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# CYCLOADDITIONS AND ANNULATIONS OF TRANSITION METAL CARBENE COMPLEXES

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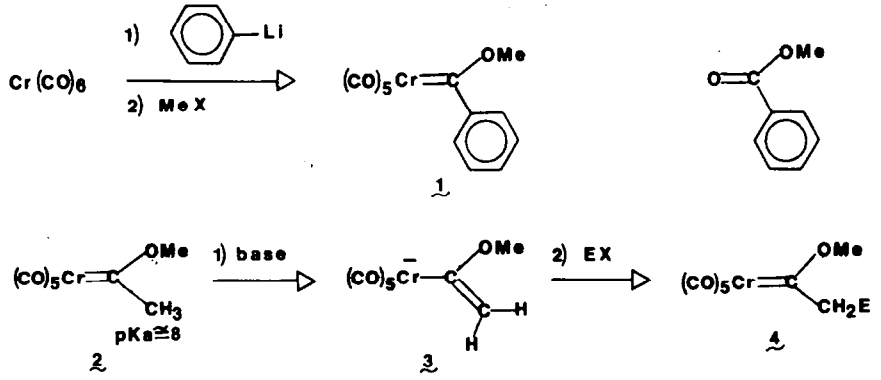
**Abstract**—The synthetic aspects of several reactions from the multifaceted chemistry of Fischer carbene complexes are examined. Their benzannulation reactions with acetylenes are utilized in the synthesis of anthracyclinones via two approaches which differ by beginning at opposite ends of the molecule with either an aryl or an alkenyl substituted chromium carbene complex. The latter has been employed in a formal synthesis of daunomycinone. The Diels–Alder reactions of $\alpha,\beta$-acetylenic chromium carbene complexes provide for a facile entry into substituted cyclohexenyl chromium carbene complexes that are subsequently employed in benzannulation reactions. These tandem cycloaddition/annulation reactions are incorporated into model studies for the synthesis of anthracyclinones and wentilactone A. Their potential is also demonstrated for coupling to yet a third reaction of organochromium compounds; aromatic nucleophilic substitutions on arene chromium tricarbonyl complexes. The annulations of $\beta,\beta$-disubstituted alkenyl complexes provides for a regio- and stereoselective synthesis of 2,4-cyclohexadienones under neutral conditions at near ambient temperatures.

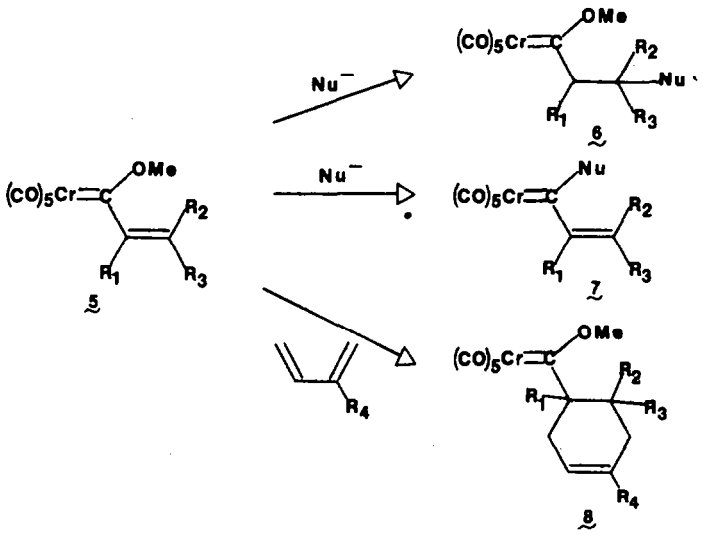
The first transition metal carbene complex to be prepared was the phenyl methoxy carbene complex 1 by E. O. Fischer in 1964.[1] His original procedure involves the addition of an organolithium compound to chromium carbonyl and is still the most commonly used method for the preparation of heteroatom stabilized complexes (Fischer type). This report opened the door and today the carbene ligand is nearly ubiquitous and occurs with most if not all of the transition metals.[2,3] It has also undoubtedly been a factor in the reinterpretation of many catalytic processes which are now viewed as involving transition metal carbene complexes as reaction intermediates.[4]

The various transition metal carbene complexes can be divided into two groups on the basis of the chemical reactivity of the carbene carbon.[2,3g,5] The name carbene complex is used for those complexes in which the carbene carbon is electrophilic and includes the heteroatom stabilized complexes such as 1. The carbene carbon is nucleophilic in a number of complexes, particularly those of the early transition metals, which have been referred to as alkylidene complexes. Both of these names are misleading in that there has never been a reaction for any of these complexes for which the intermediacy of a free carbene (alkyl or otherwise) has been demonstrated. Furthermore the chemistry of transition metal carbene complexes have been found only in the most superficial way to bear any resemblance to the chemistry of free carbenes.

There is a wealth of rich and varied reaction chemistry of transition metal carbene complexes[5] and at the moment the potential for applications to synthetic organic chemistry seems greater for the heteroatom stabilized carbene complexes[5,6] than for the alkylidene complexes.[7] The stabilized carbene complexes are convenient to use in that they are generally red crystalline solids that are handleable in air, can endure temperatures of 100° or more, are stable to mild aqueous acids and bases and are soluble in organic solvents to the point where most can be rapidly eluted from silica gel with hexane. Despite their solubility in hexane, Fischer carbene complexes such as 1 have large dipole moments and the carbene carbon displays marked electrophilic behavior. In fact, a number of the reactions of Fischer carbene complexes




Scheme 1.

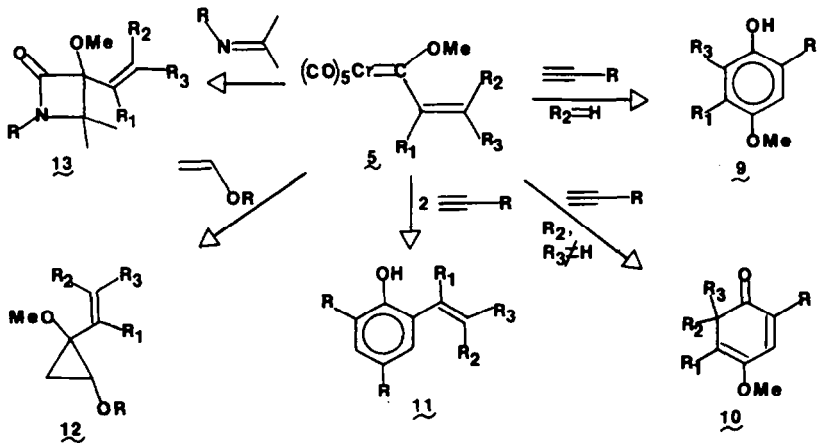


Scheme 2.

can be anticipated from the reaction chemistry of esters where the chromium pentacarbonyl group is formally replaced by an oxygen atom. The chemical properties of esters mirrored in these complexes is also usually greatly accentuated. For example, the protons of the methyl group in the complex **2** have a $pK_a = 8$, and thus is one of the most acidic methyl groups known.[8] As might be anticipated its conjugate base **3** is unreactive with all but the most reactive of electrophiles.[5d,e,9] A few other reactions that have analogs in carbon chemistry are illustrated in Scheme 2 for the $\alpha,\beta$-unsaturated complex **5**. These include Michael additions,[10] nucleophilic substitutions, and Diels–Alder reactions[6g] which occur with large rate enhancements over their ester analogs.

The chromium pentacarbonyl group does not always play a passive role and as a result there are a number of reactions of Fischer carbene complexes that are unknown and/or impossible in carbon chemistry. As illustrated for complex **5** in Scheme 3 some of these reactions involve the incorporation of a carbon monoxide ligand along with the carbene carbon and its substituent in addition to an external organic functional group. The reaction of **5** with acetylenes[5a,6] gives the benzannulated hydroquinone mono-ether **9** or the cyclohexa-2,4-dienone **10**[6d] if aromatization is blocked. The two -alkyne annulated product **11** can be obtained in cases where benzannulation is either blocked or unfavored or where the acetylene is either small or its local concentration is high.[6b] Cyclopropanation of olefins[11] and photoinduced $\beta$-lactam formation with imines[6m] are among the many other reactions with synthetic potential.

This article will discuss several of these reactions of Fischer carbene complexes within the context of their application to a number of problems in synthetic organic chemistry. One of the more versatile reactions is the benzannulation reaction of Fischer carbene complexes with acetylenes which was first reported by Dötz in 1975 for the reaction of the phenyl methoxy

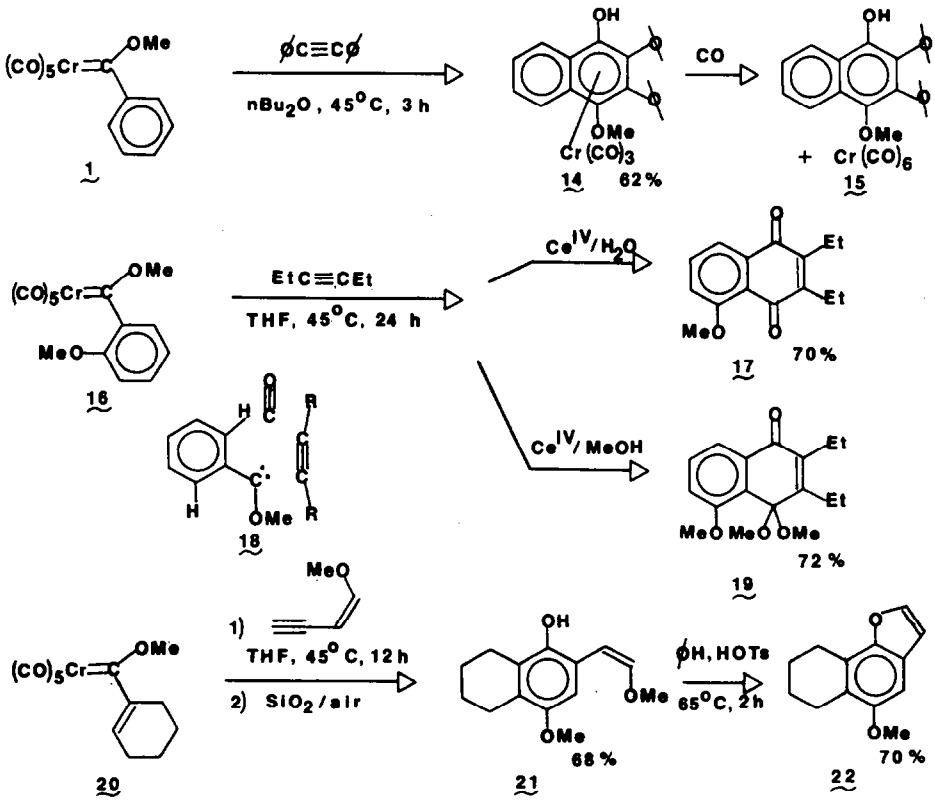


Scheme 3.

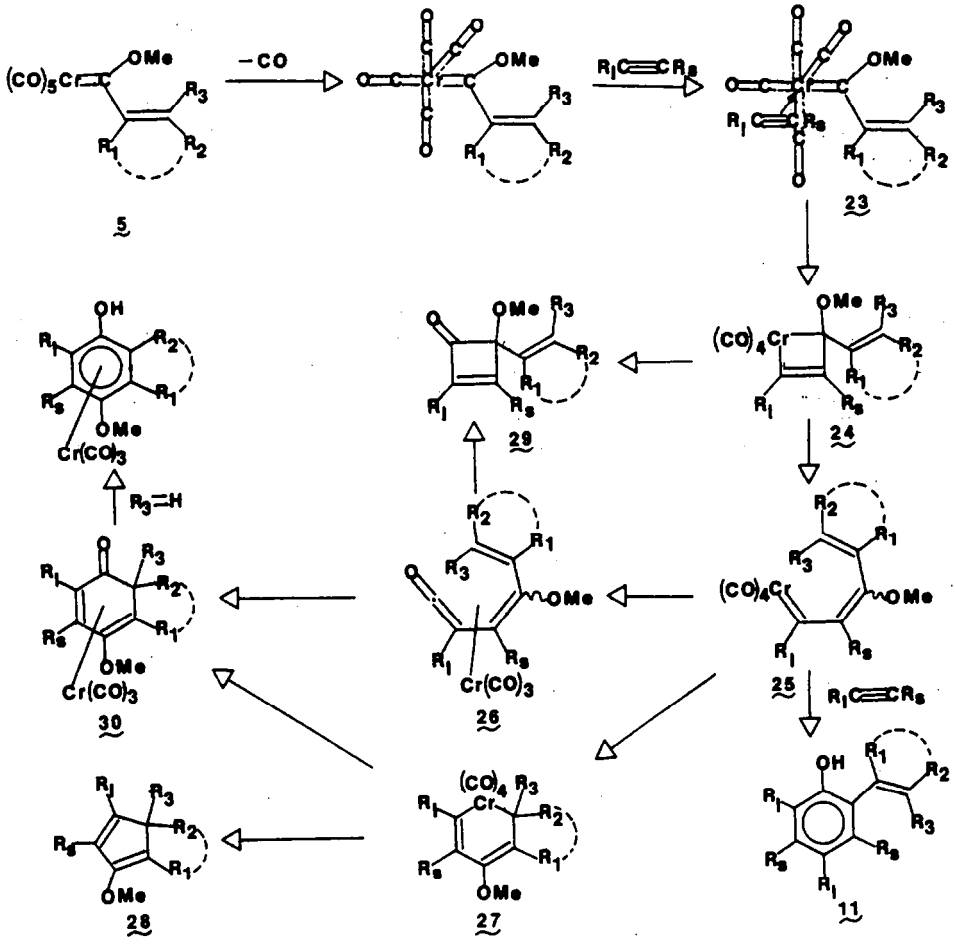
complex **1** with diphenylacetylene.[12] The annulation reaction produces in this case 4-methoxy-2,3-diphenyl-1-naphthol as its chromium tricarbonyl complex **14**. The free naphthol **15** can be obtained by simple treatment of the complex **14** with carbon monoxide which also generates chromium hexacarbonyl which can be recycled in the preparation of **1**. The oxidation state of the annulation product can be controlled during workup. Treatment of the crude mixture from the reaction of the O-methoxy phenyl complex **16** and diethylacetylene with aqueous ceric ammonium nitrate will give the naphthoquinone **17**.[6g] In a similar way the naphthoquinone mono-acetal **19** can be obtained from a workup with methanolic ceric ammonium nitrate. The annulation of simple $\alpha,\beta$-unsaturated complexes is also known[6] as illustrated by the reaction of the cyclohexenyl complex **20** with 4-methoxy butenyne to give the phenol **21**.[6c] The annulation reaction has been found to be highly regioselective with terminal acetylenes giving rise to a single isomer.[6c,k,g] The acetylene substituent becomes incorporated adjacent to the hydroxyl group in the 2-position and this regiochemical assignment has been confirmed in a number of ways including the cyclization of **21** to the benzofuran **22**.

A mechanistic accounting for the benzannulated products is outlined in Scheme 5. Very little direct experimental evidence has been published which has a bearing on the mechanism of this reaction.[5a,3g] It has been determined however that the reaction of **1** with diphenylacetylene is independent of acetylene concentration[13] and the rate constant suggests that the first and rate limiting step of the reaction is an initial dissociation of a carbon monoxide ligand from a *cis* coordination site.[14] Carbon–carbon bond formation in the ring closure of the preferred conformation of the acetylene complex **23** to give the chromacyclobutene **24** provides for a reasonable explanation of the observed regiochemistry of this reaction. It has been proposed that the ring-opened vinyl carbene complex **25** inserts carbon monoxide into the chromium–carbene bond to give the dienyl ketene complex **26** which cyclizes to the cyclohexadienone complex **30**.[5a] An alternative possibility is an electrocyclic ring closure of **25** to give the chromacyclohexadienone **27** followed by carbon monoxide insertion and a reductive elimination to give complex **30**.[3g] There is no evidence in the literature which makes it possible to distinguish between these two possibilities at this time. If $R_2$ and $R_3$ are both groups of low migratory propensity then the uncomplexed cyclohexadienones can be obtained from the reaction of $\alpha,\beta$-unsaturated complexes of the type **5**.[6d]

The anthracycline antitumor antibiotics play an important role in cancer chemotherapy and their structures have continued to provide a synthetic challenge to chemists for the last decade.[15] There are a large number of compounds in the anthracycline family including the aglycones of doxorubicin **31** and 11-deoxy doxorubicin **32**, and 7-con-*o*-methyl nogarol **33** a semisynthetic derivative of nogalamycin. The benzannulation reaction of Fischer carbene complexes with acetylenes seems particularly well-suited for deployment in the convergent synthesis of many



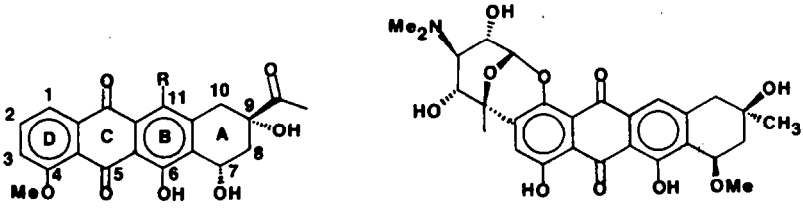

Scheme 4.



Scheme 5.

members of this family bearing a range of substitution patterns.[6e] Furthermore, approaches based on this reaction have the potential to solve the three major synthetic problems associated with this family of natural products. These are the regioselectivity, the introduction of the C-7 hydroxyl, and a convergent approach to both the 11-oxy and 11-deoxy members of the family.

Two of the general approaches that we are pursuing are diagramatically outlined in Scheme 7. It is intended that these approaches be utilized for a number of the anthracyclines and thus the substituents in the A ring are unspecified. The two routes are exact opposites in the sense the first involves building the molecule from left to right where the aromatic D ring is incorporated into the carbene complex **16** and the saturated A ring is part of the acetylene **34**. The second route on the other hand constructs the molecule from right to left and incorporates the saturated A ring into the carbene complex **20** and the aromatic D ring in the acetylene **36**. With each route the relative regiochemistry of the A versus the D ring is set up by the benzannulation

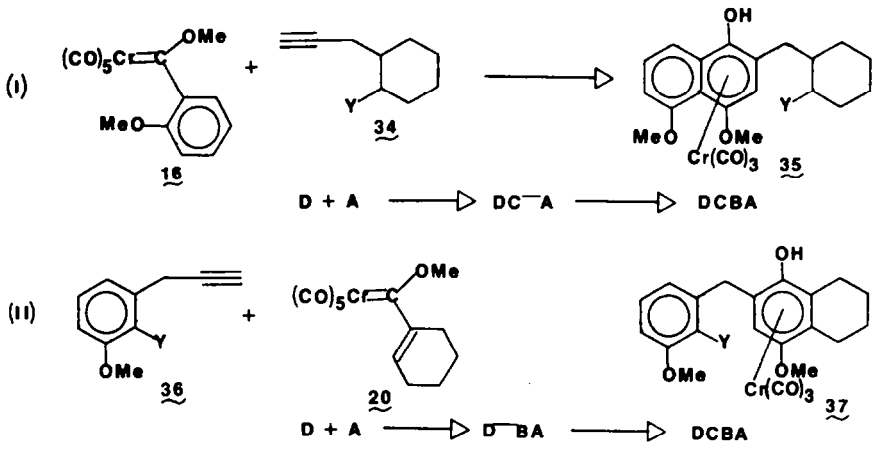


**31** daunomycinone R=OH

**32** 11-deoxydaunomycinone R=H

**33** 7-con-o-methylnogarol

Scheme 6.



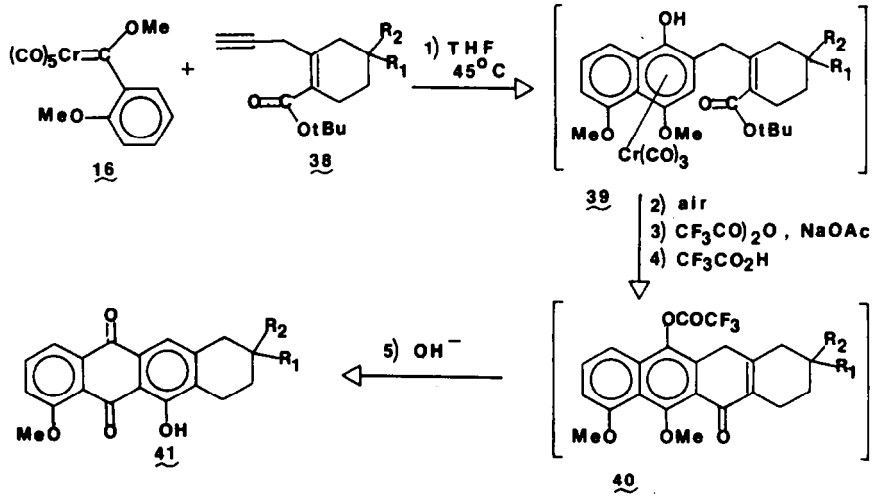

Scheme 7.

reaction which for terminal acetylenes is known to be highly regioselective.[6z,p] An added dimension to each of the two general routes is that the final ring closure can be envisioned to occur by either an electrophilic or nucleophilic aromatic substitution employing an appropriate carbon-based functional group for Y.

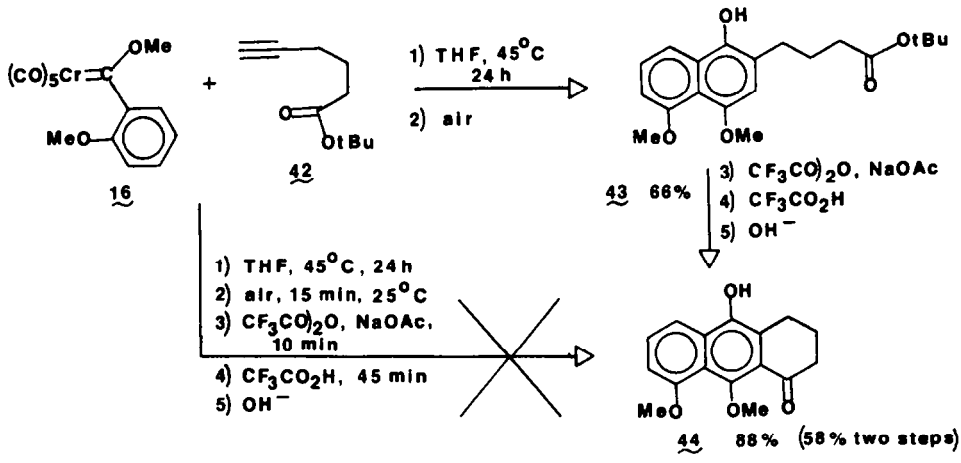
A specific approach based on the first general route is outlined in Scheme 8. The idea behind this approach is to effect a one-pot synthesis of the tetracyclic intermediate **41** from the acetylene **38** and the carbene complex **16**. The carbene complex **16** is an air-stable red crystalline solid that can be prepared in one step from chromium hexacarbonyl in high yield.[16] Exposure of complex **16** to the atmosphere for a month at room temperature gives only the slightest indication of decomposition, however, recommended storage for Fischer carbene complexes in general is in a bottle flushed with nitrogen in the refrigerator. Unlike most Fischer carbene complexes, naphthol chromium tricarbonyl complexes such as **39** are quite sensitive to air. Only a few minutes' exposure will lead to the oxidation of the chromium to give a green precipitate with concomitant release of the free naphthol into solution.

Thus the one-pot synthesis of **41** is envisioned from the following sequence of events. The benzannulation reaction of the carbene complex **16** and acetylene **38** in THF should regioselectively generate the naphthol chromium tricarbonyl complex **39** after 24 hr at 45°. Opening to air for a few minutes should oxidatively remove the chromium tricarbonyl group and leave the free naphthol in solution. Addition of trifluoroacetic anhydride and sodium acetate should protect the phenol and the addition of trifluoroacetic acid should generate the acylium ion and effect the Friedel–Crafts ring closure to give **40** prior to tautomerization. Base cleavage of the trifluoroacetyl group will leave the C ring as a hydroquinone mono ether which when flanked by an aromatic ring on either side would be expected to air oxidize to give the tetracyclic quinone **41**.

Initial efforts in the development of a one-pot double-cyclization procedure for the synthesis of **41** were concentrated on the tricyclic ketone **44** in which two rings are made in the one-pot reaction of carbene




Scheme 8.

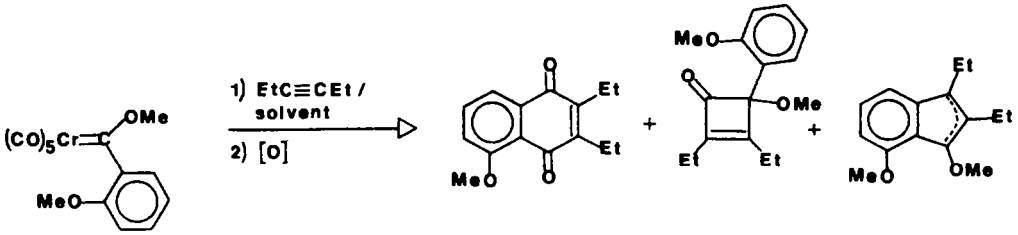



Scheme 9.

complex **16** and the much simpler acetylene **42** (Scheme 9). Initially the reaction was examined as a two-step process as a control experiment. A THF solution of the complex **16** and a slight excess of acetylene **42** are stirred at 45° for 24 hr under an argon atmosphere and upon opening to air a green precipitate forms within minutes leaving a solution of the free naphthol **43** which is purified by column chromatography on silica gel and obtained in 66% yield. The second ring closure can be effected cleanly only if the phenol functionality in **43** is first protected by dissolving in trifluoroacetic anhydride with a catalytic amount of sodium acetate. The phenol is completely trifluoroacetylated in 10 min at 25° and the solution is then diluted two-fold with trifluoroacetic acid and after 45 min at room temperature base hydrolysis gives the tricyclic ketone **44** in 88% yield. The two-step process was thus accomplished in 58% overall yield.

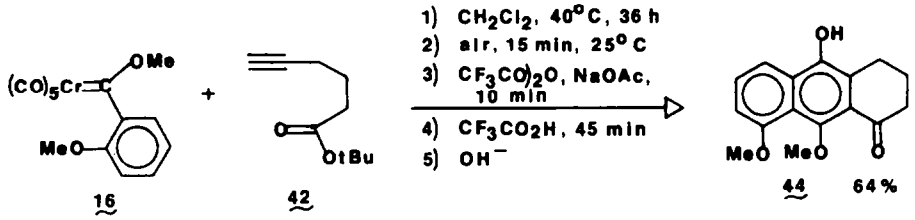
With the control experiment in hand a one-pot conversion of **16** and **42** to the tricyclic ketone **44** was attempted. After a THF solution of the two had been stirred for 24 hr at 45°, the mixture was opened to air and a green precipitate began to form. After 15 min the mixture was diluted half-fold with trifluoroacetic anhydride and a small amount of sodium acetate was added which was followed in 10 min by a half-fold dilution with trifluoroacetic acid. The reaction was stopped after 45 min upon base hydrolysis and a large number of products were formed as indicated by TLC. A small amount of **44** may have been formed but its isolation was not pursued. An explanation is that the THF is not compatible with the Friedel–Crafts reaction and thus a solution would be to find a solvent that is compatible with both the benzannulation and Friedel–Crafts reactions.

There is virtually nothing in the literature about the effects of solvent on the benzannulation of Fischer carbene complexes and acetylenes. With the one exception of a reaction in heptane which gave rise to a complex mixture,[17] the benzannulation reactions of aryl carbene complexes have always been reported in ethereal solvents. An examination of the reaction of the *o*-methoxyphenyl complex **16** and diethylacetylene is summarized in Scheme 10. It should be noticed that most solvents give comparable or higher yields of the naphthoquinone **17** than does THF and included among these are solvents that are compatible with Friedel–Crafts reactions. It was unexpectedly found




| Solvent | 17 | 45 | 46 |
|---|---|---|---|
| THF | 70 % | | |
| $CH_2Cl_2$ | 65 % | | |
| benzene | 77 % | | |
| hexane | 83 % | | |
| $CH_3CN$ | 0 % | 43 % | 12 % |
| DMF | | 28 % | 19 % |

Scheme 10.




Scheme 11.

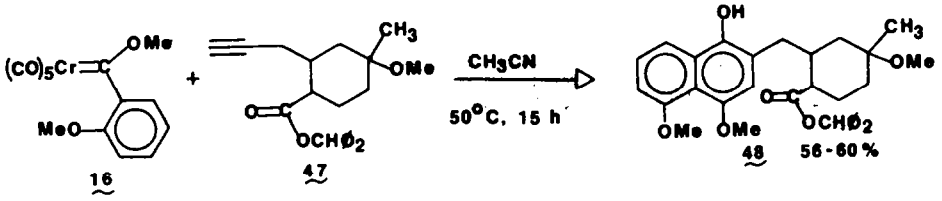
that in acetonitrile none of the quinone **17** could be found but rather that the cyclobutenone **45** was obtained as the major product. This is the first time that a cyclobutenone has been obtained in more than 5% yield from this reaction except where naphthalene formation is blocked.[5a,18] We are currently investigating the generality of cyclobutenone formation and the role of donor solvents on the benzannulation reaction.

The solvent study on the reaction of **16** with diethylacetylene was successful in identifying solvents which should be compatible with both the benzannulation and Friedel–Crafts reactions that are involved in the desired one-pot double-cyclization of the complex **16** and acetylene **42** to give the tricyclic ketone **44**. As indicated in Scheme 11, when the same one-pot procedure is carried out as before with a methylene chloride solution of **16** and **42** the tricyclic ketone **44** is obtained in 64% isolated yield and only a single spot was observed in the TLC of the crude reaction mixture. The use of other solvents and conditions will be examined to further optimize this yield.

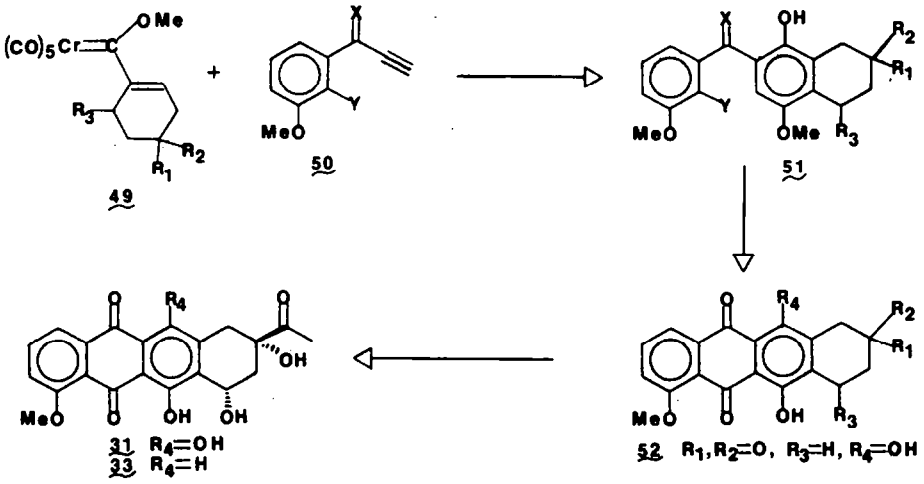
The success of this model study for the one-pot construction of the tetracyclic carbon skeleton of anthracyclines according to the approach outlined in Scheme 8 has prompted efforts towards the synthesis of more complicated acetylenes of the type **38**. The acetylene **47** is a prototype for utilization in the synthesis of 7-con-*o*-methylnogarol **38** and can be prepared from the commercially available 1,4-cyclohexanedione mono-2,2-dimethyltrimethylene ketal in seven steps in 17% overall yield.[19] The benzannulation of carbene complex **16** with acetylene **47** affords the naphthol **48** in 56–60% yield. It is interesting that no cyclobutenone formation was observed even though this reaction was carried out in acetonitrile. We have found this to be the case with other terminal acetylenes. The reaction of **16** with 1-pentyne in acetonitrile gives only the naphthol in 61% yield.[20] Investigations are continuing on the benzannulation of the carbene complex **16** with **47** and other acetylenes of the type **38**.

The second general route to anthracyclinones that is outlined in Scheme 7 has proven to be a viable approach in that we have employed it in a formal synthesis of daunomycinone **31**.[6a] This route may prove to be more versatile than the first given the greater flexibility in the preparation of $\alpha,\beta$-unsaturated complexes of the type **20** and the fact that their benzannulation reactions are less prone than aryl complexes to give rise to various side products such as cyclobutenones. For example in comparison with the carbene complex **16**, the cyclohexenyl complex **20** will react with diethylacetylene to give only 2,3-diethyl-5,6,7,8-tetrahydronaphthoquinone in good yields with either THF (65%)[6c] or acetonitrile (56%)[20] as solvent. In order to first establish the efficacy of this type of approach we chose as our initial target the tetracyclic trione **52** (Scheme 13) which has previously been converted to daunomycinone **31** in three steps.[21] The final ring to be closed on the way to **52** is the C ring, and thus the B ring is to be made by the benzannulation of the carbene complex **49** with the acetylene **50**. The problem of the relative regiochemistry of the A and D rings reduces to the regiochemistry of the alkyne incorporation since cyclization can only occur in one direction for complex **49**. As with the aryl complex **16** we would expect from our previous studies on the regiochemistry of alkyne incorporation[6c,k,p] that the alkenyl complex **49** would also react with a terminal alkyne such as **50** to give only the 2-substituted benzannulation product **51**.

The target tetracyclic ketone **52** requires the preparation of only a modestly functionalized carbene complex bearing a ketone functionality at the incipient C-9 position. The ketal complex **55** is the most reasonable choice if the standard Fischer synthesis is to be employed involving the addition of a cyclohexenyl lithium to chromium hexacarbonyl. The appropriate cyclohexenyl lithium can be conveniently obtained from the trisyl hydrazone **53** via the Bond-modification of the Shapiro olefin-synthesis.[22] Complex **55** must be prepared in two steps via the isolation of the ammonium salt **54** which is obtained by precipitation from an aqueous solution of the lithium salt upon treatment with tetramethyl ammonium bromide. Most




Scheme 12.

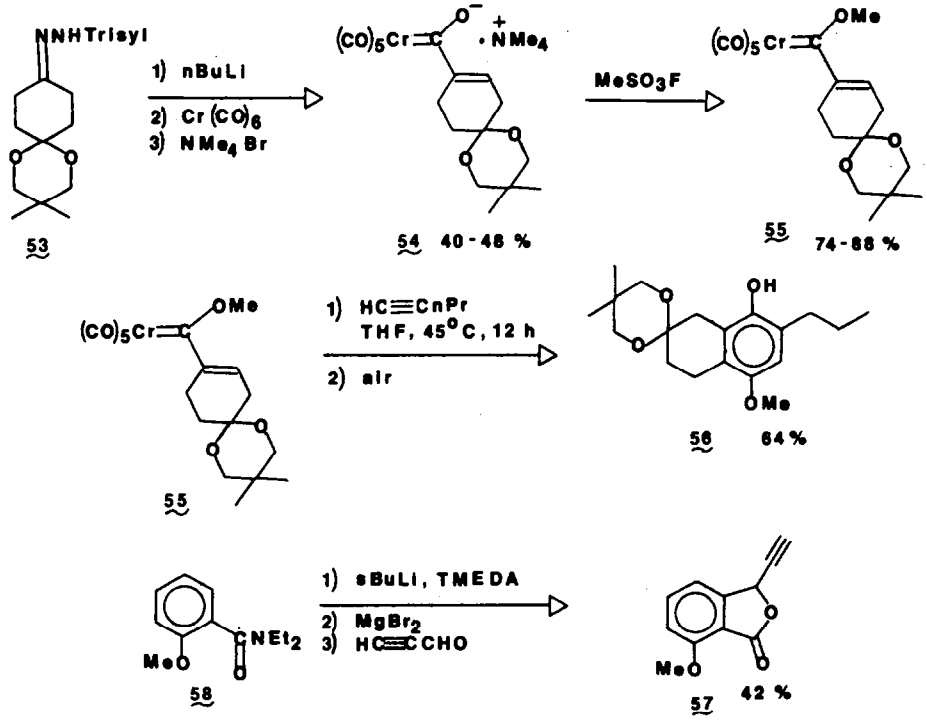


Scheme 13.

carbene complexes can be prepared in higher overall yields in a single step with direct methylation of an ethereal solution of the lithium salt, however, in this particular case the carbene complex **55** cannot be separated from methyl-2,4,6-triisopropylphenyl sulfinate. The reaction of **55** with 1-pentyne gives the phenol **56** in 64% yield and is comparable to the reaction of the simple cyclohexenyl complex **20** which reacts with 1-pentyne to give the analogous product in 61% yield.[6c]

The C ring in **52** is a quinone, and thus the correct oxidation state for the propargylic carbon in acetylene **50** is a ketone ($x = 0$). However, the benzannulation reaction has been found in general to proceed in very poor yields for either aryl or alkenyl carbene complexes with acetylene functionalities that are in conjugation with a carbonyl group. For example, the cyclohexenyl complex **20** will react with methyl propiolate to give only a 22% yield of the annulated product.[6c] Therefore, the acetylenic lactone **57** was selected as a suitable alternative and can be prepared in 42% overall yield in one step from N,N-diethyl-*o*-methoxy benzamide and propargyl aldehyde.

The benzannulation reaction proceeds nicely with the ethynyl lactone **57** and the cyclohexenyl ketal carbene complex **55** to give the tetrahydronaphthol **59**

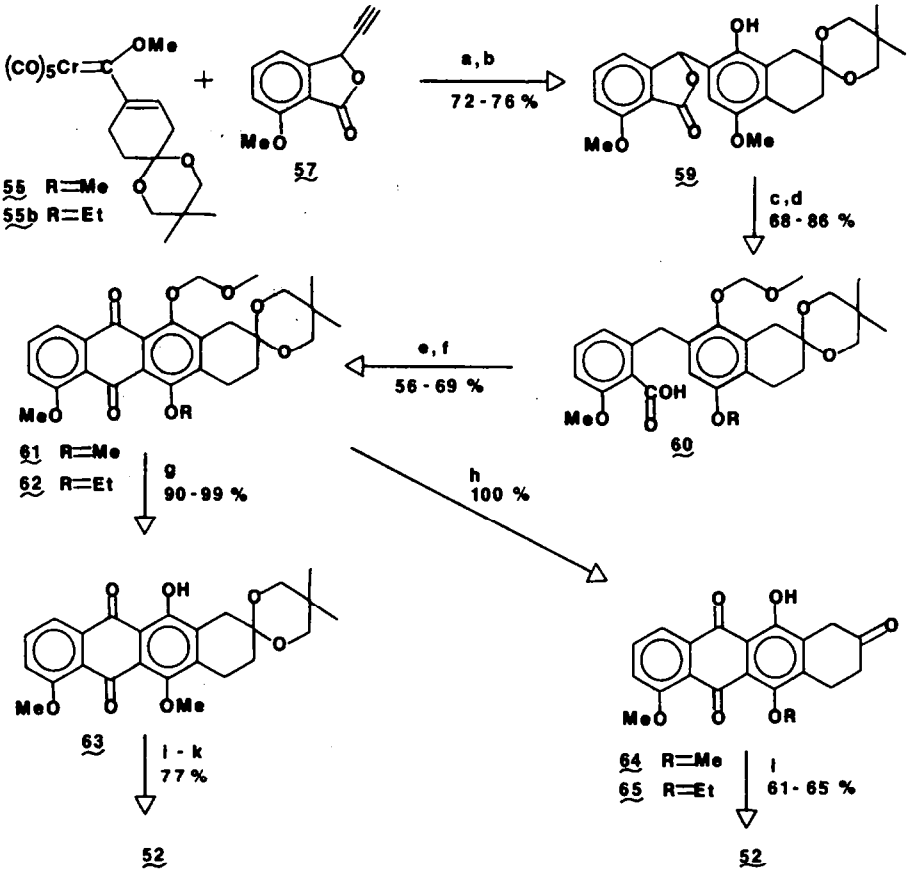


Scheme 14.

in the range of 72–76% yield (69% in acetonitrile) after an oxidative workup with ferric chloride–DMF complex[23] to remove the chromium tricarbonyl group. The final ring was closed by treating the acid **60** with trifluoroacetic anhydride in the presence of excess 2,6-di-t-butylpyridine. The intermediate anthrone was oxidized directly with oxygen in the presence of triton B[24] to the anthraquinone **61**. The methoxymethyl ether of **61** can be selectively cleaved to give the dimethyl ether **63** and subsequently oxidatively demethylated[25b] with silver oxide and hydrolyzed to give the desired tetracyclic trione **52** in 77% yield. This oxidation could not be successfully scaled up, and as an alternative we found that the dimethyl ether **64** could be cleanly demethylated selectively at the 6-position with 1:1 HBr/HOAc to give in larger scales the trione **52** which had $^1$H-NMR, IR, and mass spectra identical with those of an authentic sample. That the 6-methoxyl in **64** is selectively cleaved can also be established by the same conversion for **65** prepared from the ethoxy carbene complex **55b**. The synthesis of the tetracyclic trione **52** was achieved in nine steps from commercially available starting materials in 8% overall yield and is thus comparable to the other syntheses of this intermediate.[25]

The basic premise has thus been established that the synthetic approach outlined in Scheme 13 is viable for the synthesis of anthracyclinones. Future developments to be anticipated for the refinement of this approach include the development of a convergent synthesis for both the 11-oxy and 11-deoxy anthracyclines since the benzannulated product **51** has the oxygens in the incipient 6- and 11-positions differentially protected. A large advance in the convergence of the approach would be realized by the utilization of more highly functionalized carbene complexes. The synthesis of such complexes may be possible from more elaborate hydrazones than **53** or via the cycloaddition methods to be discussed below.

The synthetic approaches that have been discussed




a) THF, 45°C, 12 hr; b) 2 equiv. $[Fe(DMF)_3Cl_2][FeCl_4]$ in THF; c) excess $Et_2NiPr$, $ClCH_2OCH_3$ ($CH_2Cl_2$), 3 hr; d) Zn, pyridine, $CuSO_4 \cdot 7H_2O$ (10% KOH), reflux 24 hr.[42]; e) 1.2 equiv. $(CF_3CO)_2O$, 8 equiv. 2,6-di-t-butylpyridine ($CH_2Cl_2$), 0°-25°C, 4 hr.; f) Triton B (MeOH), 1 atm. $O_2$, 25°C, 5 min.; g) 1.2 equiv. $CF_3CO_2H$ ($CH_2Cl_2$), 25°C, 12 hr.; h) 4 equiv. $H_2SO_4$ (acetone), 56°C, 1 hr.; i) 10 equiv. AgO, excess 6N $HNO_3$, (acetone), 15 min.; j) 1% aq $NaHSO_3$; k) 10% aq $H_2SO_4$ (acetone), 45°C, 10 hr.; l) 1:1 48% HBr/HOAc, 55°C, 2 hr.

Scheme 15.

up to this point following the two general routes outlined in Scheme 7 have involved final ring closures via electrophilic aromatic substitution reactions. However, as shown in Scheme 16 an attractive alternative would be to take advantage of the electron withdrawing chromium tricarbonyl group that is put on the B ring (of **68**) by this benzannulation reaction (of **66** and **67**) and close the final ring by an aromatic-nucleophilic substitution reaction. The nucleophilic substitution reactions of arene chromium tricarbonyl complexes with carbanions have been examined by a number of investigators and most extensively by Semmelhack.[26] This approach has the attraction of providing for a one-pot construction of the tetracyclic intermediate **70**. As a backup to this approach the initial benzannulation product **68** could be oxidized with methanolic ceric ammonium nitrate to provide the quinone monoacetal **69**.[6p] An intramolecular Michael addition would then provide for a two-step construction of the same tetracyclic intermediate.

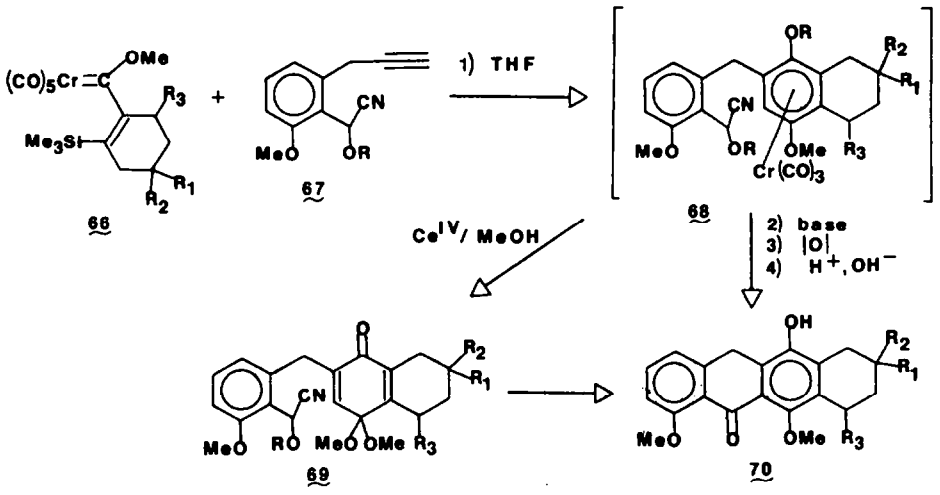
A cyanohydrin acetal will provide the carbanion of choice since it is a synthon for a carbonyl anion and it has been found to be one of the best carbanions for effecting aromatic nucleophilic substitutions on arene chromium tricarbonyl complexes.[26] There was some concern that the close proximity of the cyanohydrin functionality during the course of the benzannulation reaction might intercede via coordination to one of the reaction intermediates and interfere with the efficient formation of the normal benzannulation product. As a result of this consideration the cyanohydrin acetal of 5-hexynal **71** was prepared and as can be determined from its reactions with the O-methoxyphenyl complex **16** the cyanohydrin functionality does not prevent the formation of the normal benzannulated product from occurring in good yield.

With the cyanohydrin issue aside, there is a potentially much more delicate problem associated with the one-pot synthesis of **70** that is presented in Scheme 16. The R group in the initial benzannulated intermediate **68** is always a hydrogen atom. The deprotonation of the cyanohydrin will necessarily be preceded by deprotonation of the phenol and thus two equivalents of base will be required. The phenoxide ion will counteract the electron withdrawing effect of the chromium tricarbonyl group and may thus thwart the desired aromatic nucleophilic substitution. Recourse could then be made to the two-step procedure involving the mono-acetal **69**.

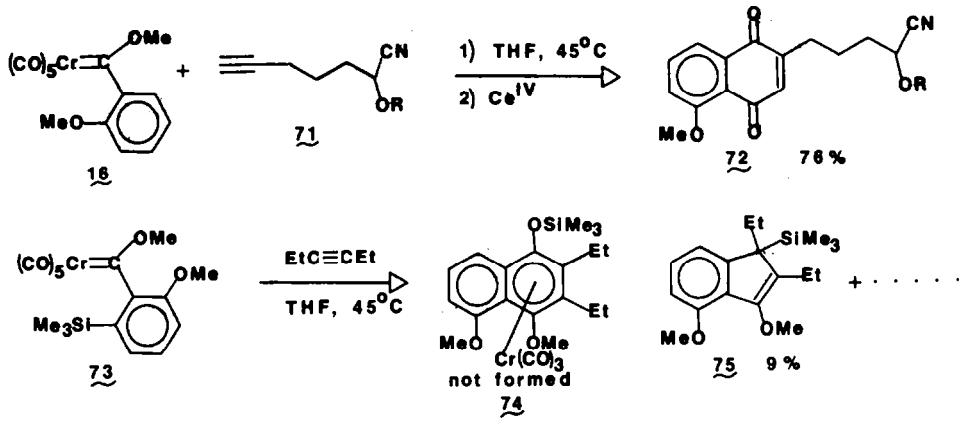
A piquant solution to this problem would be to employ a carbene complex such as **66** which has a trimethylsilyl group in the $\beta$-position and given the greater migratory propensity of silicon over hydrogen,[27] the expected benzannulation product would then be the trimethylsilyl protected phenol complex **68**. The crude solution of **68** could then be treated with one equivalent of base to effect deprotonation of the cyanohydrin acetal and the subsequent intramolecular nucleophilic attack on the coordinated arene. Oxidative workup followed by hydrolysis should yield the tetracyclic ketone **70**.

A test of the migratory aptitude of silicon in the benzannulation reaction was made by preparing the 2-methoxy-6-trimethylsilyl phenyl carbene complex **73** and examining its reaction with diethylacetylene. None of the desired benzannulation product **74** was formed as evidenced by oxidizing the crude reaction mixture with ceric ammonium nitrate and looking for the naphthoquinone **17**. The only product that was isolated and characterized, from the many that were formed, was the indene **75** in 9% yield. This result was certainly discouraging with respect to the one-pot synthesis outlined in Scheme 16 although the two-step procedure involving the quinone mono-acetal **69** is still secure.

Given the hydrolytic lability of the indene **75** it is possible that some of the many other products obtained from the reaction of complex **73** were isomeric with or derived from this product. The failure of carbon monoxide to insert is not unprecedented as indene products have been observed on other occasions.[17,28,29] In particular, it is interesting that the reaction of the carbene complex **76** which also has both ortho positions blocked has been reported to react with diphenylacetylene to give only the complexed and uncomplexed indene **78**. One possible explanation




Scheme 16.



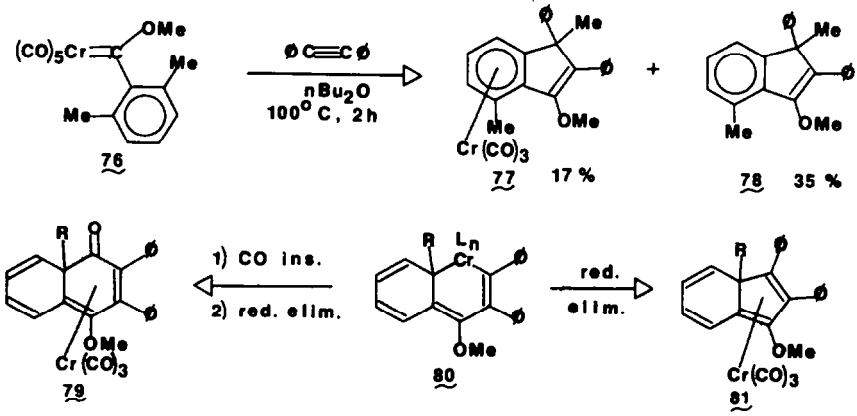

Scheme 17.

centers on the intermediate **80**. If a reductive elimination occurs rather than a carbon monoxide insertion, then **81** can be related to the product by a 1,5-sigmatropic methyl shift. Steric hindrance about a metal center can enhance reductive eliminations[30] and thus it is to be expected that trimethylsilyl would also cause reductive eliminations leading to indene products.

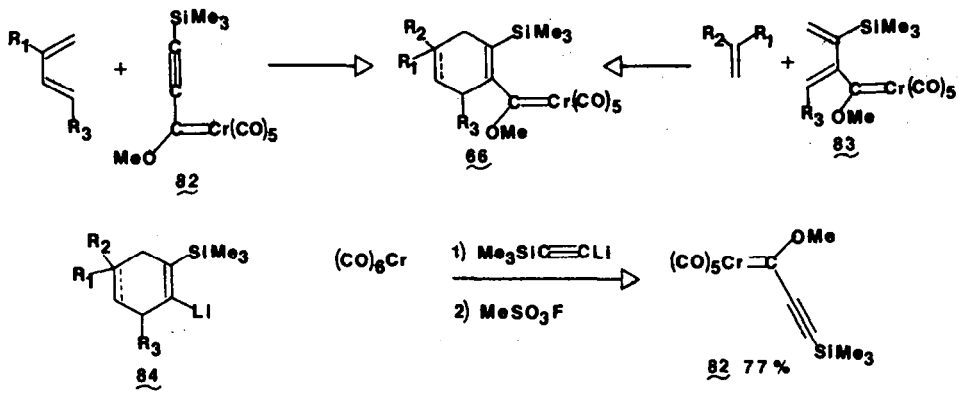
It is of course possible that the behavior of alkenyl complexes of the type **66** will be completely different and that carbon monoxide will insert and that silicon will migrate to give the protected benzannulated complex **68**. Before complexes of the type **66** can be tested they must first of course be prepared, however, it is not clear how the Fischer method can be applied to the general synthesis of complexes of this type since the corresponding vinyl lithiums of the type **84** are not likely to be preparable in a straightforward manner. As is suggested in Scheme 19 these complexes would be readily accessible via the Diels–Alder reactions of either the trimethylsilylethynyl complex **82** or the dienyl complex **83**. The former should be the most easily accessible starting material and in fact can be prepared in a single step from trimethylsilyl acetylene and chromium hexacarbonyl in 77% yield.[6a]

The Diels–Alder reactions of Fischer carbene complexes have been previously reported from our laboratories[6a,d] and are observed to proceed with rate enhancements, stereoselectivities, and regioselectivities that are normally only associated with Lewis acid catalyzed reactions. The unsubstituted vinyl complex **85** was found to react with isoprene with a rate enhancement of $2 \times 10^4$ over that of its closest carbon analog, methyl acrylate.[6a] Furthermore, as might be anticipated there is an associated increase in the regioselectivity of the reaction with isoprene which was established by oxidizing the mixture of the cycloadduct carbene complexes and comparing the resultant mixture of the methyl esters **86** and **87** with that obtained from the reaction of methyl acrylate. The chemical and spectral properties of Fischer carbene complexes such as the chemical shift of the carbene carbon of the complex **85**[31] and the acidity of the complex **2**[8] are suggestive that the high dienophilicity of $\alpha,\beta$-unsaturated Fischer carbene complexes is also a measure of the electron withdrawing nature of the pentacarbonyl chromium carbene unit.

In line with the dienophilicity of the vinyl complex **85**, the trimethylsilylethynyl complex **82** undergoes a very facile Diels–Alder reaction with 2,3-dimethylbutadiene




Scheme 18.



Scheme 19.

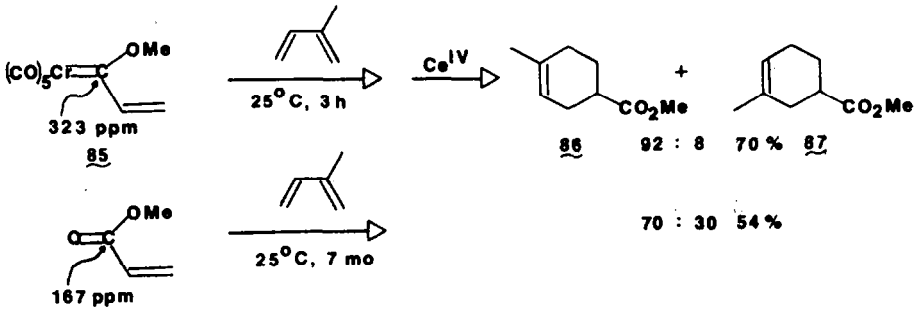
to give the cycloadduct **88** in 89% yield isolated by flash chromatography.[6a] In contrast to the reaction of complex **73**, the annulation of the β-trimethylsilyl complex **88** with 1-pentyne proceeded smoothly with carbon monoxide insertion and silicon migration to give the trimethylsilyl protected phenol chromium tricarbonyl complex **89** in 97% yield. Unlike the methyl or trimethylsilyl group in intermediate **80** the steric bulk of the trimethylsilyl group in intermediate **90** is not enough to cause reductive elimination and this result is perhaps suggestive of the relative metal–carbon bond strengths in intermediates **80** and **90**.

The cycloaddition and annulation reactions may also be carried out simultaneously with the carbene complex, the diene, and the acetylene all in one pot. Complex **82** will chemoselectively react with 2,3-dimethylbutadiene in the presence of 1-pentyne and the resulting cycloadduct will chemoselectively react with 1-pentyne to give the phenol complex **89** in 80% crystallized yield from hexane in two crops. With an oxidation workup the corresponding naphthoquinone can be isolated chromatographically in 92% yield.

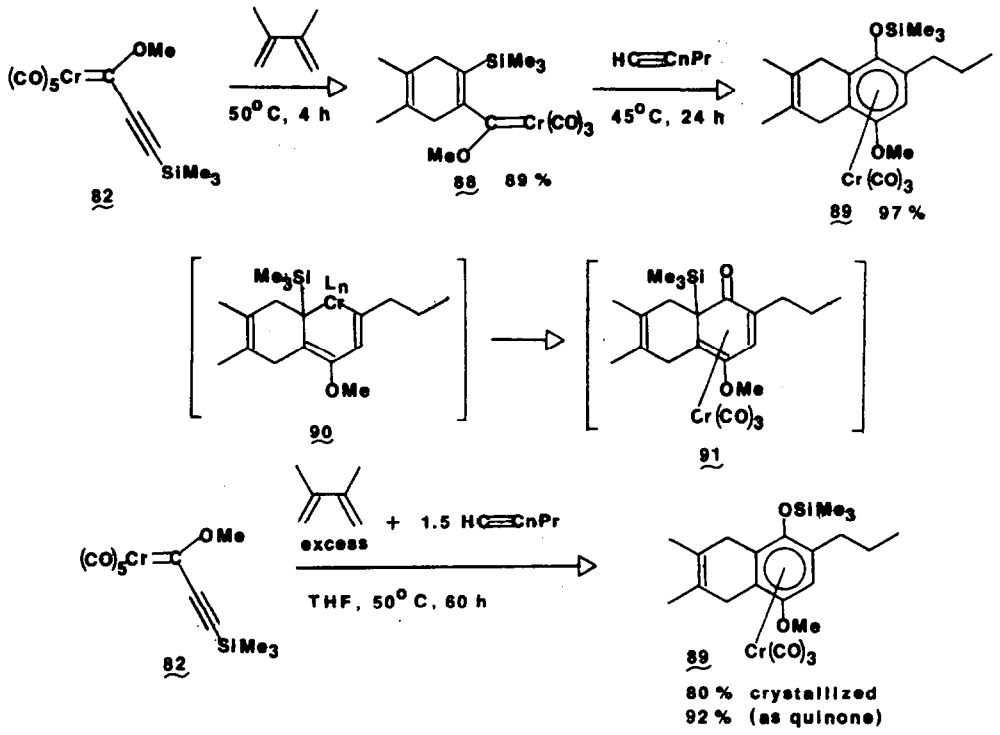
Other tandem cycloaddition/annulation reactions of the acetylene complex **82** are presented in Scheme 22. Its cycloaddition with 2-trimethylsiloxy butadiene occurs at room temperature to regioselectively give the cyclohexadienyl complex **92** which is not chromatographically stable and is treated in the crude form with 2,2-dimethyl-1,3-propanediol with a catalytic amount of trimethylchlorosilane[32] to give the ketal carbene complex **93** in 61% overall yield. The annulation of **93** with 1-pentyne proceeds to give after an oxidative workup the tetrahydronaphthol derivative **56** in 60% yield. By way of comparison the ketal complex **55**, which differs from **93** only by the trimethylsilyl group, reacts with 1-pentyne to give **56** in 64% yield.

The one-pot reaction of acetylene complex **82**, 2-trimethylsiloxy butadiene, and the lactone acetylene **57** produces after ketalization the same phenol **59** with approximately the same overall efficiency that we had previously prepared by a different method (Scheme 15) as an intermediate in anthracycline synthesis.[6c] These tandem cycloaddition/annulation reactions suggest attractive approaches to the synthesis of anthracyclines via Fischer carbene complexes particularly with respect to those that involve aromatic nucleophilic substitutions in the final ring closure such as that outlined in Scheme 16.

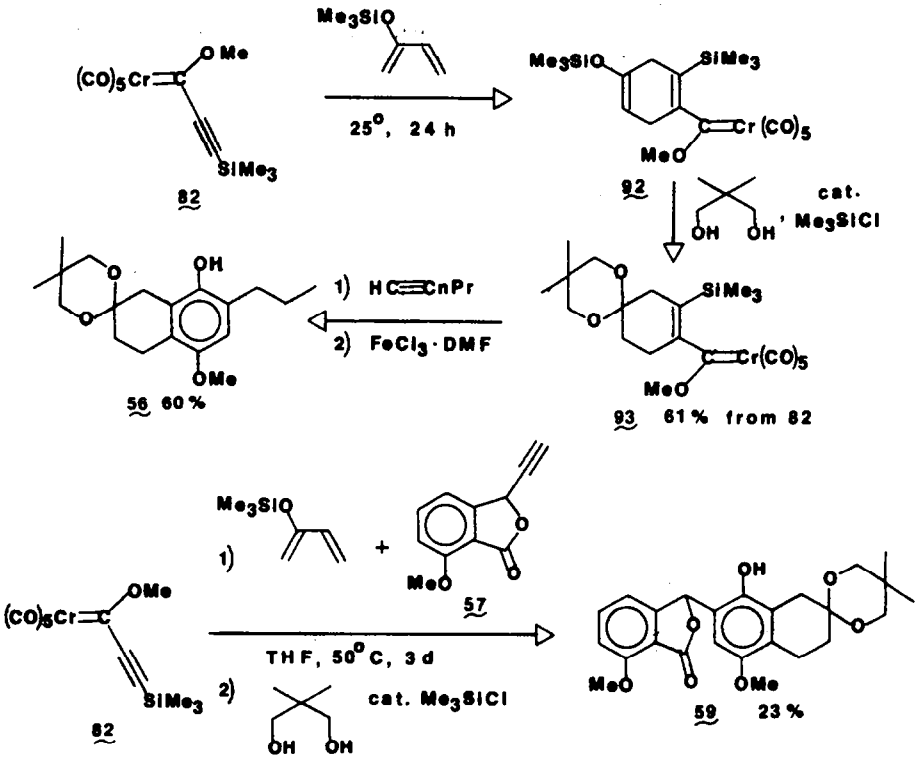
The aryl complexes **73** and **76** which are both blocked in the ortho positions react with acetylenes to give five-membered ring annulated products presumably via reductive elimination from an intermediate of the type **80** where R is methyl or trimethylsilyl. The α,β-unsaturated complex **88** on the other hand reacts with acetylenes to give only benzannulated products indicating that the intermediate **90** prefers to undergo carbon monoxide insertion rather than reductive elimination. This suggests that general intermediates of the type **95** will undergo carbon monoxide insertion and in those cases where the angular substituent ($R_1$) is of sufficiently low migratory propensity (alkyl) the annulation reaction would be expected to produce 2,4-



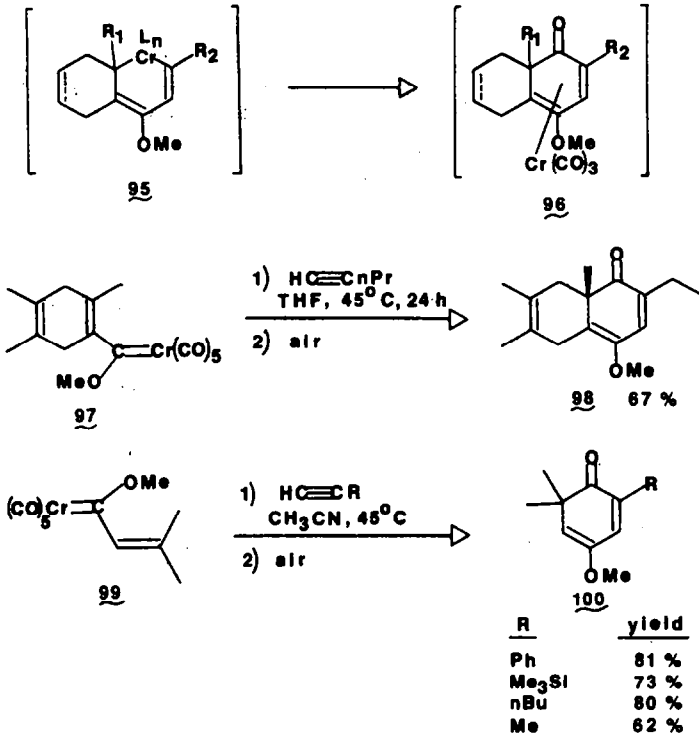
Scheme 20.




Scheme 21.




Scheme 22.



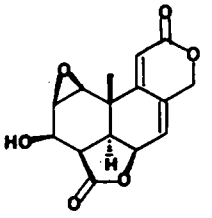

Scheme 23.

cyclohexadienones. This has in fact been found to be the case[6d] as illustrated by the reaction of the α,β-unsaturated complex **97** with 1-pentyne which gives a 67% yield of the cyclohexadienone **98** upon opening to air and separation from the crude reaction mixture by flash chromatography on silica gel.[6a]

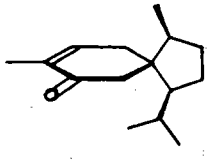
This cyclohexadienone annulation appears to be general for α,β-unsaturated chromium carbene complexes that are disubstituted in the beta positions. The isobutenyl complex **99** will react with a number of acetylenes to give good yields of the monocyclic dienones **100**.[6d] Cyclohexa-2,4-dienones are versatile intermediates that have been employed in a number of syntheses, however, their synthetic potential has not been fully realized which is probably largely due to the lack of general methods for their preparation.[33] The cyclohexadienone annulation of Fischer chromium carbene complexes provides for a direct, regioselective approach to this ring system under neutral conditions at near ambient temperatures.

This cyclohexadienone annulation is attractive in that it removes the restriction of employing the reaction of chromium carbene complexes and acetylenes only in the synthesis of planar aromatic systems with $sp^2$ carbons. The accessibility of $sp^3$ carbons greatly expands the horizons for these annulation reactions and among the many structures being synthetically pursued in this laboratory are acorenone **101**[34] and wentilactone A **102**.[35]

A key to the application of this cyclohexadienone annulation to the synthesis of natural products containing a number of chiral centers is the stereoselectivity associated with the introduction of the new $sp^3$ carbon with respect to the existing ones. The β,β-disubstituted carbene complex **103** was prepared and found to react with a number of terminal acetylenes to give the *trans*-decaladienones **104** in good yields with ⩾90% stereoselectivity in all cases.[6d] One explanation for this stereoselectivity is that a steric interaction between the methoxyl group and the pseudoaxial




wentilactone A 102



acorenone 101

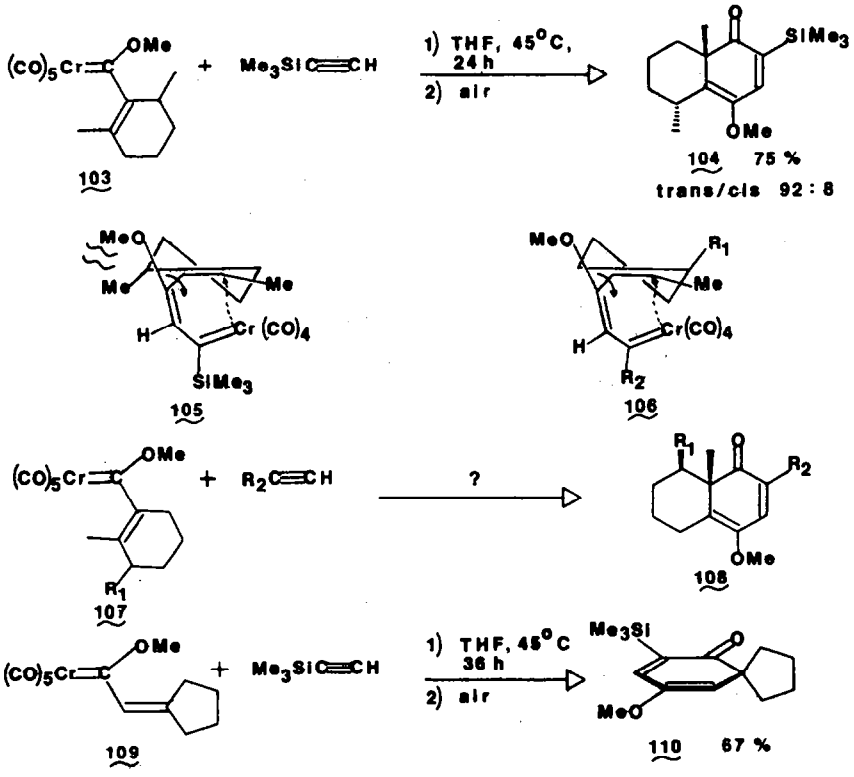
Scheme 24.

methyl group in intermediate **105** (**25** in Scheme 5) leads to a preferred approach of the chromium *syn* to the pseudoaxial methyl resulting in a *trans* relationship of the methyl groups upon cyclization to a chromacyclohexadiene intermediate (**27** in Scheme 5). The same consideration could be made for the cyclization of the vinyl ketene complex **26** (Scheme 5), however, the situation is complicated by the presence of a chiral center about the chromium atom. This model predicts that the annulation of the carbene complex **107** should give the *cis*-decaladienone **108** (via **106**) and this reaction is currently being investigated.

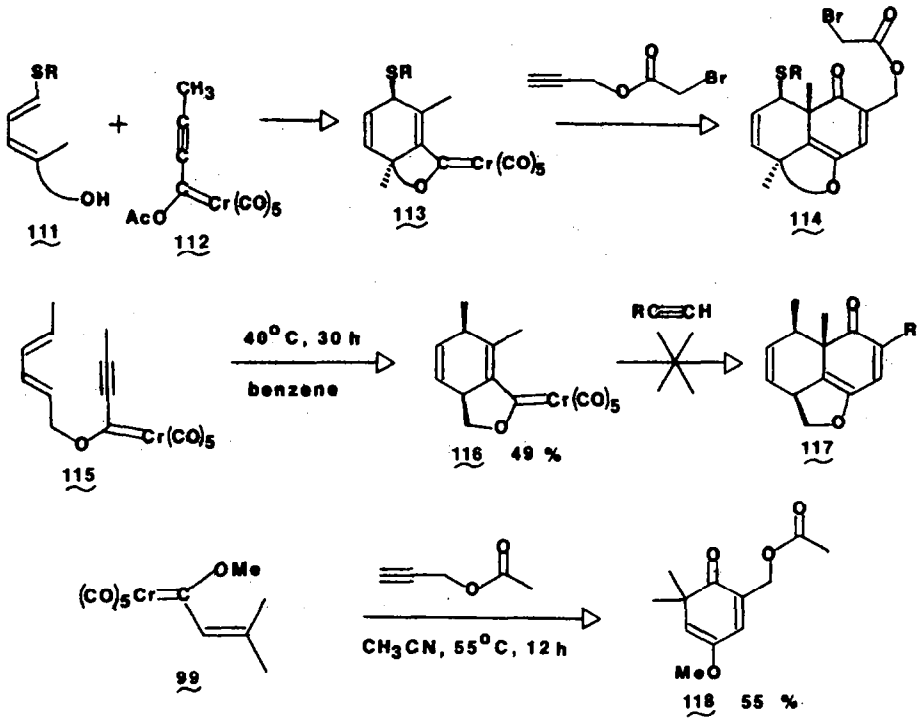
The annulation of carbene complexes in which the two beta substituents are tied together in a ring should provide an entry to spirocyclic synthesis. To examine this the carbene complex **109** was prepared from a Lewis acid catalyzed aldol reaction of the conjugate base of the methyl methoxy complex **2** and cyclopentanone.[9] The reaction of complex **109** with trimethylsilyl acetylene proceeds smoothly to give the spirocyclodecadienone **110** in 67% yield. It is anticipated that complexes of the type **109** with a chiral center in the 5-membered ring will undergo annulations with the stereoselective formation of the spirocyclic center.

The basis of the approach to the syntheses of wentilactone A and the related nagilactones is the tandem Diels–Alder cyclohexadienone annulation sequence outlined in Scheme 26. The synthesis of the $\beta,\beta$-disubstituted alkenyl complex **113** is envisioned by an intramolecular Diels–Alder reaction that is set up by the coupling of the acetoxy carbene complex **112** and the alcohol **111**.[36,37,61] As a model the complex **115** was prepared by such a coupling reaction and it was found to undergo an intramolecular cyclization with a significant rate enhancement over that of the analogous tetrolic ester.[38] The resulting cycloadduct **116** unfortunately does not undergo clean annulation with terminal acetylenes and this may be perhaps due to strain in the expected cyclohexadienone product **117**. If this is in fact the case it is expected that this could be overcome by increasing the chain length in the alcohol **111**, however, it is not clear how this may impact on the stereoselectivity of the annulation step. The synthetic approach to wentilactone A requires a cyclohexadienone annulation with a propargyl acetate derivative, and there was some concern for this step since the benzannulation of alkenyl complexes with propargyl acetate proceeds in poor yields[6c] and the reaction of aryl complexes leads to complex mixtures. To the contrary, the reaction of the isobutenyl complex **99** gives the cyclohexadienone **118** in 55% yield as the only mobile compound on TLC.

In summary, it can be said that the chemistry of Fischer carbene complexes is rich with potential for utilization in synthetic problems in organic chemistry. Included among their useful reactions are the benzannulation, cyclohexadienone annulation, and Diels–Alder reactions which have been described in this article with respect to synthetic applications that are being pursued in our laboratories. Other reactions of Fischer carbene complexes which also appear to have synthetic potential are cyclopropanations, aldol condensations,[9] and two-alkyne annulations.[6b]




Scheme 25.




Scheme 26.

## EXPERIMENTAL

Unless otherwise noted all reagents were obtained from commercial suppliers and used without further purification. THF was distilled from sodium benzophenone ketyl immediately prior to use. All reactions were carried out under either argon or nitrogen and for reactions involving carbene complexes the reaction mixtures were deoxygenated by the freeze-thaw method (−196°/25°, 3 cycles). Flash column chromatography was carried out as described by Still,[39] and this was done in air even for the various carbene complexes. The solvents for chromatography and corresponding to the indicated $R_f$ values are indicated as a ternary mixture of ether, $CH_2Cl_2$, and hexanes. All m.ps and b.ps are uncorrected. Routine proton NMR spectra were recorded either on a Bruker 270 MHz or a DS 1000 (Chicago built) 500 MHz spectrometer in $CDCl_3$ with TMS as internal standard. The multiplicities of the NMR spectral absorptions are indicated by: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and dd, doublet of doublets. The $^{13}$C-NMR spectra were recorded on a Nicolet 200 spectrometer at 50 MHz. IR spectra were recorded on a Perkin–Elmer model 283 spectrophotometer and the five largest peaks are listed plus any others that are particularly characteristic. Low resolution mass spectra were recorded on a Finnigan 1015 instrument and high resolution mass spectra were carried out at the Midwest Center for Mass Spectrometry (Nebraska). Elemental analysis were carried out by Galbraith Lab., Inc.

*Preparation of methoxy (o-methoxyphenyl)methylene pentacarbonyl chromium* **16**

*o*-Lithioanisole was prepared by adding 91.0 mmol of n-BuLi (58.7 ml of a 1.55 M soln in hexane) to a soln of 21.3 g of *o*-bromoanisole (114 mmol) in 100 ml of anhyd ether at 0° under argon. After the soln had warmed to room temp for 20 min it was transferred via cannula to a slurry of 20.0 g of chromium hexacarbonyl (91.0 mmol) in 400 ml of anhyd ether. After 30 min the slurry (the lithium acylate usually precipitates out at this point) is methylated by the dropwise addition of 13.0 g (114 mmol, Columbia) of methyl fluorosulfonate (in fume hood). The reaction is stopped after 45 min and the excess methyl fluorosulfonate is quenched by washing with 300 ml of sat $Na_2CO_3$ aq. The organic layer was washed with water and saturated brine and dried over $MgSO_4$. After the removal of the ether the solid residue was extracted into 1 l of hexane and filtered through celite. Concentration of this soln on a rotary evaporator to 200 ml with cooling to below room temp gave 14.3 g of **16** as red crystals. Further concentration to 50 ml and cooling to 0° gave an additional 8.2 g of **16**. If longer reaction times are allowed then the crude mixture is not clean enough to provide pure **16** by direct crystallization and a chromatographic purification must be used.

The 7.7 g of solid residue from the mother liquor was found to contain two carbene complexes. These could be separated chromatographically on silica gel with hexane as eluent to provide an additional 2.5 g of **16** ($R_f$ = 0.09). Complex **16** was obtained in 80.5% total isolated yield: m.p. = 71–74° (lit. 73°[16]); $^1$H-NMR, $\delta$ = 3.80 (s, 3H), 4.13 (s, 3H), 6.4–7.4 (m, 4H); mass spectrum, *m/e* (% rel. int.) 342 $M^+$ (11), 286 (10), 258 (8), 230 (22), 203 (23), 202 (100), 159 (44), 52 (58). The second carbene complex was isolated ($R_f$ = 0.05) and identified as the internally coordinated methoxy (*o*-methoxyphenyl)methylene tetracarbonyl chromium as very chromophoric dark red-brown crystals: m.p. 97–99°; $\delta$ = 4.18 (s, 3H), 4.82 (s, 3H), 6.4–7.4 (m, 4H); IR (cyclohexane), $\bar{\nu}$ = 2020 s, 1925 s, 1850 s; mass spectrum, *m/e* (% rel. int.), 314 $M^+$ (8), 286 (7), 258 (3), 230 (21), 203 (14), 202 (64), 159 (47), 91 (36), 52 (100); Anal.: $C_{13}H_{10}O_6Cr$ (C, H, Cr).

Integration of the $^1$H-NMR spectrum of the crude mixture indicates that the ratio of the two carbene complexes is 27/1. Although the pentacarbonyl complex is indefinitely stable in the solid state it will slowly lose CO in soln to give the tetracarbonyl complex. This is in fact observed for all of the annulation reactions of **16** as monitored by TLC but is of no consequence since both undergo the same annulation.

*The annulation of complex* **16** *with diethylacetylene*

A soln of 0.690 g of **16** (2.02 mmol) and 0.207 g (2.52 mmol) of 3-hexyne in 20 ml of THF was deoxygenated by the freeze-

thaw method (−196°/0°, 3 cycles). The mixture was stirred under argon at 45° and monitored by TLC. The mixture was opened to air and oxidized by vigorously stirring with 20 ml of a 0.5 M soln of ceric ammonium nitrate in 0.1 N HCl for 30 min. The organic phase was diluted with ether and washed with water and saturated brine and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel with a 1:1:4 solvent mixture ($R_f$ = 0.22) and obtained in 70% yield (0.345 g, 1.42 mmol) as a yellow solid which was identified as **17**: m.p. = 108.5–109° (ether/hexane); $^1$H-NMR, $\delta$ = 1.14 (t, 3H), 1.15 (t, 3H), 2.60 (q, 2H), 2.65 (q, 2H), 4.00 (s, 3H), 7.25 (d, 1H, J = 8.3 Hz), 7.63 (t, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 7.8 Hz); IR ($CH_2Cl_2$), $\gamma$ = 3080 s, 3005 s, 1660 s, 1592; mass spectrum, *m/e* (% rel. int.), 244 $M^+$ (20), 229 (45), 201 (55), 115 (58), 76 (100); $^{13}$C-NMR, $\delta$ = 13.6, 13.8, 19.7, 20.1, 56.1, 117.0, 118.6, 134.0, 134.2, 145.4, 149.5, 159.0, 184.1, 184.8; Anal. $C_{15}H_{16}O_3$ (C, H). The quinone **17** can be obtained in 58% yield with the same procedure from the internally coordinated methoxy (*o*-methoxyphenyl)methylene tetracarbonyl chromium.

The quinone monoacetal **19** can be obtained by pouring the crude mixture into a soln of 7.5 equivs of ceric ammonium nitrate in 100 ml of anhyd MeOH stirred over 1 g of powdered anhyd $Na_2CO_3$. After 30 min the soln was diluted with 200 ml of 2% $NaHCO_3$ aq and extracted with several portions of ether. After removal of the volatiles the crude product was purified by chromatography on activity IV basic alumina with a 1:1:4 solvent mixture ($R_f$ = 0.13) and obtained in 72% yield as a white solid: m.p. = 88–89.5° (ether/hexane); $^1$H-NMR, $\delta$ = 1.14 (t, 3H, J = 7.5 Hz), 1.24 (t, 3H, J = 7.5 Hz), 2.51 (q, 2H), 2.57 (q, 2H), 2.92 (s, 6H), 3.94 (s, 3H), 7.15 (d, 1H, J = 8.6 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.79 (d, 1H, 7.7 Hz); $^{13}$C-NMR, $\delta$ = 13.3, 14.0, 19.4, 20.0, 51.2, 56.1, 99,5, 115.2, 118.5, 125.1, 130.0, 134.4, 142.1, 154.8, 157.3, 183.2; mass spectrum, *m/e* (% rel. int.), 290 $M^+$ (18), 275 (16), 261 (100), 259 (52), 231 (78), 135 (78), 115 (85), 91 (60), 77 (88); Anal. $C_{17}H_{22}O_4$ (C, H).

*The annulation of complex* **16** *with t-butyl-5-pentynote* **42**

A soln of 0.627 g of **16** (1.83 mmol) and 0.462 g of acetylene **42** (2.75 mmol) in 10 ml of $CH_2Cl_2$ was deoxygenated by the freeze-thaw method (−196°/0°, 3 cycles). The mixture was stirred under argon at 40° and after 36 hr the clean formation of **43** was indicated by TLC. The soln was exposed to air by transferring to a new flask and stirring for 15 min at room temp. NaOAc (200 mg) was added followed in 5 min by 4 ml of trifluoroacetic anhydride. After TLC indicated that acetylation of the naphthol was complete (10 min) 6 ml of trifluoroacetic acid was added. The cyclization proceeded in 45 min to give essentially one product as indicated by TLC. The mixture was slowly added to 50 ml of water and the crude product was extracted with two 75 ml portions of ether. The combined ether layer was extracted with ten 40 ml portions of 1 N KOH. The first five portions were acidic and were discarded. The remaining five were acidified and extracted with ether. After removal of the volatiles, the crude product was purified by flash chromatography with a 1:1:1 solvent mixture ($R_f$ = 0.16) and obtained in 64% yield (0.32 g, 1.17 mmol) as a yellow solid and identified as the tricyclic ketone **44**: m.p. = 157°; $^1$H-NMR, $\delta$ = 2.13 (m, 2H), 2.68 (t, 2H, J = 6.6 Hz), 2.96 (t, 2H, J = 6.1 Hz), 3.88 (s, 3H), 3.98 (s, 3H), 6.86 (d, 1H, J = 7.8 Hz), 7.47 (t, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.4 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 3600 m, 3005 m, 2935 m, 1680 s, 1613 m, 1370 m, 1281 m; mass spectrum, *m/e* (% rel. int.), 272 $M^+$ (94), 243 (65), 85 (65), 83 (100); Anal. $C_{16}H_{16}O_4$ (C, H).

*Preparation of cyclohexenyl(methoxy)methylene pentacarbonyl chromium* **20**

To 7.68 g (20.3 mmol) of cyclohexanone 2,4,6-triisopropyl benzene sulfonyl hydrazone[22a] in 50 ml of THF at −78° was slowly added by syringe 25.54 ml (39.6 mmol) of a 1.55 M soln of n-BuLi in hexane. The resulting yellow soln was transferred to an ice-bath and the soln turned to a deep red with $N_2$ evolution. After 15 min, the resulting vinyl anion soln was transferred to a slurry of 4.46 g (20.3 mmol) of chromium hexacarbonyl in 50 ml of ether at room temp. The soln rapidly turned to yellow and was stirred for 30 min. To this was added 4 ml (50 mmol) of methyl fluorosulfonate and the resulting red soln was stirred for 20 min. Powdered $Na_2CO_3$ was added to destroy the excess methyl fluorosulfonate. After filtration and dilution with 200 ml of ether, the soln was washed with brine and dried over $MgSO_4$. After removal of solvents, the residue was extracted with several portions of hexane and filtered through celite. The crude mixture was flash chromatographed on silica gel with hexane as solvent to give 3.87 g (12.3 mmol, 62%) of **20** as a red oil: $^1$H-NMR (500 MHz), $\delta$ = 1.58–1.67 (bs, 4H), 2.16 (bs, 2H), 2.32 (bs, 2H), 4.67 (s, 3H), 6.37 (bs, 1H); $^{13}$C-NMR, $\delta$ = 21.43, 21.82, 25.25, 25.63, 64.98, 134.98, 154.17, 216.7, 223.8, 350.85; IR (neat), $\bar{\nu}$ = 2920 w, 2060 s, 1920 s, 1620 w, 1450 m, 1230 m, 1122 m, 985 m, 795 m; mass spectrum, *m/e* (% rel. int.), 316 $M^+$ (1.8), 288 (5), 260 (1.7), 232 (1.4), 204 (5), 176 (36), 52 (100); Anal. $C_{13}H_9O_6Cr$ (C, H, Cr).

*Preparation of 3-ethynyl-7-methoxy-(3H)-isobenzofuranone* **57**

To a stirred soln of 4.2 g (20 mmol) of **56** in 150 ml of THF and 3 ml of TMEDA at −78° was added 18 ml (26 mmol) of a 1.45 M soln of s-BuLi in cyclohexane.[40] After 90 min, 27 mmol of $MgBr_2$ in ether was added and the flask was transferred to an ice-bath. After 20 min the soln was cooled to −78° and 1.62 g (30 mmol) of propynal in 5 ml of the THF was added slowly. The soln was stirred for 45 min at −78° and 3 hr at room temp and then hydrolyzed with 10% HCl aq. The organic layer was washed with water and saturated brine and dried over $MgSO_4$. The product was crystallized from hexane and $CH_2Cl_2$ to give 1.58 g (8.41 mmol, 42%) of **57**: m.p. = 170–172°; $^1$H-NMR (500 MHz), $\delta$ = 2.69 (d, 1H, 2.3 Hz), 4.01 (s, 3H), 5.97 (d, 1H, 1.9 Hz), 6.99 (d, 1H, 8.3 Hz), 7.14 (d, 1H, 7.5 Hz), 7.71 (t, 1H, 8.0 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 3305 m, 3105 w, 1770 s, 1610 m, 1490 s, 1290 s, 1030 s, 640 w; mass spectrum, *m/e* (% rel. int.), 188 $M^+$ (30), 170 (8), 158 (31), 140 (40), 135 (33), 130 (47), 113 (27), 102 (100), 84 (83), 76 (55); Anal. $C_{11}H_8O_3$ (C, H).

*Preparation of the 2,4,6-triisopropylphenyl sulfonyl hydrazone of 1,4-cyclohexanedione mono-2,2-dimethyl trimethylene ketal* **53**

To a soln of 3.86 g (Aldrich, 18.53 mmol) of 1,4-cyclohexanedione mono-2,2-dimethyl trimethylene ketal in 50 ml of MeOH was added in small portions 6.8 g (23 mmol) of freshly prepared and finely powdered 2,4,6-triisopropyl benzene sulfonyl hydrazide.[41] The soln was stirred for 30 min after the hydrazone had crystallized from the soln and then chilled in a freezer for 4 hr. The hydrazone was collected and washed with 50 ml of cold MeOH to give 8.27 g (17.3 mmol, 93%, m.p. 154–157°) of **53** after drying *in vacuo* for several hours. If the order of addition is reversed, the yield will drop due to rapid decomposition of the hydrazide in MeOH. Spectral data for **53**: $^1$H-NMR (500 MHz), $\delta$ = 0.93 (s, 3H), 1.00 (s, 3H), 1.26 (d, 18H, 6.8 Hz), 1.86–1.87 (m, 4H), 2.25–2.34 (m, 4H), 2.90 (m, 1H), 3.45 (d, 2H, 11.3 Hz), 3.52 (d, 2H, 11.3 Hz), 4.21 (sept, 2H, 6.8 Hz), 7.16 (s, 2H); IR ($CHCl_3$), $\bar{\nu}$ = 3260 w, 2960 s, 2830 m, 1640 w, 1595 m, 1360 m, 1010 m, 1640 w, 1595 m, 1360 m, 1010 m, 652 m; mass spectrum, *m/e* (% rel. int.), 478 $M^+$ (2.2), 399 (1.8), 282 (22), 267 (15), 203 (18), 198 (28), 128 (44), 97 (72), 69 (100), 43 (90); Anal. $C_{26}H_{42}O_4N_2S$ (C, H).

*Preparation of 4-(2,2-dimethyl trimethylene ketal)-1-cyclohexenyl(methoxy)methylene pentacarbonyl chromium* **55**

To a soln of 11.34 g (23.7 mmol) of **53** in 90 ml of THF at −78° was added 28.8 ml (46.1 mmol) of a soln of n-BuLi in hexane. After the addition the golden yellow soln was transferred to an ice-bath and stirred for an additional 15 min. The soln of the vinyl anion was transferred by cannula to a slurry of 5.2 g (23.6 mmol) of chromium hexacarbonyl in 100 ml of ether at room temp. The resulting lithium acyl metallate was cation exchanged by removing the solvents, dissolving the residue in 30 ml of water which had previously been purged with argon, and diluted with 70 ml of saturated aqueous solution of tetramethyl ammonium bromide. $CH_2Cl_2$ was added until all of the yellow crystals dissolved. The $CH_2Cl_2$

layer was separated, washed with brine, dried over $MgSO_4$, and diluted with hexane until yellow crystals appeared. The soln was chilled to give 4.62 g (9.7 mmol, 41%) of the tetramethyl ammonium acyl metallate.

The ammonium salt (6.1 g, 12.8 mmol) was dissolved in 180 ml of $CH_2Cl_2$ and treated with 1.4 ml (16.6 mmol) of methyl fluorosulfonate. After 90 min the reaction was quenched by shaking with 50 ml of cold sat $Na_2CO_3$ aq, followed by a brine wash, drying with $MgSO_4$ and removal of solvents. The residue was extracted with 50 ml of hexane, filtered, concentrated, and flash chromatographed on silica gel with a 1:1:4 solvent mixture to give 4.68 g (11.25 mmol, 88%) of **55** (m.p. 69–71°). $^1$H-NMR (500 MHz), $\delta$ = 0.94 (s, 3H), 1.02 (s, 3H), 2.00 (t, 2H, 6.3 Hz), 2.30 (bs, 2H), 2.65 (bs, 2H), 3.49 (d, 2H, 11.4 Hz), 3.57 (d, 2H, 11.4 Hz), 4.63 (s, 3H), 6.18 (bs, 1H); IR ($CHCl_3$), $\bar{\nu}$ = 2960 w, 2062 m, 1945 s, 1110 m, 645 m; mass spectrum, *m/e* (% rel. int.), 416 $M^+$ (6.2), 388 (0.2), 360 (1.2), 332 (10), 304 (18), 276 (32), 220 (23), 190 (32), 128 (55), 108 (53), 80 (81), 52 (100); Anal. $C_{18}H_{20}O_8Cr$ (C, H, Cr).

The analogous ethoxy carbene complex **58** was prepared from the ammonium salt and ethyl fluorosulfonate using the same procedure. Chromatography as above gave a 46% yield of **58**; $^1$H-NMR (500 MHz) $\delta$ = 0.96 (s, 3H), 1.02 (s, 3H), 1.60 (t, 3H, 6.9 Hz), 2.01 (bs, 2H), 2.30 (bs, 2H), 2.65 (bs, 2H), 3.50 (d, 2H, 11.2 Hz), 3.57 (d, 2H, 11.3 Hz), 4.90 (bs, 2H), 6.13 (bs, 1H).

*Preparation of* 2-[3(7-*methoxy*-1-(3H) *isobenzofuranonyl*)]-4-*methoxy* - 7 - (2,2 - *dimethyl trimethylene ketal*) - 5,7,8,9 - *tetrahydro*-1-*naphthol* **59**

A deoxygenated soln of 0.424 g (1.02 mmol) of **55** and 0.21 g (1.12 mmol) of **57** in 10 ml of THF was heated at 45° for 18 hr. The mixture was oxidized by pouring into a soln of 2 equivs of ferric chloride–DMF complex[23] in 50 ml of THF. After dilution with $H_2O$ and extraction with ether the organic phase was washed with $H_2O$ and brine and dried over $MgSO_4$. Crystallization from ether/hexane gave 0.288 g of **59**. Flash chromatography on silica gel with a 2:2:1 solvent mixture gave additional **59** for a total of 0.341 g (0.782 mmol, 76%, $R_f$ = 0.18, m.p. 212° dec): $^1$H-NMR (500 MHz), $\delta$ = 0.91 (s, 3H), 1.11 (s, 3H), 2.06–2.17 (m, 2H), 2.70–2.74 (m, 2H), 2.94 (d, 1H, 16.2 Hz), 2.88 (d, 1H, 16.2 Hz), 3.50 (d, 2H, 11.5 Hz), 3.64–3.67 (m, 5H), 4.00 (s, 3H), 4.67 (s, 1H, exchange with $D_2O$), 6.38 (s, 1H), 6.71 (s, 1H), 6.91 (d, 1H, 8.2 Hz), 7.04 (d, 1H, 7.5 Hz), 7.56 (t, 1H, 7.8 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 3550 w, 2978 m, 1760 s, 1610 m, 1485 s, 1290 m, 1110 m, 1070 m, 1040 m; mass spectrum, *m/e* (% rel. int.), 440 $M^+$ (0.6), 395 (11), 354 (56), 323 (9), 310 (22), 309 (100), 267 (34), 163 (13); calc for $C_{25}H_{28}O_7$ *m/e* 440.1835, meas. 440.1824.

2 - (2 - *Methoxy* - 6 - *methylene benzoic acid*) - 4 - *methoxy* - 7 - (2,2 - *dimethyl trimethylene ketal*) - 5,6,7,8 - *tetrahydro* - 1 - *naphthyl methoxymethyl ether* **60**

The phenolic functionality in **59** was protected by refluxing 1.114 g (2.53 mmol) with 4 ml of diisopropyl ethyl amine and 4.4 ml of chloromethyl methyl ether in 80 ml of $CH_2Cl_2$ for 3 hr. All of the volatiles were removed and the residue was extracted with ether, washed with cold 2% HCl and saturated brine and dried over $MgSO_4$. Crystallization from $CH_2Cl_2$/hexane gave 0.64 g of the methoxymethyl ether and another 0.476 g was obtained by flash chromatography on silica gel with a 2:2:1 solvent mixture followed by crystallization to give a total of 1.115 g (2.30 mmol, 91%, $R_f$ = 0.33) of the methoxymethyl ether of **9**, m.p. 163–164°.

The lactone function of the above intermediate was reduced (0.4763 g, 0.984 mmol) by refluxing with a mixture of 13 g of Zn powder, 1.8 ml of pyridine, and 0.29 g of $CuSO_4 \cdot 7H_2O$ in 30 ml of 10% KOH aq for 24 hr.[42] After the solids were removed by centrifugation, the basic layer was washed with ether and carefully acidified in an ice-bath with cold 10% HCl to pH = 2–3. After extraction with $CHCl_3$, 0.454 g (0.934 mmol, 95%) of the acid **10** was obtained as a foamy solid: $^1$H-NMR (500 MHz), $\delta$ = 0.97 (s, 3H), 1.03 (s, 3H), 2.08 (t, 2H, 6.6 Hz), 2.73 (t, 2H, 6.5 Hz), 3.11 (s, 2H), 3.54–3.60 (m, 7H), 3.66 (s, 3H), 3.87 (s, 3H), 4.12 (s, 2H), 4.84 (s, 2H), 6.48 (s, 1H), 6.72 (d, 1H, 7.6 Hz), 6.78 (d, 1H, 8.3 Hz), 7.21 (t, 1H, 7.9 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 2950 (s, broad), 1720 m, 1580 m, 1470 s, 1430 m, 1200 s, 1110 s; mass spectrum, *m/e* (% rel. int.), 486 $M^+$ (3), 468 (1), 458 (1), 442 (12), 424 (3), 368 (10); calc for $C_{27}H_{24}O_8$ *m/e* 486.2253, meas. 486.2274.

Compound **60a** (R = Et) was obtained from **55b** and the acetylene **51** following the above procedures in 56% overall yield for the four steps: $^1$H-NMR (500 MHz), $\delta$ = 0.97 (s, 3H), 1.04 (s, 3H), 1.31 (t, 3H, 6.9 Hz), 2.08 (t, 2H, 6.6 Hz), 2.76 (t, 2H, 6.6 Hz), 3.11 (s, 2H), 3.55 (s, 3H), 3.58 (dd, AB, 4H, 11.4 Hz), 3.87 (q, 2H, 6.9 Hz), 4.11 (s, 2H), 4.83 (s, 2H), 6.44 (s, 1H), 6.71 (d, 1H, 7.8 Hz), 6.79 (d, 1H, 8.3 Hz), 7.23 (t, 1H, 8.0 Hz).

*Cyclization of acid* **60** *to* 4,6-*dimethoxy*-9-(2,2-*dimethyl trimethylene ketal*)-11-(*methoxy methyloxy*)-7,8,9,10-*tetrahydronaphthalene*-5,12-*dione* **61**

A soln of 0.25 g (0.530 mmol) of **60** in 150 ml of $CH_2Cl_2$ was charged with 1.2 ml of 2,6-di-t-butyl pyridine (5.3 mmol) and cooled in an ice-bath. After addition of 0.112 ml (0.8 mmol) of freshly distilled trifluoroacetic anhydride the soln was warmed to room temp and stirred for 4 hr. All of the solvents were removed on a rotary evaporator and the evacuated flask filled with $O_2$. After addition of 50 ml of MeOH and 8 ml of a 40% soln of Triton B in MeOH the soln was stirred for 20 min before pouring into water.[24] The product was extracted with ether, washed with cold 1% HCl and dried over $MgSO_4$. The crude product was eluted through silica gel with a 2:2:1 solvent mixture to give 0.175 g (0.364 mmol, 69%, $R_f$ = 0.31) of **61** as yellow crystals (m.p. 67–70°): $^1$H-NMR (500 MHz), $\delta$ = 1.00 (s, 3H), 1.04 (s, 3H), 2.09 (t, 2H, 6.7 Hz), 3.00 (t, 2H, 6.7 Hz), 3.29 (s, 2H), 3.54 (d, 2H, 11.6 Hz), 3.62 (d, 2H, 11.4 Hz), 3.67 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 5.18 (s, 2H), 7.22 (d, 1H, 8.3 Hz), 7.59 (t, 1H, 8.1 Hz), 7.7 (d, 1H, 7.7 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 3030 w, 1670 s, 1580 m, 1200 s, 1100 m; mass spectrum, *m/e* (% rel. int.), 482 $M^+$ (3), 450 (0.5), 437 (0.5), 364 (1), 338 (2), 309 (2), 294 (2), 281 (2); calc for $C_{27}H_{30}O_8$ *m/e* 482.1940, meas. 482.1931.

The same cyclization/oxidation procedure was carried out on **60a** (R = Et) to give **62** in 57% yield: $^1$H-NMR (500 MHz), $\delta$ = 1.00 (s, 3H), 1.05 (s, 3H), 1.49 (t, 3H, 6.9 Hz), 2.09 (t, 2H, 6.7 Hz), 2.99 (t, 2H, 7.0 Hz), 3.29 (s, 2H), 3.55 (d, 2H, 11.4 Hz), 3.62 (d, 2H, 11.4 Hz), 3.67 (s, 3H), 3.99 (s, 3H), 4.09 (q, 2H, 6.9 Hz), 5.18 (s, 2H), 7.22 (d, 1H, 8.2 Hz), 7.59 (t, 1H, 8.0 Hz), 7.70 (d, 1H, 7.8 Hz); IR ($CHCl_3$), $\bar{\nu}$ = 2970 m, 1665 s, 1580 w, 1180 m, 970 m; mass spectrum, *m/e* (% rel. int.), 496 $M^+$ (40); calc for $C_{28}H_{32}O_8$ *m/e* 496.2097, meas. 496.2083.

4,6 - *Dimethoxy* - 11 - *hydroxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,9,12 - *trione* **64**

A soln of 0.175 g (0.364 mmol) of **61** in 86 ml of acetone was treated with 0.13 g (1.26 mmol) of conc $H_2SO_4$ and heated at 56° for 60 min. The reaction was quenched by pouring into sat $NaHCO_3$ aq, extracted into EtOAc and dried over $MgSO_4$. Removal of solvents left 0.132 g (0.364 mmol, 100%, $R_f$ = 0.17/2:2:1) of **64**, m.p. 220° (dec): $^1$H-NMR (500 MHz), $\delta$ = 2.61 (t, 2H, 7.0 Hz), 3.27 (t, 2H, 6.9 Hz), 3.65 (s, 2H), 3.93 (s, 3H), 4.04 (s, 3H), 7.34 (d, 1H, 8.5 Hz), 7.69 (t, 1H, 8.0 Hz), 7.91 (d, 1H, 7.8 Hz), 13.17 (s, 1H); IR ($CHCl_3$), $\bar{\nu}$ = 3050 m, 1712 s, 1665 s, 1630 m, 1580 s, 1355 s, 1272 m, 1200 s; mass spectrum, *m/e* (% rel. int.), 352 $M^+$ (35), 337 (20), 323 (2), 309 (5), 295 (15), 267 (3); calc for $C_{20}H_{16}O_6$ *m/e* 352.0947, meas. 352.0946.

The same conditions can be employed to hydrolyze **62** (R = Et) to **65**: $^1$H-NMR (500 MHz), $\delta$ = 1.51 (s, 3H), 2.60 (t, 2H, 6.9 Hz), 3.26 (t, 2H, 6.8 Hz), 3.63 (s, 2H), 4.03 (s, 3H), 4.05 (q, 2H, 7.1 Hz), 7.53 (d, 1H, 8.3 Hz), 7.67 (t, 1H, 8.0 Hz), 7.89 (d, 1H, 7.4 Hz), 13.16 (s, 1H); IR ($CHCl_3$), $\bar{\nu}$ = 3000 m, 1710 s, 1660 s, 1620 s, 1620 m, 1580 s; mass spectrum, *m/e* (% rel. int.), 366 $M^+$ (100), 348 (60), 309 (50), 295 (60).

4,6 - *Dimethoxy* - 9 - (2,2 - *dimethyl trimethylene ketal*) - 11 - *hydroxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,12 - *dione* **63**

To a soln of 21 mg (0.0436 mmol) of **61** in 12 ml of $CH_2Cl_2$ was added 4.1 $\mu$l (0.0553 mmol) of trifluoroacetic acid. The soln was stirred for 11 hr at room temp and poured into a sat

$NaHCO_3$ aq and extracted with EtOAc and dried over $MgSO_4$. The crude mixture was eluted through silica gel with a 2:2:1 solvent mixture to give 18.9 mg (0.0432 mmol, 99%, $R_f$ = 0.31) of **63**, m.p. = 74–77°: $^1$H-NMR (500 MHz), $\delta$ = 1.06 (s, 6H), 2.12 (t, 1H, 6.6 Hz), 2.99 (t, 2H, 6.5 Hz), 3.13 (s, 2H), 3.56 (d, 2H, 11.4 Hz), 3.63 (d, 2H, 11.3 Hz), 3.91 (s, 3H), 4.02 (s, 3H), 7.31 (d, 1H, 8.6 Hz), 7.66 (t, 1H, 8.0 Hz), 7.90 (d, 1H, 7.7 Hz), 13.32 (s, 1H); IR ($CHCl_3$), $\bar{\nu}$ = 3000 w, 2970 w, 1660 s, 1620 m, 1580 s, 1355 s, 1270 m, 1200 s, 1110 s; mass spectrum, *m/e* (% rel. int.), 438 $M^+$ (55), 423 (10), 365 (20), 352 (20), 337 (30), 324 (50), 310 (50), 295 (40); calc for $C_{25}H_{26}O_7$ *m/e* 438.1678, meas. 438.1666.

6,11 - *Dihydroxy* - 4 - *methoxy* - 7,8,9,10 - *tetrahydronaphthacene* - 5,9,12 - *trione* **52**

(a) *From quinone* **64**. A sample of **64** (25 mg, 0.071 mmol) was stirred rapidly in 32 ml of a 1:1 mixture of AcOH and 48% HBr at 53° for 2 hr. The mixture was diluted with water, extracted with EtOAc, washed several times with water and then sat $NaHCO_3$ aq, and dried over $MgSO_4$. The crude $^1$H-NMR indicated that the demethylation was selective and that none of trihydroxy compound was formed. The crude product was eluted through silica gel with $CH_2Cl_2$/EtOAc (3:1) to give 14 mg (0.0414 mmol, 61%) of **52**, m.p. 249–250° (dec): $^1$H-NMR (500 MHz), $\delta$ = 2.66 (t, 2H, 7.2 Hz), 3.26 (t, 2H, 7.0 Hz), 3.64 (s, 2H), 4.10 (s, 3H), 7.39 (d, 1H, 8.4 Hz), 7.78 (t, 1H, 8.2 Hz), 8.03 (d, 1H, 7.6 Hz), 13.30 (s, 1H), 13.81 (s, 3H); IR ($CHCl_3$), $\bar{\nu}$ = 1710 s, 1610 s, 1575 s, 1410 s, 1380 s, 1250 s, 1200 s, 1065 w, 995 m; mass spectrum, *m/e* (% rel. int.), 338 $M^+$ (100), 310 (40). The above spectral data are identical with those obtained from an authentic sample of **52** kindly provided by Professor Andrew S. Kende.

(b) *From quinone* **65**. A soln of 14.3 mg (0.0393 mmol) in 14 ml of a 1:1 mixture of 48% HBr and AcOH was heated at 55° for 2 hr. After the same workup as above, the crude mixture was eluted through silica gel with a 2:2:1 solvent mixture to give 7.2 mg (0.0213 mmol, 54%) of a compound that had the same $^1$H-NMR spectrum as described above for **52**.

(c) *From quinone* **63**.[25b] To a solution of 5 mg (0.0114 mmol) of **12** in 0.5 ml of acetone was added 14 mg (0.113 mmol) of freshly prepared AgO[43] in one portion. The resulting red soln was acidified with 0.1 ml of 6 N $HNO_3$. After 15 min the crude mixture was poured into a 1% $NaHSO_3$ aq and extracted with EtOAc. Removal of solvents left 4.6 mg (96%) of the crude dihydroxy compound, which without purification was dissolved in 3 ml of EtOAc and acetone (1:1). This was then treated with 3 ml of 10% $H_2SO_4$ and then heated at 45° for 10 hr after workup and purification as described above 3 mg (77%) of a compound that had spectral data identical to that described above for **52**. We have not been successful in obtaining good yields for the oxidation step on scales larger than 25 mg.

*Preparation of trimethylsilyl ethynyl(methoxy)methylene pentacarbonyl chromium* **82**

A soln of trimethylsilylethynyl lithium was prepared by dropwise addition of 15.0 mmol of a 1.54 M soln of n-BuLi in hexane to a soln of 15.0 mmol (1.47 g, 2.07 ml) of trimethylsilyl acetylene in 30 ml of ether at −78° under $N_2$. After 30 min the acetylide soln was warmed to 0° over a period of 20 min and then transferred via cannula to a slurry of 3.7 g of chromium hexacarbonyl (16.8 mmol) in 150 ml of ether at 0°. The mixture was warmed to room temp and 25 ml of ether at 0°. The mixture was warmed to room temp and 25 ml of THF was added which causes a reddening of the soln and the dissolution of the remaining chromium hexacarbonyl. The soln was cooled to 0° after 90 min and 2.57 g (22.5 mmol, 1.8 ml) of methyl fluorosulfonate was added dropwise. The reaction was quenched by stirring with sat $NaHCO_3$ aq for 20 min. The organic layer was washed with saturated brine and dried over $MgSO_4$. After removal of volatiles, the residue was extracted with hexane and the crude product was purified by flash chromatography on silica gel with hexane ($R_f$ = 0.39). The hexane solution was concentrated to 10 ml on a rotary evaporator and the remaining solvent was removed with high vacuum with cooling to below 0°. The carbene complex **82** was thus obtained in 77% yield (3.83 g, 11.5 mmol) as a dark red solid: m.p. 26–27°; $^1$H-NMR, $\delta$ = 0.31 (s, 9H), 4.35 (s, 3H); IR ($CHCl_3$), $\bar{\nu}$ = 2050 m, 1990 w, 1950 s; mass spectrum, *m/e* (% rel. int.), 332 $M^+$ (3), 276 (3), 248 (3), 220 (5), 192 (20), 149 (80); calc for $C_{12}H_{12}O_6CrSi$ *m/e* 331.98079, found 331.98094; Anal. $C_{12}H_{12}O_6CrSi$ (C, H).

*The cycloaddition/annulation of complex* **82** *with* 2,3-*dimethylbutadiene and* 1-*pentyne*

A soln of 0.349 g of **82** (1.05 mmol), 0.16 ml of 1-pentyne (1.58 mmol), and 10 ml of 2,3-dimethylbutadiene in 25 ml of THF was deoxygenated by the freeze-thaw method (−196°/0°, 3 cycles). The mixture was heated at 50° for 60 hr under argon. After the volatiles were removed by rotary evaporator the trimethylsilyl protected phenol complex **89** was crystallized from a hexane soln of the residue and obtained in 80.3% yield (0.383 g, 2 crops) as analytically pure yellow crystals, m.p. 121–123.5°: $^1$H-NMR (500 MHz), $\delta$ = 0.34 (s, 9H), 1.04 (t, 3H, 7.3 Hz), 1.63 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H), 2.28 (m, 1H), 2.59 (m, 1H), 3.05–3.30 (m, 4H), 3.70 (s, 3H), 4.93 (s, 1H); IR ($CHCl_3$), $\bar{\nu}$ = 1945, 1865, 1850 sh; mass spectrum, *m/e* (% rel. int.), 454 $M^+$ (20), 398 (15), 370 (100), 353 (10), 325 (30); Anal. $C_{22}H_{30}O_5CrSi$ (C, H, Cr).

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