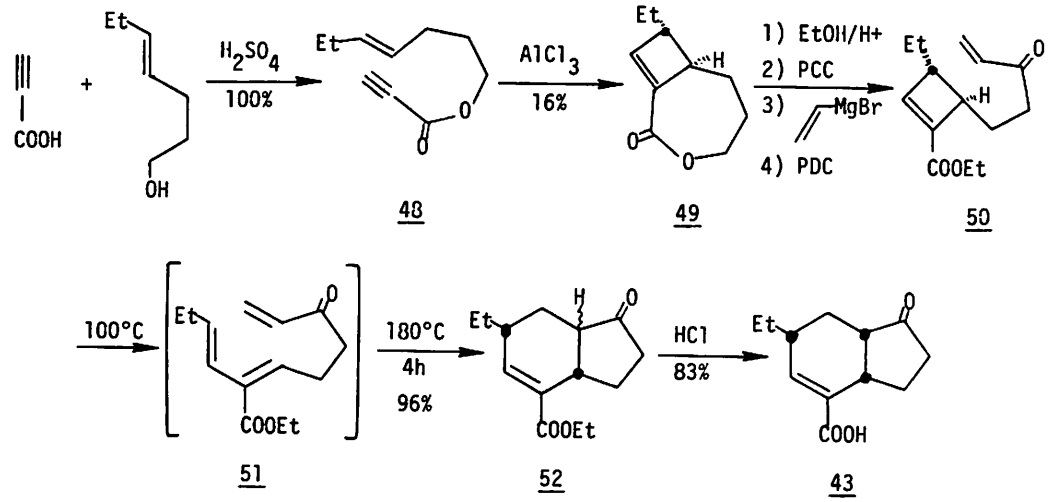
44 45 46 47

INTRAMOLECULAR DIELS-ALDER REACTIONS

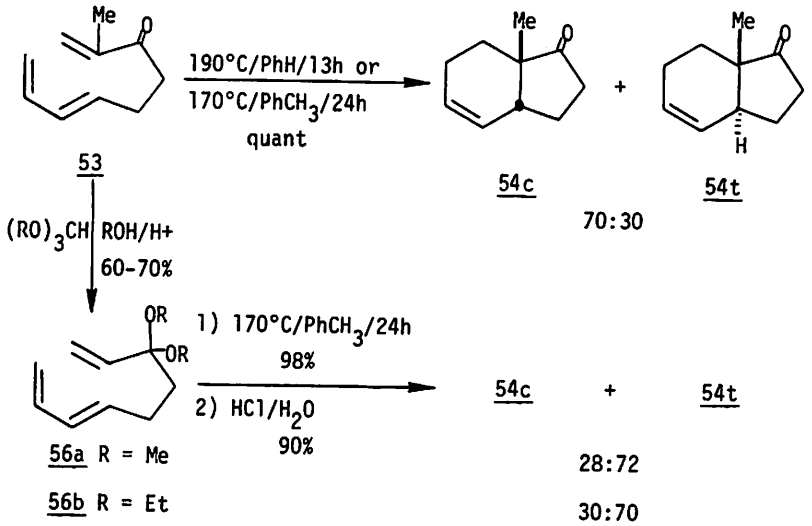
In recent years, an enormous amount of research effort has been aimed at understanding the reactivity, stereo- and regioselectivity, and energetics of the intramolecular Diels-Alder reaction (24). By requiring the diene and dienophile to be part of the same molecule, one can change some of the normal reactivity requirements and stereo- and regiochemical preferences to give products that one would not expect from an intermolecular Diels-Alder reaction.

The acid component of the natural phytotoxin coronatine, coronafacic acid, 43, again was a model for our study of intramolecular cycloadditions (25). An intramolecular Lewis-acid promoted [2 + 2] cycloaddition of the ester 48 (prepared in quantitative yield from the corresponding acid and alcohol) afforded the cyclobutene 49. This is the first example of

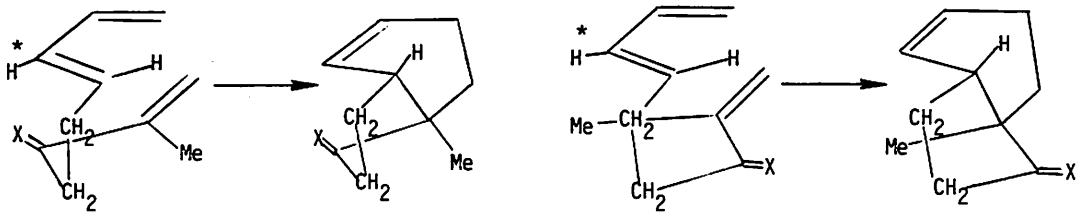
an intramolecular acid-promoted [2 + 2] cycloaddition of this type (26) and is a quite efficient way of constructing such molecules albeit in only fair yield. Conversion of 49 into the desired enone 50 was straightforward. Heating 50 to 100°C produced the trienone 51 with the necessary stereochemistry about the diene system to eventually produce 43. Heating of 51 to 180°C furnished the adduct 52 in 96% yield as a ~60:40 mixture of cis and trans ring juncture isomers. Hydrolysis of this mixture produced coronafacic acid 43 in good yield, ending a short and efficient synthesis of 43.



The fact that both cis and trans isomers of the hydrindenone 52 were formed in the intramolecular cycloaddition prompted us to examine this technique as a general method for the synthesis of the CD-ring portion of steroids. Sutherland (27) had already investigated the cyclization of the trienone 53 and reported that the predominant product was the cis hydrindenone 54c (the major component of a 30:4:3 mixture). We repeated this work and found that a quantitative yield of the hydrindenones were produced as a 70:30 mixture of cis and trans isomers, 54ct (28). However, close examination of molecular models of the transition states 55nx leading to the isomers (endo → cis, exo → trans) indicated that the endo transition state 55n could not attain the necessary geometry for the favorable secondary orbital overlap, which causes most endo transition states to be stabilized, because of the restrictions of the short methylene chain joining the two components. More importantly, it was



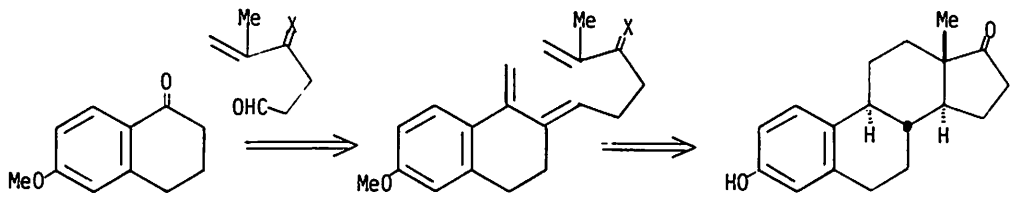
predicted that simple ketals would cause the cycloaddition to occur preferentially via the exo transition state, 55x. The endo transition state 55n for the ketals [X = $(OR)_2$] should now experience significant steric interference between one of the two alkoxy groups and the C-H bond of the butadiene system (marked with an asterisk). The corresponding exo transition state 55x should therefore be more stable with the methyl group in the endo position in place of the dialkoxymethylene group. This prediction proved to be true. Formation of the dimethyl or diethyl ketal 56 was straightforward. Heating 56a to 170°C for 1 day



55n 54c 55x 54t

produced a mixture of ketal and enol ether which could be hydrolyzed to a mixture of 54ct in which the trans isomer now predominated in a 28:72 ratio. The diethyl ketal 56b gave almost identical results. Thus, by a simple modification of the readily available trienone, one can prepare stereoselectively trans hydrindenones as potential CD-ring intermediates for steroid synthesis (29).

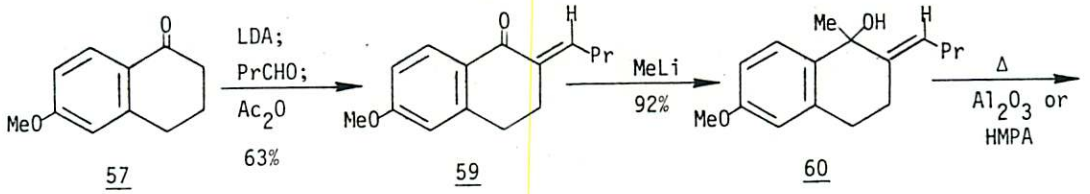
Unfortunately, all attempts at increasing the ratio of trans: cis to more than 3:1 have been unsuccessful, e.g., using lower temperatures, bulkier alkoxy groups, and Lewis and Bronsted acid catalysts. However, an examination of the transition state models 55nx indicates that if the starred H were replaced by an alkyl group (i.e., methyl or methylene), the difference between the two transition states would become much greater (due to the large interaction of the alkyl group with one of the alkoxy groups of the ketal) and should cause the reaction to occur totally via the exo transition state to give the desired trans isomer. This has been shown to be the case in octalone systems (30) but never in hydrindenones. To test this concept we have undertaken a very short total synthesis of steroids and, in particular, estrone 58 from commercially available 6-methoxy-α-tetralone 57 via the scheme shown.



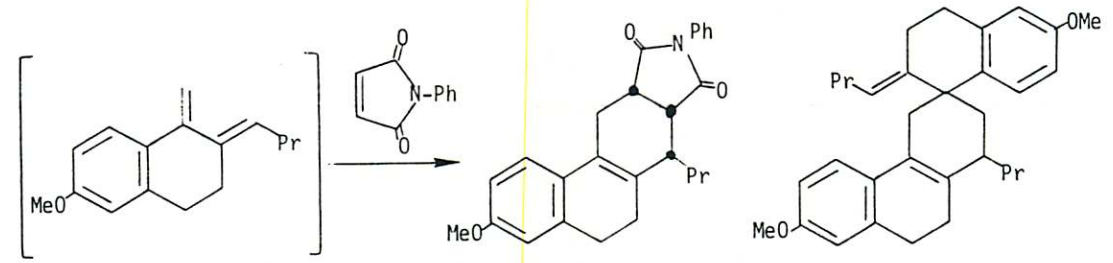
57 58

Before preparing the fully substituted substrate, we synthesized model compounds to determine reaction conditions. Condensation of the lithium anion of 57 with butanal followed by addition of acetic anhydride produced a good yield (63%) of the E-enone 59 in addition to recovered starting ketone (~30%). The geometry of the olefinic unit was determined by a europium shift reagent study. Normal Wittig olefination of 59 proved unsuccessful as did the silyl-Wittig modification due presumably to the unreactivity of the carbonyl group. However, methyllithium added very well (92%) to the ketone to produce the allylic benzylic tertiary alcohol 60. Thermolysis of this alcohol absorbed on alumina or in a solution in HMPA caused dehydration to give the desired exocyclic methylene compound 61 which could be trapped by added N-phenylmaleimide to give 62 in good yield. If no trapping agent was present, the diene underwent a Diels-Alder dimerization to give 63. In the des-methoxy series, the diene corresponding to 61 could be isolated by reaction of the ketone corresponding to 59 with the silyl Wittig reagent followed by silica gel chromatography. This pure diene dimerized to the analogue of 63 overnight at 25°C in quantitative yield.

The information gained in the model study was then applied to the total synthesis of estrone. Alkylation of the lithium anion of the known isopropylidenedithiane 64 with the bromo acetal from acrolein followed by acidic hydrolysis produced the aldehyde 65. Aldol condensation as described above gave the dienone 66 in a one-pot reaction in 48% yield with 44% of the ketone recovered. Addition of methyllithium to 66 gave the alcohol 67 which was dehydrated by heating in HMPA to give the triene 68 which cyclized directly to the intramolecular Diels-Alder reaction product 69 as a mixture of isomers in which

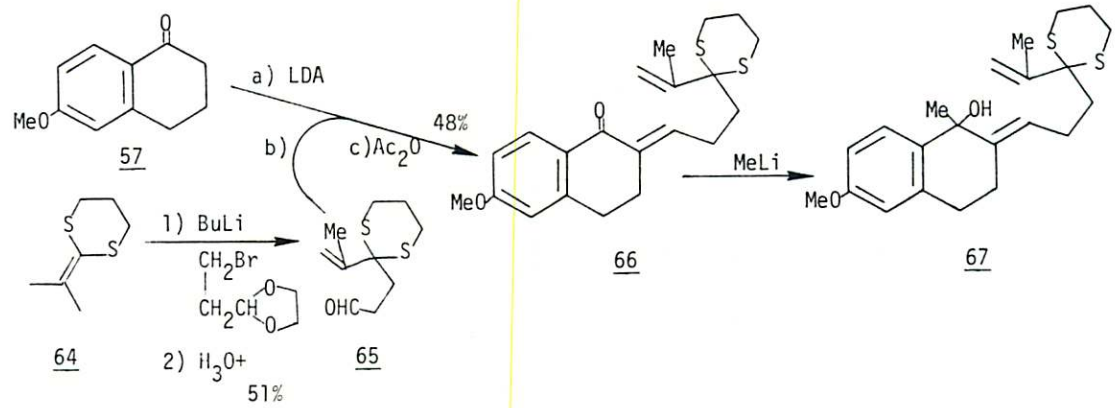


57 59 60

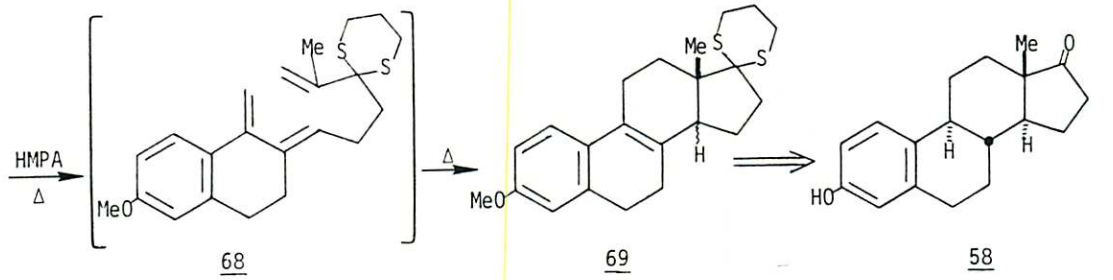


61 62 63

the trans greatly predominated. The final conversion of 69 into (±)-estrone 58 was accomplished in three straightforward steps (hydrolysis, reduction, demethylation) to end a very short, stereoselective synthesis of estrone which demonstates the power of the intramolecular Diels-Alder reaction in total synthesis.



57 64 65 66 67



68 69 58

CONCLUSION

The foregoing examples help to illustrate the high utility of the new dienes for intermolecular Diels-Alder reactions, the anionic oxy-Cope rearrangement, and intramolecular cycloadditions for the total synthesis of biologically active natural products. We have shown that these methods can be applied in an elegant manner to complex molecules. Further developments and extensions of these methods are currently underway and will be reported in due course.

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