# Two Regiocomplementary Approaches to Angular Furanocoumarins with Chromium Carbene Complexes: Synthesis of Sphondin, Thiosphondin, Heratomin, and Angelicin

**William D. Wulff,*[1a] J. Stuart McCallum,[1b] and Fen-Ann Kunng**

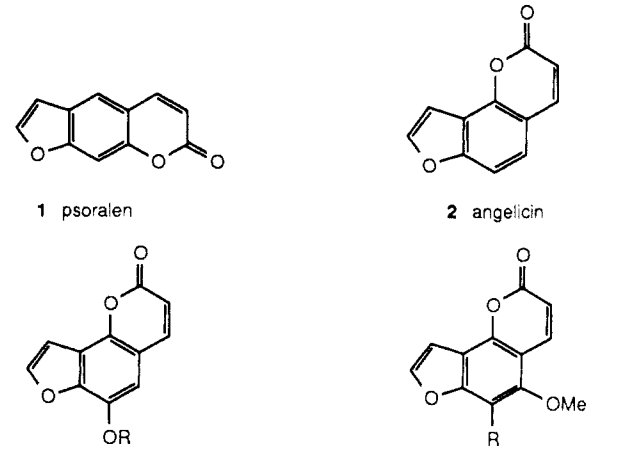
*Contribution from the Searle Chemistry Laboratory, Department of Chemistry, The University of Chicago, Chicago, Illinois 60637.* *Received August 12, 1986. Revised Manuscript Received June 9, 1988*

**Abstract:** Two regiocomplementary syntheses of the angular furanocoumarin sphondin are described utilizing the benzannulation reaction of furylcarbene complexes of chromium. The high regioselectivity of an intermolecular synthesis employing the reaction of [(2-furyl)(methoxy)methylene]pentacarbonylchromium (**8**) and methyl 4-pentynoate is thought to be controlled by the preferred conformation of an alkyne–carbene complex intermediate. By utilizing the same acetylene, heratomin and an unnatural derivative of sphondin, 6-methoxy-2-oxo-(2*H*)-thiofuro(2,3-*h*)benzopyran [thiosphondin (**35**)] were prepared from [(2-furyl)(3-methyl-2-butenoxy)carbene]pentacarbonylchromium (**37**) and [(2-thiofuryl)(methoxy)carbene]pentacarbonylchromium (**31**), respectively. An intramolecular synthesis of sphondin from [(3-furyl)[[2-(phenylthio-5-(trimethylsilyl)-4-pentynyl]oxy]-carbene]pentacarbonylchromium (**10e**) incorporates the acetylene with reversed regiochemistry due to the geometrical constraints of the intramolecular annulation. Control over the formation of the regiochemistry correct for the carbon skeleton of sphondin is possible due to the regioselectivity in the annulation of unsymmetrical aromatic substituents (3-furyl) on the carbene carbon. The intramolecular synthesis is thus related to the intermolecular synthesis by a double reversal in the regiochemistry. A convergent synthesis of sphondin and angelicin is described which has the phenol **72** produced from the intramolecular benzannulation of complex **10e** as a branch point and is differentiated by whether the phenol functionality is retained or reduced.

Psoralen (**1**) (Chart I) is the parent compound of a relatively large number of furanocoumarins for which the rings are linearly fused.[2a] Most prominent among the wide range of biological activities associated with this class of compounds is their ability to cross-link DNA via the formation of [2 + 2] cycloadducts and the use of psoralen phototherapy as the treatment of choice for the most severe forms of psoriasis. A new development on the clinical horizon is the treatment of cutaneous T-cell lymphoma, a stubborn cancer that resists conventional therapies, with 8-methoxypsoralen phototherapy.[2b] Angelicin is the parent compound of the much smaller and less available class of furanocoumarins that have an angular configuration and occur in a limited number of plant species relative to the linear class. Both classes of these compounds have evolved primarily as a defense mechanism against plant pathogens and herbivores, and the recent work by Berenbaum[3] suggests that the biosynthetic pathway leading to the angular attachment of the furan ring may have been a response to selective pressures exerted by specialized herbivores that had adapted to feeding on linear furanocoumarins. It has recently been found that sphondin is phototoxic to mosquito larvae at a level only slightly less than that observed for psoralen.[4]

The reaction of transition-metal carbene complexes with acetylenes is one of increasing synthetic importance particularly with regard to the benzannulation reaction which allows for the regioselective construction of a new benzene ring under neutral conditions and near ambient temperatures.[5] In 1978, Dötz demonstrated that aryl substituents on the carbene carbon other than benzene derivatives could be benzannulated in the reaction of chromium carbene complexes with acetylenes.[6] These were found to include the heteroaryl complexes of furan and thiophene. It was found that the benzofuran nucleus is generated from the reaction of furylcarbene complexes with simple acetylenes as exemplified by the reactions presented in Scheme I. The 2-furyl complex **8** gave the benzofuran chromium tricarbonyl complex **9** in 19% yield, and the 3-furyl complex **10a** with the same

**Chart I**




**3** heratomol R = H
**4** sphondin R = Me
**5** heratomin R = $CH_2CHC(CH_3)_2$
**6** isobergapten R = H
**7** pimpinellin R = OMe

(1) (a) Eli Lilly Young Scholar, 1986–1987. (b) Dow Chemical predoctoral fellow, 1982–1984.

(2) (a) For leading references to the chemistry of plant furanocourmarins and their medical, toxicological, and environmental significance, see: Ivie, G. W. *Rev. Latinoam. Quim.* **1987**, *18*, 1–6. (b) Edelson, R. L. *Sci. Am.* **1988**, *259*, 68–75.

(3) (a) Berenbaum, M.; Feeny, P. *Science (Washington, D.C.)* **1981**, *212*, 927. (b) Berenbaum, M. R. *Oecologia* **1981**, *49*, 236. (c) Berenbaum, M. *Ecology* **1981**, *65*, 1254. (d) Berenbaum, M. R.; Zangeri, A. R.; Nitao, J. K. *Phytochemistry* **1984**, *23*, 1809. (e) Berenbaum, M. B.; Zangeri, A.; Nitao, J. K. *Evolution (Lawrence, Kans.)* **1986**, *40*, 1215.

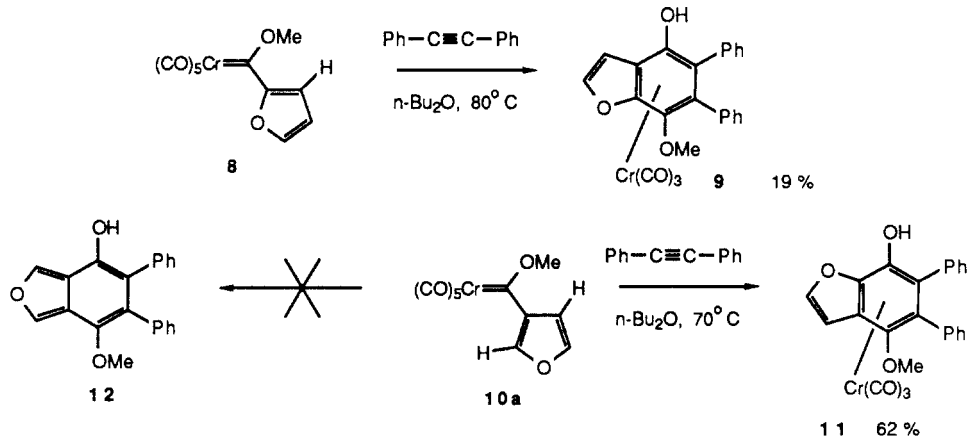
(4) Kagan, J.; Szczepanski, P.; Bindokas, V.; Wulff, W. D.; McCallum, J. S. *J. Chem. Ecol.* **1986**, *12*, 899.

(5) For recent reviews of the chemistry of Fischer carbene complexes, see: (a) Dötz, K. H.; Fischer, H.; Hofmann, P.; Kreissel, F. R.; Schubert, U.; Weiss, K. Transition *Metal Carbene Complexes*; Verlag Chemie: Deerfield Beach, FL, 1984. (b) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (c) Wulff, W. D.; Tang, P. C.; Chan, K. S.; McCallum, J. S.; Yang, D. C.; Gilbertson, S. R. *Tetrahedron* **1985**, *41*, 5813. (d) Wulff, W. D. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, CT, 1987; Vol. 1.

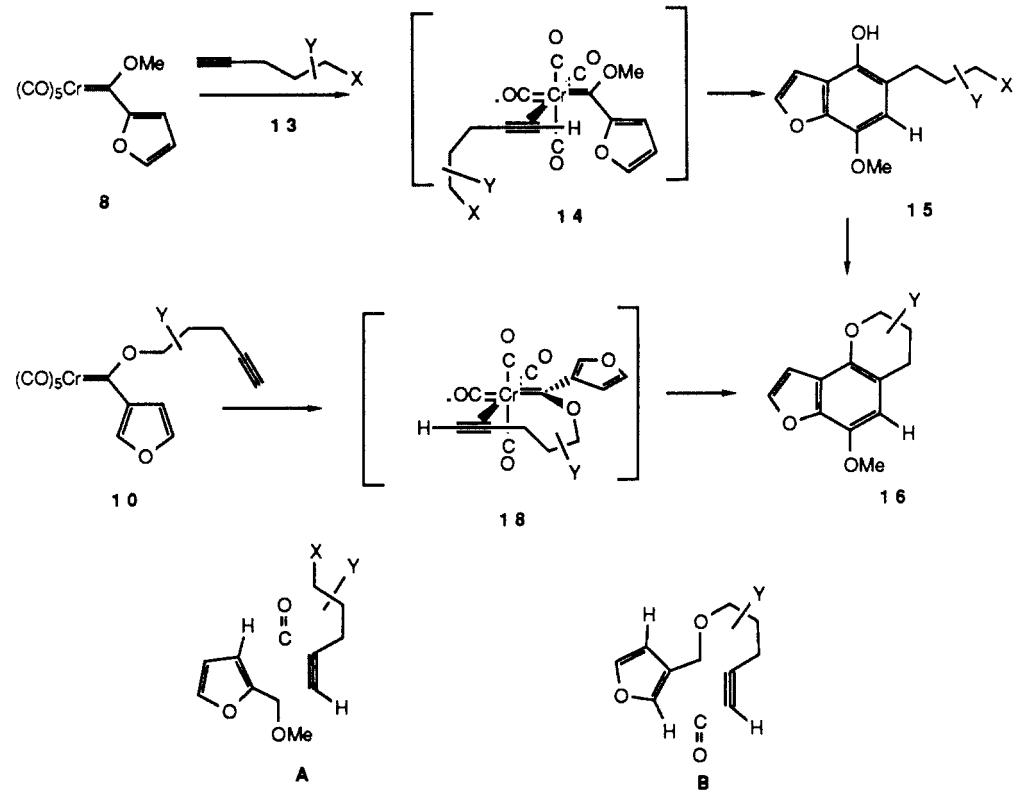
(6) Dötz, K. H.; Dietz, R. *Chem. Ber.* **1978**, *111*, 2517.

0002-7863/88/1510-7419$01.50/0 

**Scheme I**




**Scheme II**

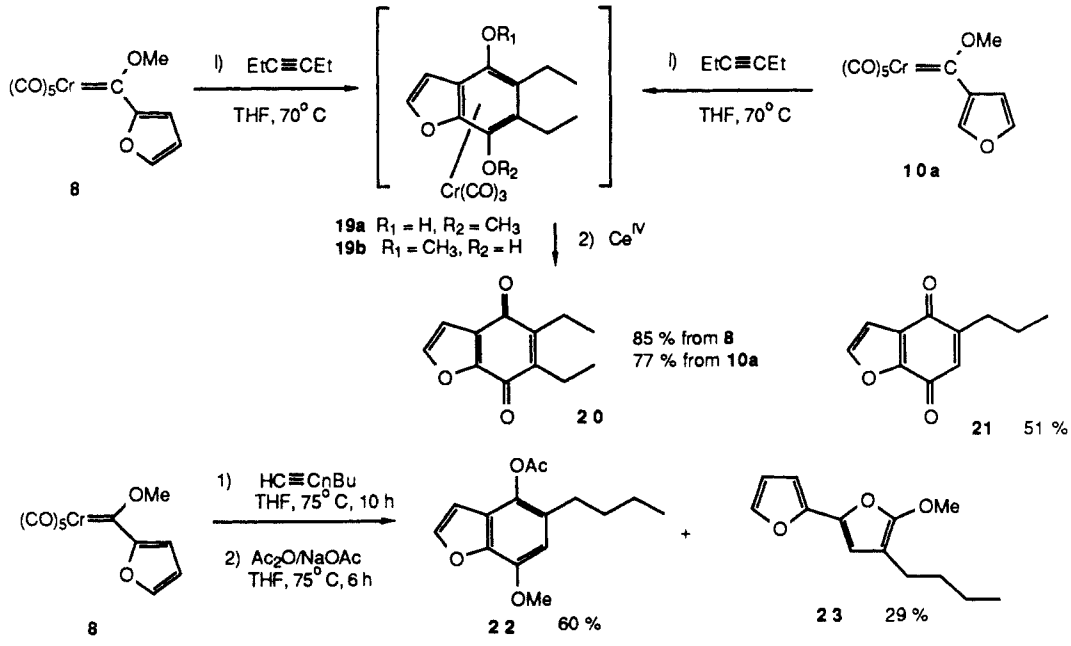



acetylene gave exclusively the benzofuran complex **11** in 62% yield. There are two possible modes of cyclization in the 3-furyl complex **10a**; however, the less stable isobenzofuran **12** was not observed in this reaction. At the time, there was some doubt as to the general synthetic utility of these reactions, particularly since the only other reaction of complex **8** was the reaction with 1-pentyne which gave a 23% yield of the benzannulated product. During the course of this work, Yamashita has utilized the benzannulation reactions of the 2-furyl complex **8** in the synthesis of khellin.[7] In this report we describe the synthesis of sphondin[8] via two regiocomplementary routes which serve to demonstrate the flexibility that is possible in employing the benzannulation reaction of carbene complexes with acetylenes in the controlled construction of an aromatic nucleus. A synthesis of angelicin[9] is also described that is convergent with the approach to sphondin. A synthesis of heratomin (**5**)[10] is described utilizing this methodology and the synthesis of an unnatural derivative of sphondin in which the furan ring is replaced by thiophene. This derivative of sphondin was found to display higher phototoxic activity toward mosquito larvae than sphondin.[11]

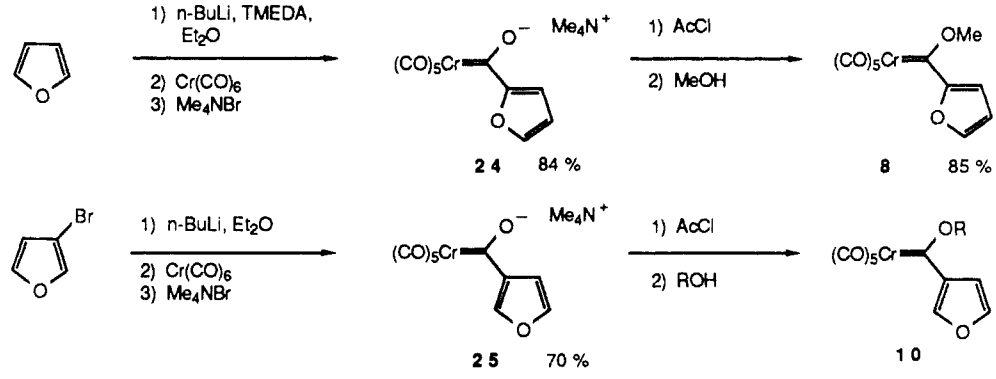
**Retrosynthetic Analysis.** A suitably functionalized intermediate of the type **16** in Scheme II would be a convenient precursor for the synthesis of the angular furanocoumarin sphondin. The two routes for the preparation of **16** outlined in Scheme II both involve the benzannulation reaction of chromium carbene complexes and acetylenes. The first approach involves the reaction of the 2-furylcarbene complex **8** and a functionalized acetylene of the type **13**. The regiochemistry indicated for the formation of the benzannulated product **15** is anticipated from what has been established for the intermolecular reactions of a number of other carbene complexes.[12] It is thought that the regiochemistry has

(7) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *107*, 5823.
(8) Shondin has been previously synthesized from naturally occuring courmarins: Seshadri, T. R.; Sood, M. S. *J. Indian Chem. Soc.* **1962**, *39*, 539.
(9) For a nonregioselective synthesis of angelicin, see: Reisch, J.; Mester, I. *Chem. Ber.* **1979**, *112*, 1491.
(10) Gupta, B. D.; Banerjee, S. K.; Handa, K. L.; Atal, C. K., *Phytochem.*, **1976**, *15*, 1319.
(11) Kagan, J.; Wulff, W. D.; Kunng, F. A., unpublished results.
(12) (a) Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471. (b) Dötz, K. H.; Muhlemeier, J.; Schubert, U.; Orama, O. *J. Organomet. Chem.* **1983**, *247*, 187. (c) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677.

**Scheme III**




**Scheme IV**




as its basis the preferred conformation of the complexed alkyne in the intermediate **14**. The pieces that would be assembled in this intermolecular approach to **16** are indicated in structure A. A one-step synthesis of **16** should be possible from the intramolecular benzannulation[13] of the carbene complex **10** in which two of the three rings are constructed in a single reaction. The geometrical constraints for this intramolecular annulation are such that the alkyne must be incorporated with a reversal in the regiochemistry as indicated in structure **18**. The correct regiochemistry for the tricyclic intermediate **16** should be obtainable by this intramolecular approach if the 3-furyl substituent is employed in the carbene complex **10** such that there is an overall double reversal of regiochemistry. The pieces that would be assembled in the intramolecular approach are indicated in structure B. The success of this approach requires that the annulation of the 3-furylcarbene complex **10** occurs exclusively at the 2-position of the furyl substituent and as indicated by the reaction in Scheme I it has already been established that this is the case.[6]

**Preliminary Studies.** Our initial investigations were with the reactions of **8** and **10a** with diethylacetylene and revealed (Scheme III) that the scope of the benzannulation reaction of the 2-furyl complex **8** is not as limited as initially indicated by the original report[6] (Scheme I). The difference may be due to the fact that we made no effort to isolate the relatively air-sensitive arene chromium tricarbonyl complexes of the type **19**, but rather oxidized the crude reaction mixtures and isolated only the organic products. The quinone **20** was obtained in good yields from the reaction of diethylacetylene with either the 2-furyl complex **8** or the 3-furyl complex **10a**. The reaction of the terminal acetylene 1-pentyne with complex **8** gave a higher yield (51%) of the quinone **21** upon oxidative workup of the crude reaction mixture with ceric ammonium nitrate (CAN) than was observed for the corresponding arene chromium tricarbonyl complex (23%). If the reaction with 1-hexyne is worked up with a nonoxidative procedure involving treatment with acetic anhydride,[14] then the acetylated phenol **22** can be isolated in 60% yield along with the furan **23** in 29% yield.[15] The furan **23** is acid and moderately air sensitive and cannot be stored for reasonable periods. It can normally only be separated from the crude reaction mixture without loss if the silica gel is pretreated with triethylamine and the chromatographic solvents are degassed.[16]

The furyl complexes **8** and **10** were prepared by the method of Connors,[17] involving the sequential treatment of the metal acylate with acetyl chloride and methanol (Scheme IV) which was found to be more useful than the direct methylation of an in situ generated lithium metal acylate according to the general Fischer synthesis for two reasons. First, if the ammonium metal acylate **24** is isolated, then the metalation of furan can be accomplished faster and in higher yields by a procedure that utilizes

(13) (a) Semmelhack, M. F.; Bozell, J. J. *Tetrahedron Lett.* **1982**, 2931. (b) Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. D.; Zask, A. *Tetrahedron* **1985**, *41*, 5803.

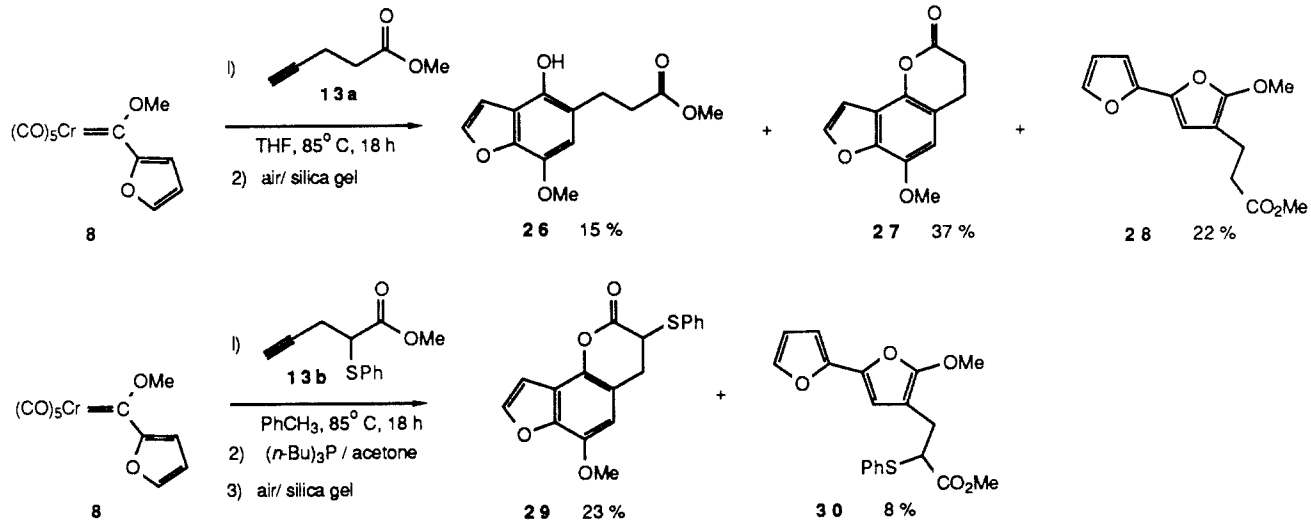
(14) Yamashita, A.; Scahill, T. A.; Toy, A. *Tetrahedron Lett.* **1985**, 2969.

(15) McCallum, J. S.; Kunng, F. A.; Gilbertson, S. R.; Wulff, W. D. *Organometallics*, in press.

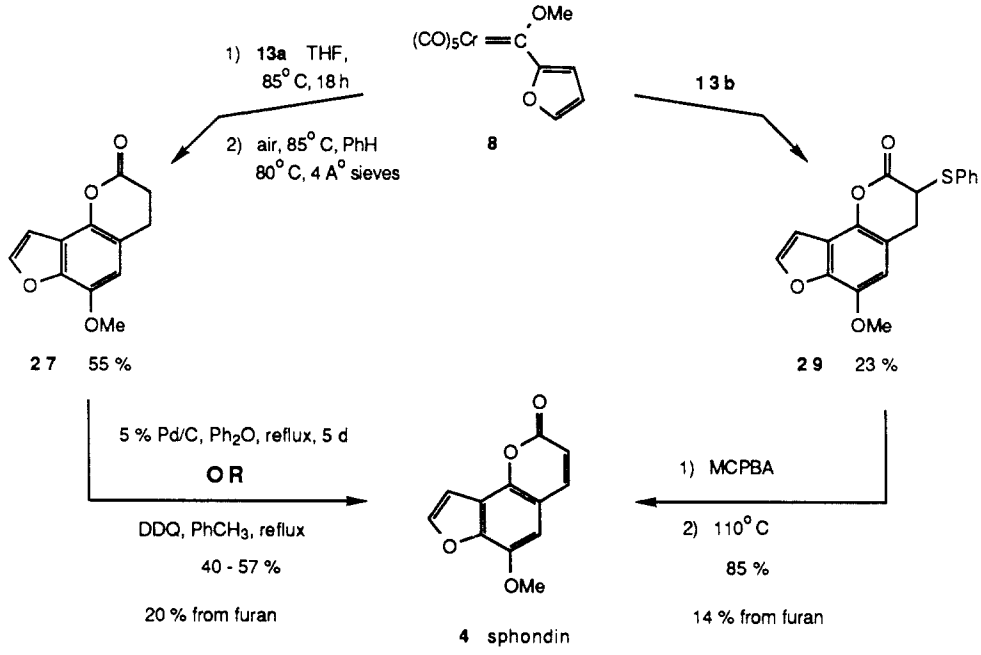
(16) Wulff, W. D.; Gilbertson, S. R.; Springer, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 520.

(17) (a) Connors, J. A.; Jones, E. M. *J. Chem. Soc. A* **1971**, 3368. (b) Connors, J. A.; Jones, E. M. *J. Chem. Soc. A* **1971**, 1974.

Scheme V




Scheme VI




TMEDA, the presence of which otherwise complicates the direct methylation of the lithium metal acylate.[15] Second, Connors' method can be extended to the preparation of a variety of complexes of the type **10** by simple substitution of the appropriate alcohol in the alcoholysis of the mixed anhydride intermediate.

**Intermolecular Approach; Synthesis of Sphondin, Thiosphondin, and Heratomin.** The most readily available functionalized acetylene that can be envisioned for the intermolecular approach to sphondin according to Scheme II is methyl 4-pentynoate (**13a**). The reaction of complex **8** with acetylene **13a** was carried out at 85 °C in THF for 18 h, opened to air, and chromatographed on silica gel in the presence of air. Three compounds eluted from the column which were identified as the desired benzannulated product **26** in 15% yield, the lactonized benzannulated product **27** in 37% yield, and the furan **28** in 22% yield (Scheme V). The combined yield of the benzannulated products was 52%, and this could not be optimized[15] by employing nonpolar solvents as was anticipated by our study of the effect of solvent on the benzannulation of aryl complexes.[18] The combined yield of the benzannulated products **26** and **27** was 52% in THF, 50% in methanol, and 45% in hexane, and the yield of the furan product was 22% in THF and 15% in hexane.[15] The reasons for the lack of a solvent effect on this reaction and the dependence of the product distribution (phenol versus furan) upon the nature of the alkyne has been discussed elsewhere.[15] Utilization of the more highly functionalized alkyne **13b**, whose synthesis is to be described below, could potentially provide for a more convergent synthesis; however, its reaction with complex **8** unfortunately gave the annulated product **29** in only 23% yield. In this reaction, ligand displacement was effected by treatment with tributylphosphine,[13] and the yield of the furan **30** was not optimized in this reaction since no precautions were taken to pretreat the silica gel with triethylamine or degas the chromatography solvents.[16] From the results described here and from the work of Dötz[6] and Yamashita[7] it can be observed that the benzannulated products from the reaction of the 2-furyl complex **8** with terminal acetylenes occur in 50–60% yields, whereas the yields with disubstituted acetylenes are in the 75–85% range.

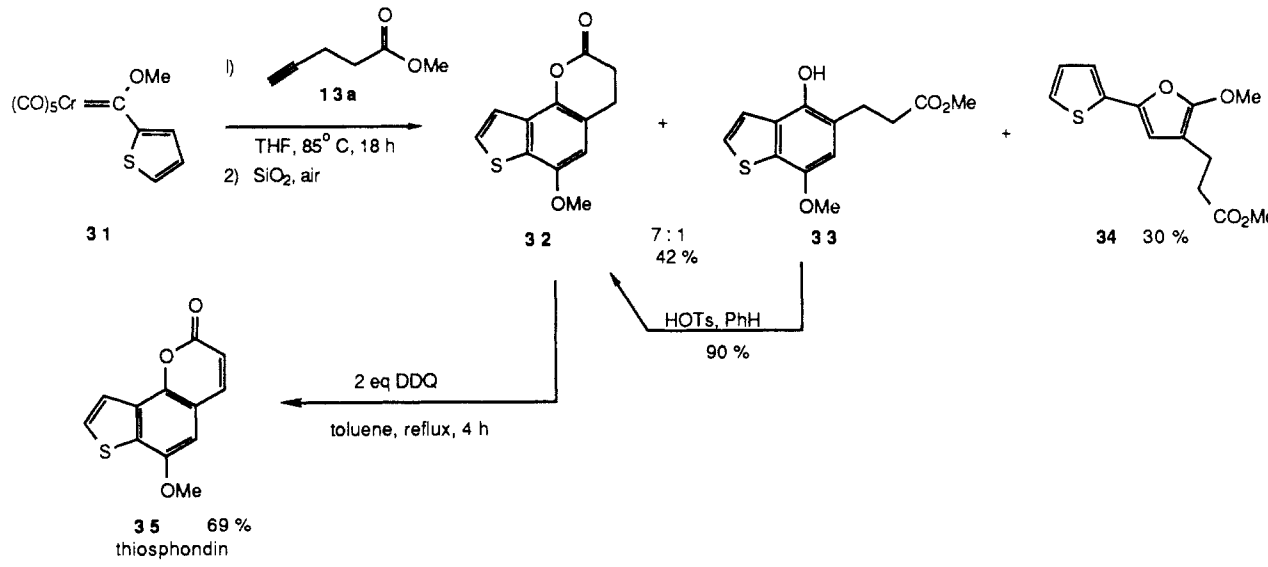
The two syntheses of sphondin via the intermolecular approach are presented in Scheme VI. The benzannulation of the 2-furyl

(18) Chan, K. S.; Peterson, G. A.; Brandvold, T. A.; Faron, K. L.; Challener, C. A.; Hyldahl, C.; Wulff, W. D. *J. Organomet. Chem.* **1987**, *334*, 9.

(19) Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 946.

(20) Shimomura, H.; Sashida, Y.; Nakata, H.; Kawasaki, J.; Ito, Y. *Phytochemistry* **1982**, *21*, 2213.

**Scheme VII**

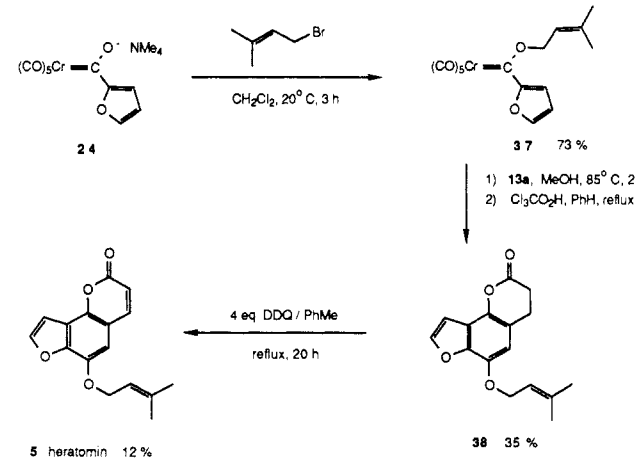



complex **8** and methyl 4-pentynoate (**13a**) was effected simply by heating the two in THF for 18 h at 85 °C. It was most convenient to treat the crude reaction mixture with acid prior to purification to complete the lactonization and provide the tricyclic intermediate **27** in 55% overall yield. All methods aimed at introducing the double bond into lactone **27** via functionalization of its enolate failed. Reaction of a solution of **27** in THF with LDA or $(TMS)_2NLi$ at temperatures ranging from −78 to −20 °C followed by quenching with (TMS)Cl, $D_2O$, or PhSSPh all resulted in the formation of complex, highly colored mixtures of polar materials. It is likely that ketene products are produced in these reactions.[21] An attempted iodination–dehydroiodination procedure involving heating a DMSO solution of **27** to 100 °C in the presence of iodine and sulfuric acid also failed.[22] Barton's ketone dehydrogenation procedure utilizing benzeneseleninic anhydride failed when applied to the lactone **27**.[23a] The reaction of lactone **27** with 1 equiv of benzeneseleninic anhydride in chlorobenzene at 120 °C in the presence of 1 equiv of pyridine required 40 h to go to completion and gave only a small amount of material (15%) that was tentatively identified as an aromatic electrophilic substitution product on the benzene ring.[23b]

It was possible to dehydrogenate the lactone **27** with palladium on carbon in refluxing diphenyl ether,[19] which gave a 52% yield of a material that was identical with an authentic sample of sphondin that was kindly provided by Professor Hiroko Shimomura.[20] This oxidation step could alternatively be effected with 2,3-dichloro-5,6-dicyanoquinone (DDQ) in 57% yield. This intermolecular approach allows for a very short synthesis of sphondin in two steps from methyl 4-pentynoate and four steps from furan. The intermolecular approach with the alkyne **13b** falls down at the benzannulation step, but due to the incorporation of the phenylthio group in the alkyne **13b**, the introduction of the double bond in the final step is now greatly facilitated. The overall yield for sphondin from furan is 20% with the alkyne **13a** and 14% with alkyne **13b**.

It was anticipated that **35**, an unnatural derivative of sphondin, which has the furyl oxygen replaced by sulfur, would display a greater phototoxicity than sphondin. This derivative should be readily accessible with the methodology developed for sphondin from the thiophene carbene complex **31**.[24] Previous studies revealed that the thiophene complex **31** would give the benz-

**Scheme VIII**



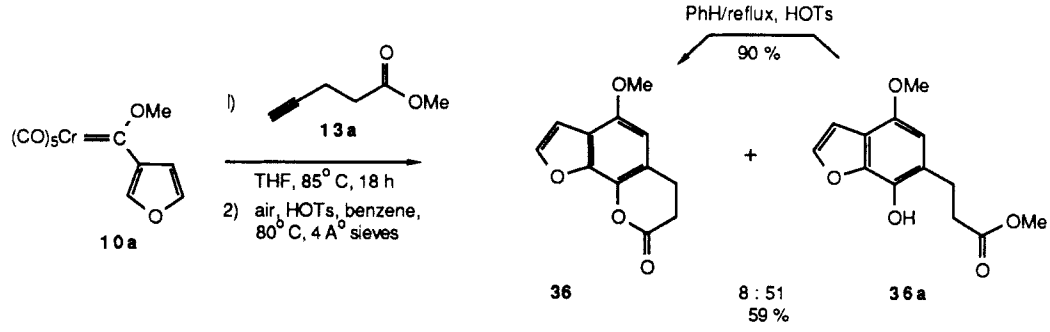

annulated product in 40% yield with 1-pentyne.[6] Similar results were found here with the terminal acetylene **13a** which gave a 42% combined yield of the phenol **33** and the lactone **32** in its reaction with complex **31** (Scheme VII). Furan products had not been reported from the reaction of complex **31**; however, in the present case of the reaction with **13a**, the furan **34** was isolated in 30% yield. The oxidation of the thiolactone **32** with DDQ was more successful than with lactone **27** and gave thiosphondin **35** in 69% yield. It was satisfying to find that initial tests with mosquito larvae revealed that thiosphondin displays significantly higher phototoxic activity than sphondin.[11]

The utilization of the same methodology for the preparation of heratomin requires the carbene complex **37** which can be readily accessed from the ammonium salt **24** and prenyl bromide in 73% yield (Scheme VIII). The alternative synthesis from **24** via Connors' method[17] involving sequential treatment with acetyl chloride and prenyl alcohol does work but in slightly lower yield (55%). The annulation/lactonization sequence with alkyne **13a** occurs in a slightly lower yield (35%) than the corresponding methoxycarbene complex **8**. The final dehydrogenation of the lactone **38** proved problematic. Attempted catalytic dehydrogenation failed, which may be due to the possibility of a Claisen rearrangement of the isoprenyl ether at the temperatures required. Treatment of lactone **38** with DDQ did give a small amount of a material (12%) that had a $^1H$ NMR spectrum identical with that reported for heratomin (**5**).[10] The dehydrogenation failed when DDQ was substituted by chloranil.

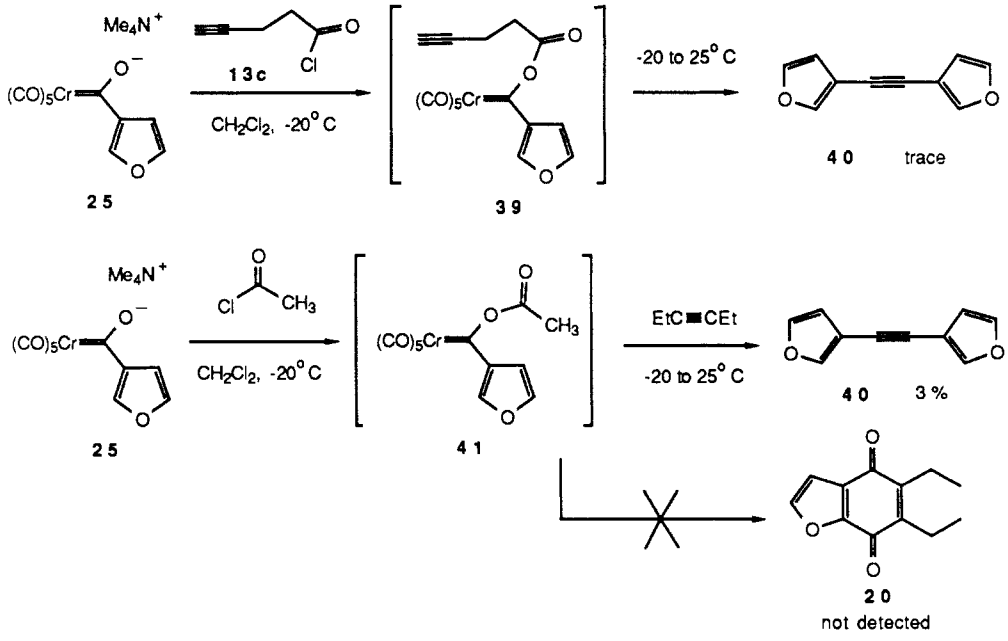
**Intramolecular Approach: Acyloxy versus Alkoxy Complexes.** As described above, it was found that the 2-furyl complex **8** undergoes the benzannulation reaction in 75–85% yields with

(21) Sullivan, D. F.; Woodburg, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038.
(22) Fatwa, W. *Chem. Ind.* **1979**, *5*, 315.
(23) (a) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1978**, 130. (b) Barton, D. H. R.; Hui, R. A. H. R.; Ley, A. V. *J. Chem. Soc., Perkin Trans 1*, **1982**, 2179.
(24) Fischer, E. O.; Held, W.; Kreissl, F. R.; frank, A.; Huttner, G. *Chem. Ber.* **1977**, *110*, 656.

**Scheme IX**



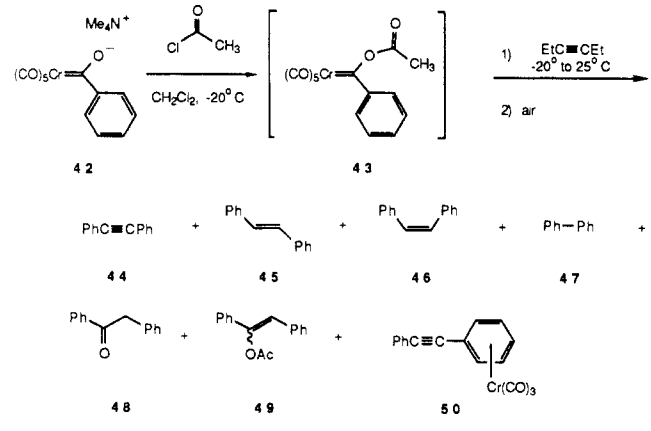

**Scheme X**




disubstituted acetylenes and in 50–60% yields with terminal acetylenes. The scope of the benzannulation reactions of the isomeric 3-furyl complex **10a** with acetylenes has not been as greatly explored. As indicated in Scheme III, the reaction of the 3-furyl complex **10a** with diethylacetylene gives approximately the same yield of the quinone **20** as does the 2-furyl complex **8**. The reactions of the 3-furyl complex **10a** with terminal acetylenes are unknown. For this reason we investigated the reaction of the 3-furyl complex **10a** with methyl 4-pentynoate (**13a**) (Scheme IX) and found that, after acidic workup to complete lactonization, the tricyclic dihydrofuranocoumarin **36** was obtained in the same yield as its regioisomer **27** from the reaction of the 2-furyl complex **8**. To our knowledge, there are no known coumarins with the ring system of **36**.

The general plan for the synthesis of sphondin via an intramolecular approach is outlined in Scheme II. The key intramolecular benzannulation of a carbene complex of the type **10** should lead to the angular tricyclic intermediate **16** in which the A and B rings of sphondin are constructed in a single transformation. The target of our first effort at an intramolecular synthesis was dihydrosphondin (**27**) since this would tie into the intermolecular synthesis (Scheme VI); however, as indicated in Scheme X, these efforts met with complete failure. When the tetramethyl ammonium salt **25** was treated with 4-pentynoyl chloride in methylene chloride at −20 °C, the solution became intensely purple, indicative of the formation of the (acyloxy)carbene complex **39**. Upon warming to room temperature this color dissipated and there was no evidence for the presence of the tricyclic lactone **27** in the crude reaction mixture. The only product that could be observed by TLC or GC was a trace amount of a material that was identified as the di-3-furylacetylene (**40**) on the basis of its $^1$H NMR and mass spectra. (Acyloxy)carbene complexes have been reported to be thermally and photochemically unstable,[17] and we suspect that the complex **39** decomposed before it underwent an intramolecular reaction with an acetylene. This suspicion was supported by the fact that the acetoxy complex **41**, whose preparation and reactions with alcohols have previously been described,[17] failed to react in an intermolecular reaction with diethylacetylene to produce the quinone **20** after an oxidative workup. Again, the only product that could be detected by TLC or GC was the di-3-furylacetylene (**40**).

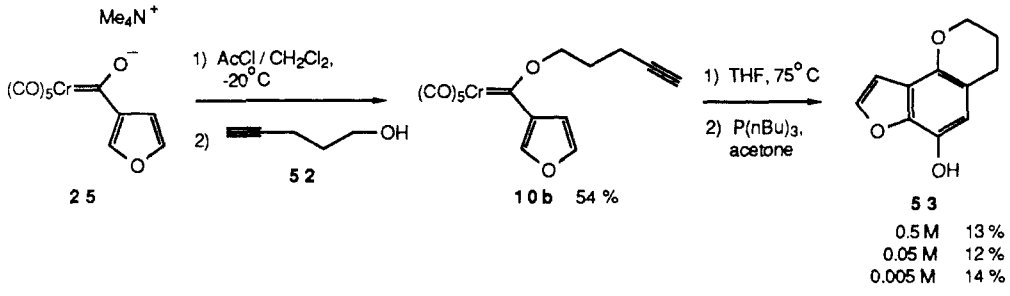
**Scheme XI**




The products from the treatment of the in situ generated acetoxy complex **43**[25] with diethylacetylene followed by warming to room

(25) Fischer, E. O.; Selmayr, T.; Kreissl, F. R. *Chem. Ber.* **1977**, *110*, 2947.

**Scheme XII**

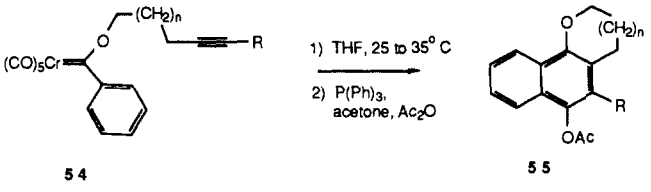



temperature were examined in detail. There has not been a previous report of the reaction of an acetoxy complex with an alkyne. Furthermore, although acetoxy complexes are known to be thermally unstable at room temperature,[17,25] there has been no report of the products of the thermal decomposition of acetoxycarbene complexes of the group 6 pentacarbonyls. The reaction in Scheme XI produced a large number of products of which a few have been identified as those shown. There was no predominant product, and although the yields of the products indicated in Scheme XI were not determined, it was estimated that none of these compounds was formed in greater than 5% yield. None of the products that could be identified were found to contain the elements of diethylacetylene, and in fact, the same product distribution is obtained if diethylacetylene is deleted from this reaction. Most of the products are carbene ligand coupling products which are known thermal decomposition products from alkoxycarbene complexes.[26] The isolation of diphenylacetylene is indicative of the formation of a carbyne complex, since it was established that symmetrical acetylenes are the thermal decomposition products from carbyne complexes of the group 6 carbonyls.[27] In this case, these products would suggest the intermediacy of *trans*-acetoxytetracarbonylphenylcarbynechromium.

It is now well established that (acyloxy)carbene complexes of the type **41** will undergo alcoholysis at the carbene carbon rather than at the carbonyl carbon to generate new alkoxycarbene complexes.[13,17] In an effort to demonstrate the feasibility of an intramolecular benzannulation of a 3-furylcarbene complex of the type **10** (Scheme II), the acetoxy complex **41** was generated in situ and reacted with 4-pentynol (**52**) to produce the stable carbene complex **10b** (Scheme XII). This complex was found to undergo an intramolecular reaction at 75 °C in THF; the crude reaction mixture was treated with tributylphosphine to displace chromium tricarbonyl groups from any of the possible products. After workup, the desired tricyclic intermediate **53** could only be isolated in 14% yield. This was by far the major product that was mobile on TLC, and the remainder of the mass balance was not accounted for. The low yield of **53** was the source of some concern for the success of the synthesis of sphondin via the intramolecular route, since the carbene complex **10b** represents the simplest member of the family of complexes of the type **10** (Scheme II) that is suitable for the intramolecular approach.

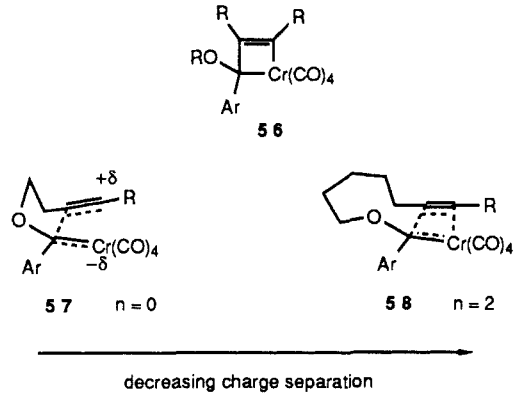
A solution to the low selectivity of the intramolecular reaction of the complex **10b** for the benzannulated product **53** arose from a consideration of the substituent effects of the intramolecular benzannulations of the phenyl complexes **54** that have been reported by Semmelhack and co-workers.[13] Two notable trends are evident for Semmelhack's data that are reproduced in Scheme XIII. First, disubstituted acetylenes give much higher yields of the benzannulated product than terminal acetylenes, and second, the yields of the benzannulated product from terminal acetylenes increase with ring size. It was suggested that the source of the low yields for some of these reactions was the result of competing intermolecular reactions which would correlate with the lower yields of terminal versus disubstituted acetylenes. We thought that the difference in the yields of the products **55** derived from

**Scheme XIII**




| n | R | Yield |
|---|---|---|
| 0 | H | 16 % |
| 0 | Me | 81 % |
| 1 | H | 18 % |
| 1 | Me | 62 % |
| 2 | H | 38 % |
| 2 | Me | 62 % |

**Chart II**



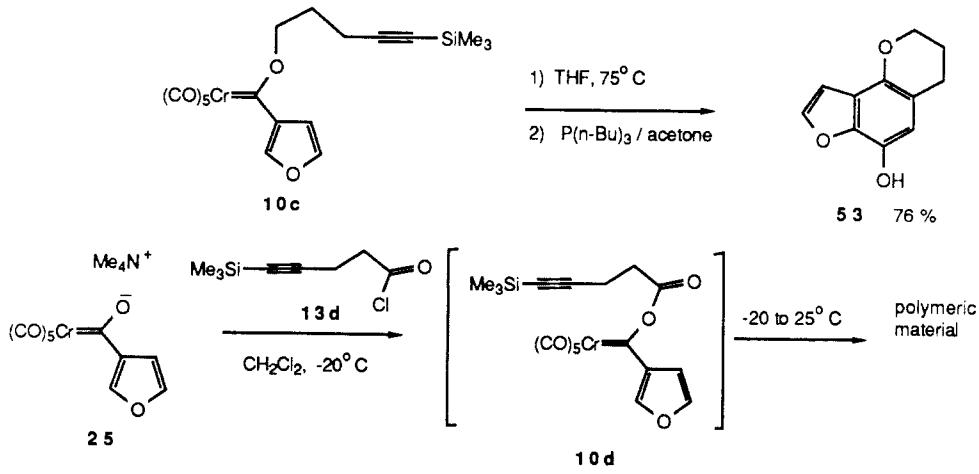

terminal and internal alkynes is not due to competing intermolecular reactions of **51** with itself, since we found that the yield of **54** from the intramolecular annulation of **10b** is concentration independent; the yield of **53** is 13% at 0.5 M, 12% at 0.05 M, and 14% at 0.005 M.

Another interpretation of these trends has to do with the intramolecular addition of the alkyne triple bond to the chromium–carbon bond in the step that generates the chromacyclobutene intermediate **56**. If the formation of the carbon–carbon bond and the chromium–carbon bond are nonsynchronous, then the expected charge separation in the transition state would be with partial positive charge on the carbon terminus of the alkyne as indicated in structure **57** in Chart II. This picture is consistent with the higher yields of product from disubstituted acetylenes, since the positive charge in **57** would be stabilized when R was methyl relative to when R was hydrogen. This picture is also consistent with the increase in yields of the benzannulated product for terminal acetylenes observed with increasing ring sizes, as the formation of the carbon–carbon bond and the chromium–carbon bond may be more synchronous as the size of the ring increases and the strain energy associated with the chromacyclobutene intermediate decreases.

Irrespective of the origins of the trends observed for the data from the reactions of the carbene complexes **54**, the trends themselves suggest that a solution to the intramolecular approach to sphondin is to employ an intramolecular annulation of a silylated terminal acetylene in a carbene complex of the type **10c**, since

(26) Fischer, E. O.; Heckl, B.; Dötz, K. H.; Müller, J.; Werner, H. *J. Organomet. Chem.* **1969**, *16*, P29.
(27) Fischer, E. O. *Adv. Organomet. Chem.* **1976**, *14*, 1.

Scheme XIV




a silyl substituent on the acetylene can serve as a synthon for hydrogen. This was in fact realized when the complex **10c** was heated to 75 °C in THF, and after workup up with tributylphosphine,[13] the tricyclic intermediate **53** was isolated in 76% yield (Scheme XIV), compared to 14% yield for the cyclization with complex **10b** containing a terminal acetylene. Obtaining the desilylated product was a bonus since a separate protonolysis step was not necessary. The desilylation most likely occurred during the ligand displacement step with tributylphosphine, since this step included treatment of the reaction mixture with $CCl_4$/MeOH to destroy the excess phosphine which occurs with the generation of hydrogen chloride. Given the influence of the trimethylsilyl group on this reaction, the original intramolecular approach to sphondin outlined in Scheme II was reinvestigated by utilizing the acid chloride **13d** to generate the acyloxy complex **10d** in situ; however, as before when this complex was warmed to room temperature, the disappearance of complex **10d** was not accompanied by the formation of any predominant product that was mobile on TLC or volatile with respect to GC analysis.

**Intramolecular Synthesis of Sphondin.** The intermolecular approach to sphondin that was previously described and the intramolecular approach for which success was finally achieved are presented together in Scheme XV. The phenylthio group in the acetylenic alcohol **13f** was introduced to allow for eventual introduction of a double bond in the pyran ring of the benzannulated product **60**. The intramolecular benzannulation of the 3-furylcarbene complex **10e** was effected by simply heating to 85 °C, and it was found most convenient to directly convert the crude product to the tricyclic intermediate **60** by methylation of the free phenol, protodesilylation, and oxidative removal of any remaining chromium tricarbonyl group coordinated to the benzene ring. This transformation has been carried out on scales ranging from 0.2 to 20 g with overall yields of 56–94%. Oxidation and sulfoxide elimination gave exclusively the pyran **61**, which was oxidized to sphondin with Collin's reagent in 52% yield. This final oxidation could also be accomplished with PDC in 50% yield in the presence of molecular sieves and acetic acid;[28] however, oxidation of **61** only with PDC or PCC at ambient or elevated temperatures produced low yields of sphondin (1–15%) after reaction times of several days.[29] Attempted oxidation of **61** with chromium carbonyl and *tert*-butyl hydroperoxide failed.[30]

The intermolecular route to sphondin was accomplished in four steps from chromium hexacarbonyl in 20% overall yield, and the intramolecular route was accomplished in eight steps from chromium hexacarbonyl in 17–24% overall yield. These two regiocomplementary routes to the synthesis of sphondin are made possible by the high degree of control in the regioselectivity of the intermolecular reaction of carbene complexes with terminal alkynes and in the intramolecular synthesis due to the high degree of control of the regioselectivity in the annulation reactions of carbene complexes bearing unsymmetrical aromatic substituents.[6,12c]

Attempts to introduce the carbonyl oxygen in **61** via the coupling of an electrophilic oxygen source with the proper conjugate base of **61** failed. As indicated by a quenching experiment with deuteriated water (Scheme XVI) the most kinetically acidic proton was found not to be the allylic proton, but rather the 2-furyl proton.

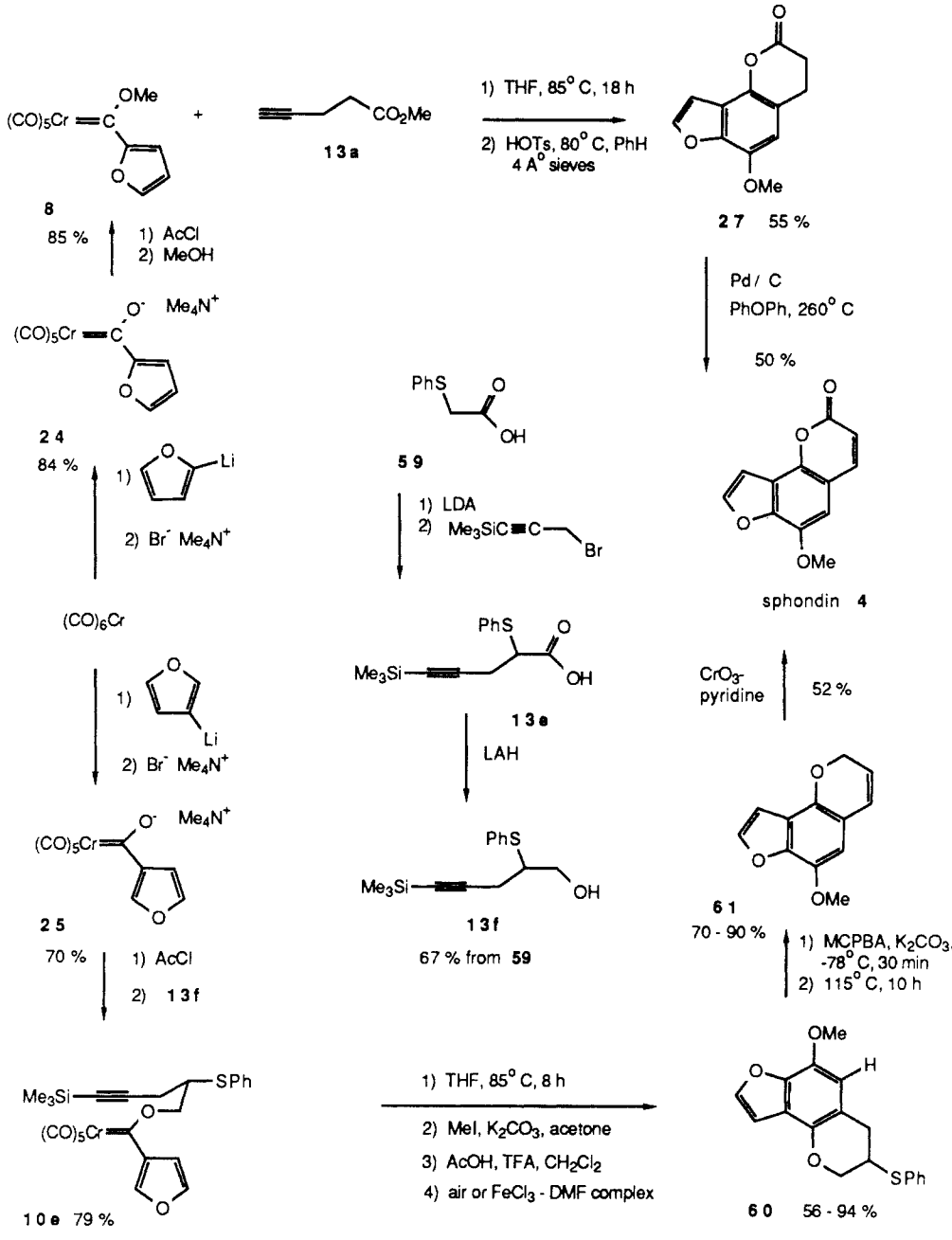
An interesting observation was made in the unsuccessful efforts at optimizing the allyl oxidation of **61** beyond that provided by pyridinium chlorochromate. The reaction of **61** with benzeneseleninic anhydride[23] produced the seleninic ester **63** (Scheme XVII). PCC oxidation of this intermediate provided a 32% yield of a compound that is isomeric with sphondin and was identified as the chromanone **64** on the basis of its $^1H$ and $^{13}C$ NMR spectra. It may prove interesting to consider whether or not this methodology can be more generally applied to the selective oxidation of benzopyrans to either coumarins or chromanones.

**Modification of the Phenol Functionality: A Synthesis of Angelicin Convergent with That of Sphondin.** The phenol carbon of the benzannulated product is derived from a carbon monoxide ligand of the carbene complex. The utilization of the benzannulation reaction of chromium carbene complexes and alkynes has been limited to the synthesis of phenols and quinones in which the carbon monoxide oxygen is retained in the final synthetic target. As outlined in Scheme XVIII, the benzannulation reaction would have much greater synthetic flexibility if the phenol functionality (or derivatives thereof) could be either reduced or utilized in the formation of carbon–carbon bonds.

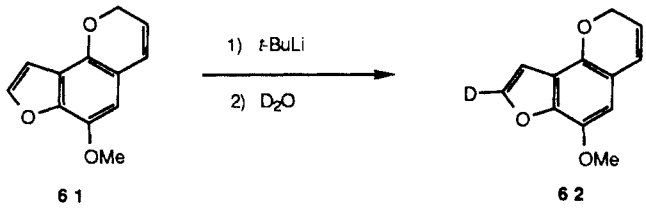
The synthesis of angelicin outlined in Scheme XIX includes the first example of the utilization of such a strategy in a total synthesis.[31] The intramolecular benzannulation of the carbene complex **10e** (Scheme XV) thus provides the basis for a convergent synthesis of either sphondin or angelicin, which converges in the retroanalysis at the phenol **72** from an intermediate in which the oxygen is retained as the methyl ether in **60** or is reduced via its triflate **73** by the methodology we had developed for this purpose.[31,32] The key step in the synthesis of angelicin was the palladium-catalyzed reduction of the triflate **73** with formic acid which was found to proceed smoothly to provide the reduced benzofuran **74** in 89% yield.[31] The final transformations involve the oxidation and sulfoxide elimination to give the furanobenzopyran **75** in 80% yield and subsequent oxidation with pyridinium dichromate to provide synthetic angelicin which was found to have $^1H$ NMR, $^{13}C$ NMR, mass and infrared spectra, as well as a melting point (mixed) identical with those of a sample

(28) Czerneck, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
(29) Bonadies, F.; DiFabio, R.; Bonini, C. *J. Org. Chem.* **1984**, *49*, 1647.
(30) Pearson, A. J.; Chen, Y. S.; Han, G. R.; Hsu, S. Y.; Ray, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 267.
(31) Peterson, G. A.; Kunng, F. A.; McCallum, J. S.; Wulff, W. D. *Tetrahedron Lett.* **1987**, *28*, 1381.
(32) See also: Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron. Lett.* **1986**, *27*, 5541.

**Scheme XV**




**Scheme XVI**

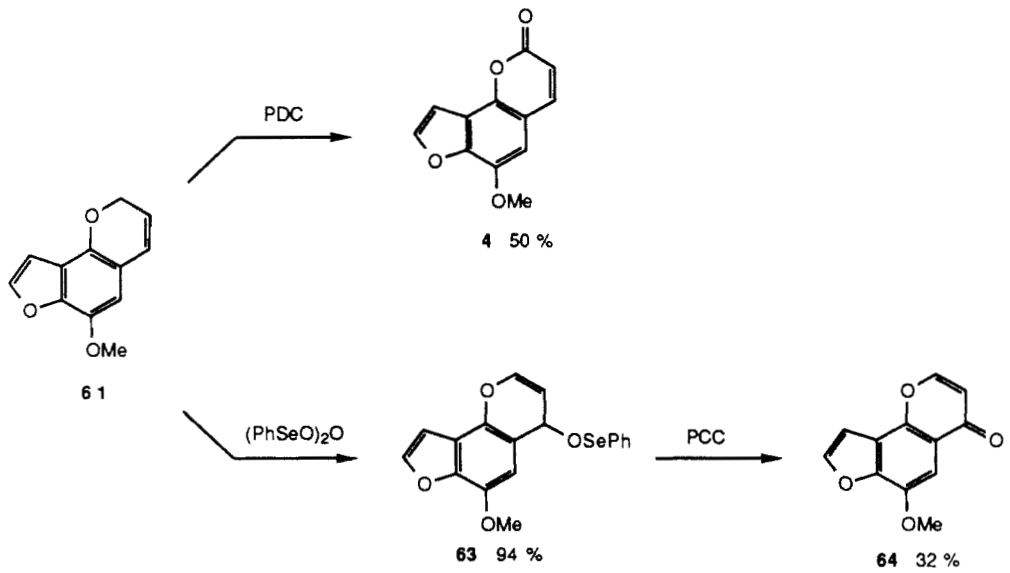



of the natural material that was kindly provided by Professor May Berenbaum.[3]

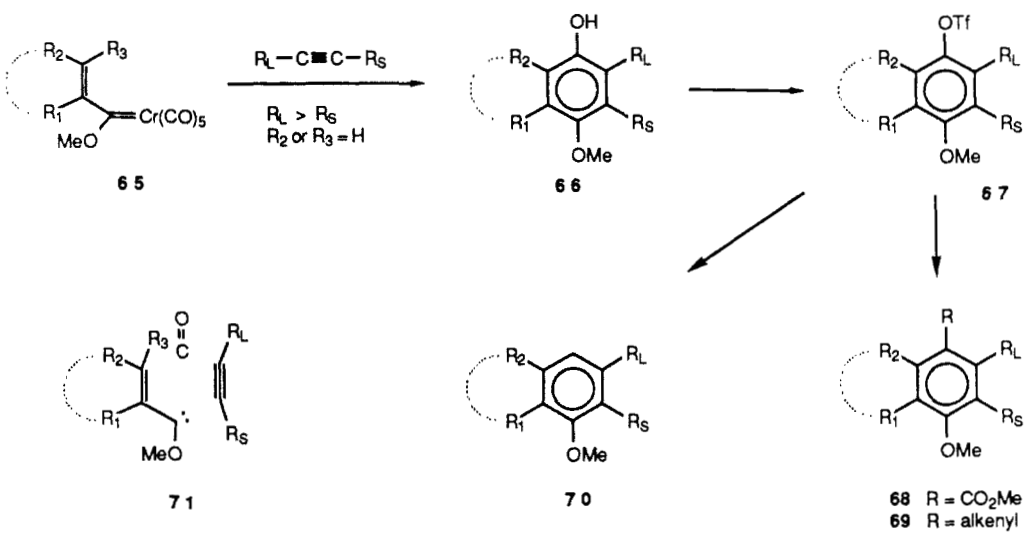
## Conclusion

The success of the two regiocomplementary approaches to the synthesis of sphondin outlined in Scheme II is a tribute to the power and flexibility of the benzannulation reaction of chromium carbene complexes and acetylenes for the synthesis of aromatic compounds. In the synthesis of sphondin this is illustrated in the reactions of 2-furyl- and 3-furylcarbene complexes **8** and **10e** and, in the synthesis of thiosphondin, in the reactions of the thiophene complex **31**. The two regiocomplementary syntheses of sphondin highlight the control in regiochemistry that is possible with the benzannulation reaction. The source of this control stems from the fact that the preferred direction of alkyne incorporation observed for the intermolecular benzannulation is not geometrically possible if the alkyne is tethered to the carbene carbon with the result that the intramolecular reaction is constrained to have the opposite regiochemical outcome. Also described are the first attempts at the benzannulation of (acyloxy)carbene complexes which were found to fail for reasons that appear to be due to the preferential and unselective formation of products derived from coupling of carbene ligands. The reversal in regiochemistry upon going from inter- to intramolecular annulation can be reversed again such that both modes can be used for the synthesis of the same molecule (sphondin). This is made possible since control over the regiochemistry can also be exercised in the direction of cyclization to unsymmetrical aryl substituents. The intramolecular synthesis of sphondin also required a solution to the failure of terminal alkynes in the intramolecular annulation which was resolved with the use of a trimethylsilyl as a synthon for hydrogen. The angular furanocoumarins were also exploited in the first synthetic application where a benzannulated product was chem-

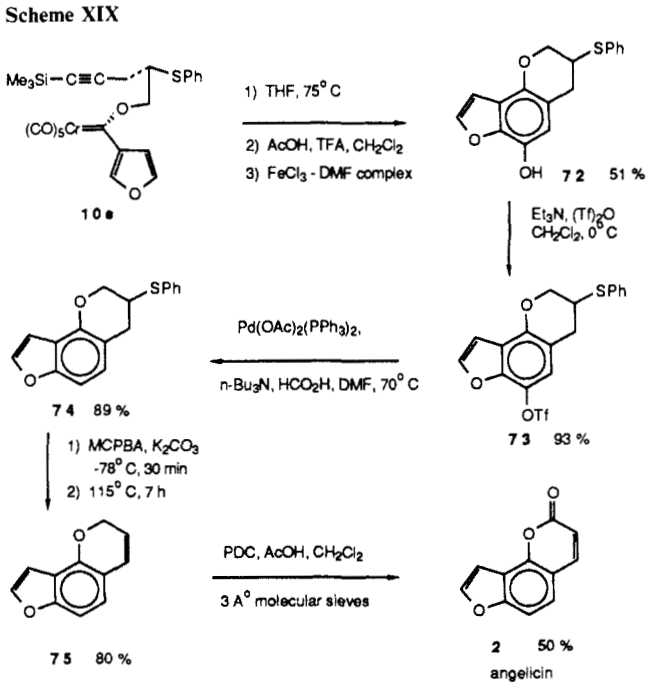
**Scheme XVII**




**Scheme XVIII**




**Scheme XIX**




ically modified at its phenol functionality and was demonstrated in a synthesis of angelicin that is convergent with the intramolecular route to sphondin.

## Experimental Section

All reagents were obtained from commercial suppliers and used as received unless otherwise noted. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl immediately before use. Methylene chloride was distilled over phosphorus pentoxide, and DMF was distilled over barium oxide. Preparative silica gel chromatography was conducted according to the method of Still[33] unless otherwise noted. Preparative radial TLC refers to the use of the Chromatotron device (Harrison Research) equipped with plates coated with Merck silica gel PF. Analytical TLC was performed on Machery-Nagel 0.25-mm silica gel plates.

$^1$H NMR spectra were obtained with one of the following instruments: Bruker HS-270 operating at 270 MHz, Nicolet NTC 200 (wide bore) operating at 200 MHz, or the University of Chicago DS-1000 operating at 500 MHz. The $^1$H NMR spectra were acquired or zero-filled so as to provide a spectrum with a digital resolution of 0.15 Hz or better. $^{13}$C NMR spectra were obtained with the NTC 200 system operating at 50 MHz or with a Varian XL-400 operating at 100 MHz and are referenced to tetramethylsilane. The number of protons directly attached to carbon atoms was determined by use of gated decoupling, off-resonance single-frequency decoupling or Dept[25] techniques. Infrared (IR) spectra were recorded with either a Perkin-Elmer Model 283 double-beam instrument or a Nicolet SX-20 FTIR. Low-resolution mass spectra were determined

(33) Still, W. C.; Kahn, M.; Meta, A. *J. Org. Chem.* **1978**, *43*, 2923.

at 70 eV with either a Finnigan 1015 quadrupole instrument or a VG Analytical 70-250 spectrometer, or at the University of Illinois, Urbana, by J. Carter Cook Jr., with a VG 7070 spectrometer. High-resolution spectra were determined with an AEI MS-9, the VG 70-250 instrument, or at the University of Illinois. Microanalysis were performed by Galbraith, Knoxville, TN, or by Micro-Tech, Skokie, IL.

**Tetramethylammonium [(3-Furyl)(oxido)carbene]pentacarbonylchromium (25).** This metal acylate was prepared according to the procedure utilized for the 2-furyl derivative.[15,17] To a solution of 1.8 mL of 3-bromofuran (20 mmol) in 30 mL of THF at −78 °C was added 12.5 mL of 1.6 M *n*-butyllithium/hexane (20 mmol). This solution was stirred at −78 °C for 10 min and then added to 4.4 g of $Cr(CO)_6$ suspended in 50 mL of THF with vigorous stirring over a period of 5 min. The mixture was stirred for 10 min and then the solvent was removed. The colored components of the residue were extracted into a minimum amount of water which had been deoxygenated by sparging with argon. This solution was filtered through Celite and treated with a deoxygenated, saturated aqueous solution of 9.3 g of $NMe_4Br$ (60 mmol) to cause immediate formation of a yellow-brown precipitate. The flask was cooled to 0 °C after sparging with argon and allowed to stand for 1 h. The yellow solid was collected by vacuum filtration and dried under high vacuum for 24 h. This material was dissolved in $CH_2Cl_2$ and filtered through Celite, and crystallization was induced by the addition of heptane followed by concentration and cooling. A 70% yield of **25** was obtained as orange prisms in three crops. Crystallization solutions were sparged with argon before standing, and the mother liquors were filtered through Celite before the next crystallization. **25**: $^1$H NMR (acetone-$d_6$) $\delta$ 3.49 (s, 12 H, $N(CH_3)_4$), 6.38 (d, 1 H, $J$ = 2 Hz, 3-C*H*), 7.31 (t, 1 H, $J$ = 2 Hz, 5-C*H*), 7.92 (br s, 1 H, 2-C*H*); orange prisms from $CH_2Cl_2$/heptane; mp 96–98 °C dec.

**Reaction of [(2-Furyl)(methoxy)carbene]pentacarbonylchromium (8) with 3-Hexyne.** A solution of 250 mg of **8**[15,17] (0.83 mmol) and 0.15 mL of 3-hexyne (1.3 mmol) in 5 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and heated to 75 °C under argon for 18 h in a one-necked flask that was fitted with a threaded vacuum stopcock.[18] The reaction mixture was poured into 11 mL of 0.5 M CAN in 0.1 N $HNO_3$ (5.8 mmol CAN) and stirred open to the air for 30 min. The mixture was extracted with diethyl ether, washed twice with water, and dried over $Na_2SO_4$. Column chromatography (silica gel, 2:10 EtOAc/hexane) provided an 85% yield (0.143 g) of quinone **20** which was crystallized from MeOH/$H_2O$ as yellow needles, mp 64–65 °C. The following spectral data were collected for **20**: $^1$H NMR ($CDCl_3$) $\delta$ 1.12 (m, 6 H, $CH_2CH_3$), 2.58 (m, 4 H, $CH_2CH_3$), 6.80 (d, 1 H, $J$ = 1.9 Hz, 3-C*H*), 7.62 (d, 1 H, $J$ = 1.9 Hz, 2-C*H*); IR ($CHCl_3$) 3005 w, 1655 s, 1570 m, 1480 m, 1360 m, 1170 m, 1060 w, 855 m, 660 w cm$^{-1}$. Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.56; H, 6.15. For an account of the outcome of this reaction without an oxidative workup see ref 15.

**Reaction of [(3-Furyl)(methoxy)carbene]pentacarbonylchromium (10a)[6] with 3-Hexyne.** This reaction was carried out in a manner identical with that employed for the reaction of complex **8** with 3-hexyne. A 77% yield of the quinone **20** was obtained. The proton NMR spectra and $R_f$ value of the product from this reaction were identical with that for the quinone **20** produced from the reaction of complex **8**.

**Reaction of [(2-Furyl)(methoxy)carbene]pentacarbonylchromium (8) with 1-Pentyne.** This reaction was carried out in a manner identical with the reactions of **8** with 3-hexyne. Quinone **21** was obtained in 51% yield and crystallized from MeOH/$H_2O$ as yellow plates, mp 56–57 °C. This material was somewhat unstable even in the crystalline form, and darkened to brown upon prolonged exposure to air. 4,7-Dioxo-5-propyl-(4,7*H*)-benzo[*b*]furan (**21**): $^1$H NMR ($CDCl_3$) $\delta$ 0.99 (t, 3 H, $J$ = 7.7 Hz, $CH_2CH_3$), 1.58 (sext, 2 H, $J$ = 7.7 Hz, $CH_2CH_2CH_3$), 2.47 (dt, 2 H, $J$ = 7.8, 1.4 Hz, $CH_2CH_2CH_3$), 6.49 (t, 1 H, $J$ = 1.4 Hz, 6-C*H*), 6.84 (d, 1 H, $J$ = 2 Hz, 3-C*H*), 7.66 (d, 1 H, $J$ = 2 Hz, 2-C*H*); IR ($CHCl_3$) 1670 s, 1570 m, 1470 m, 1365 m, 1160 m, 930 w, 890 w, 880 w cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 190 M$^+$ (100), 175 (30), 162 (31), 147 (72), 134 (48), 105 (28), 94 (51), 66 (72). For an account of the outcome of this reaction without an oxidative workup see ref 6.

**Reaction of [(2-Furyl)(methoxy)carbene]pentacarbonylchromium (8) with Methyl 4-Pentynoate (13a).** A solution of 277 mg of complex **8**[15,17] (0.75 mmol) and 0.225 mL of methyl 4-pentynoate (**13a**; 1.60 mmol) in 6 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and then heated to 85 °C for 18 h under argon. The THF solvent was removed and replaced with 50 mL of diethyl ether, and the mixture was stirred in air for 1.5 h and filtered through Celite. Solvent removal afforded 241 mg of a light yellow oil. This material was chromatographed by preparative radial TLC (silica gel, 3:10 EtOAc/hexane) to provide phenol **26** (15%), its corresponding lactone **27** (37%), and furan **28** (21.5%). The $^1$H NMR spectrum of the crude reaction mixture showed essentially the same ratio of products **26**, **27**, and **28** (integration of aromatic protons) as that isolated. Furan **28** was markedly unstable, and if not kept under argon at −20 °C, it decomposed in a matter of days.

The crude reaction mixture could alternatively be dissolved in benzene and heated to reflux in the presence of a catalytic amount (0.05 equiv) of *p*-toluenesulfonic acid to effect complete conversion to the lactone **27** if the condensate was passed over 4-Å molecular sieves to remove the generated methanol. Under these conditions, the lactone **27** was isolated in 55% yield from complex **8** after chromatography (silica gel, 3:10 EtOAc/hexane). The catalysts Nafion-H, triethylamine, and Sephadex 50-H were slightly less effective than *p*-toluenesulfonic acid in promoting the conversion of **26** to **27**; the yields were 85–90% for these catalysts versus 95% for *p*-toluenesulfonic acid. The following data were collected for phenol **26** and lactone **27**. The data for furan **28** will be reported separately.[15] Methyl 4-hydroxy-7-methoxy-5-benzo[*b*]pyranpropionate (**26**): $^1$H NMR ($CDCl_3$) $\delta$ 2.75 (t, 2 H, $J$ = 6.0 Hz, $CH_2CO_2CH_3$) 2.94 (m, 2 H, $CH_2CH_2CO_2CH_3$), 3.68 (s, 3 H, $CO_2CH_2$), 3.95 (s, 3 H, $ArOCH_3$), 6.48 (s, 1 H, 6-C*H*), 6.87 (d, 1 H, $J$ = 2.2 Hz, 3-C*H*), 7.51 (d, 1 H, $J$ = 2.2 Hz, 2-C*H*), 7.53 (s, 1 H, ArO*H*); $^{13}$C NMR ($CDCl_3$) $\delta$ 24.2 ($CH_2$), 35.6 ($CH_2$), 52.4 ($CH_3$), 56.7 ($CH_3$), 104.7 (CH), 109.0 (CH), 119.6 (Q), 120.4 (Q), 139.9 (Q), 141.5 (Q), 144.0 (CH), 144.3 (Q), 176.6 (Q); IR ($CHCl_3$) 3340 m, 3000 m, 2640 m, 1705 s, 1530 m, 1480 s, 1435 m, 1345 s, 1150 s, 1040 m, 930 m, 875 m, 855 w, 655 m cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 250 M$^+$ (12), 218 (62), 190 (9), 176 (100), 161 (4), 147 (8), 133 (7), 119 (9), 91 (10); *m/e* calcd for $C_{13}C_{14}O_5$ 250.0841, measd 250.0840; colorless solid, mp 76–78 °C. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.18; H, 5.63. 6-Methoxy-2-oxo-(2,3,4*H*)-furo[2,3-*h*][1]benzopyran (**27**): $^1$H NMR ($CDCl_3$) $\delta$ 2.84 (dd, 2 H, $J$ = 6.5, 8.0 Hz, $CH_2CO_2CH_3$), 3.06 (t, 2 H, $J$ = 7.3 Hz, $CH_2CH_2CO_2CH_3$), 3.99 (s, 3 H, $ArOCH_3$), 6.57 (s, 1 H, 5-C*H*), 6.89 (d, 1 H, $J$ = 2.5 Hz 9-C*H*), 7.59 (d, 1 H, $J$ = 1.9 Hz, 8-CH); $^{13}$C NMR ($CDCl_3$) $\delta$ 24.1 ($CH_2$), 29.7 ($CH_2$), 56.7 ($CH_3$), 103.9 (Q), 106.0 (CH), 115.7 (Q), 119.4 (Q), 138.7 (Q), 142.2 (Q), 144.4 (Q), 145.5 (CH), 168.7 (Q); IR ($CHCl_3$) 3020 w, 2960 w, 2940 w, 2920 w, 2850 w, 1760 s, 1540 m, 1490 s, 1360 s, 1150 s, 950 m, 880 w, 830 w, 560 w cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 218 M$^+$ (62), 177 (11), 176 (100), 175 (28), 147 (7), 138 (7), 119 (9), 95 (8); *m/e* calcd for $C_{12}H_{10}O_4$ 218.0579, measd 218.0581; colorless solid, mp 142–143 °C. Anal. Calcd for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.03; H, 4.51.

For the purpose of optimization of the yield of the lactone **27**, this reaction was examined in a number of solvents. No solvent was found for which the yield of **27** exceeded that in THF (55%); however, an interesting effect of the nature of the solvent on the product distribution was noted which will be reported separately.[15]

**Methyl 4-Pentynoate (13a).** A solution of 21 g of 4-pentyn-1-ol (0.25 mol) in 400 mL of acetone was cooled to 0 °C, and 130 mL of Jones' reagent [70 g of $Cr(CO)_3$/500 mL of $H_2O$/61 mL of $H_2SO_4$] was added over a period of 3 h. The mixture was warmed to 20 °C, stirred for 3 additional h, and then filtered through Celite. The acetone was removed, and the remaining aqueous solution was extracted 5 times with diethyl ether. This ether solution was concentrated to a thick oil, which was dissolved in saturated aqueous sodium carbonate solution. This solution was extracted twice with diethyl ether; then the aqueous phase was acidified to pH 2 by the addition of 25% aqueous HCl and extracted 10 times with diethyl ether. The combined ether solutions from the second extraction were dried over $MgSO_4$ and filtered through Celite. Hexane was added to the filtrate, and the solvent was removed to provide 17 g (69%) of 4-pentynoic acid as colorless plates: $^1$H NMR ($CDCl_3$) $\delta$ 1.99 (t, 1 H, $J$ = 2.7 Hz, alkynyl H), 2.51 (dt, 2 H, $J$ = 2.7, 7.3 Hz, propargylic $CH_2$), 2.62 (t, 2 H, $J$ = 7.4 Hz, $CH_2CO_2H$); colorless plates from hexane/diethyl ether, mp 42–46 °C (lit.[34] mp 54.5–56.5 °C).

A mixture of 6.0 g of this acid (61 mmol) and 25 mL of methanol was heated to reflux in benzene in the presence of ~30 mg of *p*-toluenesulfonic acid for 2.5 days. Periodic removal of the condensate collected in a Dean–Stark trap drove the esterification to completion. The reaction mixture was poured into saturated aqueous bicarbonate solution, and the mixture was extracted with diethyl ether. The ether phase was washed with brine and dried over $MgSO_4$. Solvent removal provided a colorless oil that was distilled at ambient pressure to provide 4.1 g (60%) of the desired ester **13a**: $^1$H NMR ($CDCl_3$) $\delta$ 1.99 (t, 1 H, $J$ = 2.5 Hz, alkynyl H), 2.48 (m, 2 H, propargyl $CH_2$), 2.56 (m, 2 H, $CH_2CO_2CH_3$), 3.71 (s, 3 H, $CO_2CH_3$); colorless oil, bp 143–144 °C (760 mm) [lit.[35] bp 101–102 °C (175 mm)].

**Reaction of [(2-Furyl)(methoxy)carbene]pentacarbonylchromium (8) with Methyl 2-(Phenylthio)-4-pentynoate (13b).** A solution of 83 mg of complex **8**[15,17] (0.27 mmol) and 67 mg of **13b** (0.30 mmol) in toluene was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and heated to 85 °C for 18 h under an argon atmosphere. After solvent

(34) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*, 203.
(35) Schulte, K. E.; Reiss, K. P. *Chem. Ber.* **1954**, *87*, 964.

removal the residue was dissolved in acetone, 340 μL of tri-*n*-butylphosphine[13] was added, and then the mixture was stirred for 1 h. The acetone was then removed, and the residue was chromatographed (silica gel, 3:10 EtOAc/hexane) to provide two compounds, the desired lactone **29** (22.5%) and a compound identified as the furan **30** (8%). This reaction was repeated and the crude mixture oxidized by exposure to air; examination of the $^1$H NMR of the crude reaction mixture showed that **29** and **30** were present in the ratio of 1:1 before phosphine treatment or chromatography. 6-Methoxy-2-oxo-3-(phenylthio)-(2,3,4*H*)-furo-[2,3-*h*][1]benzopyran (**29**): $^1$H NMR δ 3.18 (ddd, 1 H, *J* = 0.5, 5.1, 16.5 Hz, 4-C(H)*H*), 3.53 (ddd, 1 H, *J* = 0.7, 5.5, 16.5 Hz, 4-C(H)*H*), 4.00 (s, 3 H, Ar-OC$H_3$), 4.17 (t, 1 H, *J* = 5.3 Hz, 3-C*H*), 6.54 (s, 1 H, 5-C*H*), 6.91 (d, 1 H, *J* = 2.0 Hz, 9-C*H*), 7.31 (m, 3 H, S-Ar), 7.51 (m, 2H, S-Ar), 7.61 (d, 1 H, *J* = 2.0 Hz, 8-C*H*); colorless solid. This compound was further characterized by its conversion to sphondin. The other product from the reaction was identified as the furan **30** on the basis of the following spectral data: $^1$H NMR ($CDCl_3$) δ 2.79 (dd, 1 H, *J* = 6.0, 16.0 hZ, C(H)*H*$CH_2CO_2CH_3$), 2.90 (dd 1 H, *J* = 9, 16 Hz, C(H)*H*$CH_2CO_2CH_3$), 3.63 (s, 3 H, $CO_2CH_3$), 3.80 (dd, 1 H, *J* = 6.0, 9.0 Hz, methine C*H*), 3.94 (s, 3 H, ArOC$H_3$), 6.31 (s, 1 H, 4-C*H*), 6.36 (d, 1 H, *J* = 3.5 Hz, 3′-C*H*), 6.40 (dd, 1 H, *J* = 2.5, 3.5 Hz, 4′-C*H*), 7.29 (m, 3 H, -S-Ar), 7.33 (d, 1 H, *J* = 2.0 Hz, 5′-C*H*), 7.55 (m, 2 H S-Ar); colorless semisolid.

**Methyl 2-(Phenylthio)-4-pentynoate (13b) and 2-(Phenylthio)-5-(trimethylsilyl)-4-pentyn-1-ol (13f).** A solution of 2.5 g of (phenylthio)acetic acid (14.9 mmol) and 3.65 mL of HMPA (29.8 mmol) in 40 mL of THF was added to a solution of 29.8 mmol of freshly prepared LDA in 50 mL of the THF at 0 °C. This mixture was stirred at 0 °C for 1 h, then ~4.5 g of 3-(trimethylsilyl)propargyl bromide (~22 mmol) was added, and stirring was continued for 1–2 h at 0 °C. To this mixture was added 75 mL of 1 M HCl, and the acidified mixture (pH 2) was extracted 3 times with diethyl ether. The ethereal fractions were combined, washed with saturated aqueous $NH_4Cl$, and dried over $MgSO_4$, and the solvent was removed to provide 6–7 g of crude 2-(phenylthio)-5-(trimethylsilyl)-4-pentynoic acid (**13e**) as a yellow oil. This crude material was not purified, but was taken on to either **13b** or **13f**.

All of the crude acid **13e** was dissolved in 100 mL of diethyl ether and treated with an ethereal solution of ~24 mmol of diazomethane (prepared from 7.3 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide by treatment with KOH). The excess diazomethane was destroyed by the slow addition of a 30% solution of acetic acid in ether until nitrogen production ceased. The mixture was washed with saturated aqueous $NH_4Cl$, dried over $MgSO_4$, and the solvent removed to provide a pale yellow oil. Flash chromatography (silica gel, 1:12 EtOAc/hexane) gave 3.83 g (87%) of 5-(trimethylsilyl)-2-(phenylthio)-4-pentynoic acid methyl ester. A solution of 1.00 g (3.41 mmol) of this ester in 3 mL of anhydrous methanol was treated with 2 mL of 0.2 N KOH in methanol. Stirring for 1.75 h caused complete cleavage of the TMS group (TLC monitoring). The reaction mixture was poured into 50 mL of pH 4 buffer solution, extracted with saturated aqueous $NH_4Cl$, and dried over $MgSO_4$. Solvent removal provided 734 mg (99%) of the desired **13b** which required no further purification. Methyl 2-(phenylthio)-4-pentynoate (**13b**): $^1$H NMR ($CDCl_3$) δ 2.08 (t, 1 H, *J* = 2.5 Hz, alkynyl *H*) 2.62 (ddd, 1 H, *J* = 2.5, 6.5, 17 Hz, C(H)*H*C(H)CH), 2.75 (ddd, 1 H, *J* = 2.5, 8.5, 17.5, C(H)*H*C(H)CH), 3.72 (s, 3 H, $CO_2CH_3$), 3.79 (dd, 1 H, *J* = 7.8 Hz, methine *H*), 7.33 (m, 3 H, S-Ph), 7.49 (m, 2 H, S-Ph); colorless oil.

A solution of the crude acid **13e** [prepared from 2.5 g of (phenylthio)acetic acid as above] in 250 mL of diethyl ether at 0 °C was treated with 2.4 g of LAH (63 mmol) which was slowly added in small portions with vigorous stirring. After addition was complete, the mixture was warmed to 20 °C and stirred for 2 h. The remaining LAH was destroyed by the careful addition of saturated aqueous $NH_4Cl$, and the reaction mixture was filtered through Celite. Chromatography (silica gel, 3:10 EtOAc/hexane) provided 2.62 g [67% from (phenylthio)acetic acid] of alcohol **13f** as a colorless oil: $^1$H NMR ($CDCl_3$) δ 0.19 (s, 9 H, Si-($CH_3$)$_3$), 1.54 (t, 1 H, *J* = 6.3 Hz, $CH_2OH$), 2.66 (dd, 2 H, *J* = 6.7, 1.6 Hz, $CH_2$), 3.13 (pent, 1 H, *J* = 6 Hz CH), 3.60 (m, 2 H, $CH_2$), 6.74 (m, 3 H, SPh), 7.31 (m, 2 H, SPh); $^{13}$C NMR ($CDCl_3$) δ 0.1 ($CH_3$), 23.1 ($CH_2$), 50.4 (CH), 63.2 ($CH_2$), 87.2 (Q), 103.2 (Q), 127.6 (CH), 128.9 (CH), 132.8 (CH), 132.9 (Q).

**Dehydrogenation of 6-Methoxy-2-oxo-(2,3,4*H*)-furo[2,3-*h*]-1-benzopyran (27) to 6-Methoxy-2-oxo-(2*H*)-furo[2,3-*h*]-1-benzopyran [Sphondin (4)].** A mixture of 20 mg of **27** (0.14 mmol) and 32 mg of DDQ (0.14 mmol) in 3 mL of toluene was heated to reflux for 18 h, or until no further change was discernable by TLC. Two additional equivalents of DDQ were added and heating continued for a total of 8 days, or until no **27** remained. The mixture was filtered through silica gel (benzene eluant) and chromatographed (silica gel, 5:20:15 EtOAc/hexane/benzene) to provide a 57% yield of **4** as a light brown solid which was crystallized from benzene/hexane to give light brown needles melting at 191–191.5 °C (corrected). Treatment of **27** with 5% platinum on carbon or 5% palladium on carbon in refluxing diphenyl ether[19] for 5–7 days provided similar yields (40–50%) of **4**. The following data was collected for sphondin: $^1$H NMR (acetone-$d_6$) δ 4.03 (s, 3 H, ArOC$H_3$), 6.35 (d, 1 H, *J* = 9.5 Hz, 4-C*H*); 7.14 (s, 1 H, 5-C*H*), 7.17 (d, 1 H, *J* = 2.1 Hz, 9-C*H*),7.97 (d, 1 H, *J* = 2.1 Hz, 8-C*H*), 8.00 (d, 1 H, *J* = 9.5 Hz, 3-C*H*); $^{13}$C NMR (acetone-$d_6$) δ 56.6 ($CH_3$), 104.7 (CH), 105.1 (CH), 114.6 (Q), 114.9 (CH), 118.9 (CH), 143.6 (Q), 143.7 (Q), 145.4 (Q), 147.42 (CH), 147.48 (Q), 160.6 (Q); IR ($CHCl_3$) 3000 m, 1710 s, 1575 s, 1460 m, 1390 m, 1340 s, 1300 s, 1295 m (d), 1260 m, 1040 m, 950 m, 830 m, 660 w cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 216 M$^+$ (100), 201 (44), 188 (23), 173 (47), 145 (34), 89 (17), 63 (12); *m/e* calcd for $C_{12}H_8O_4$ 216.1029, measd 216.0426; light yellow needles from benzene/hexane, mp 191–191.5 °C corr; colorless needles from ethanol, mp 188.5 °C, mixed melting point with natural material, 188.5 °C. The IR, $^1$H and $^{13}$C NMR, and mass spectra were identical with those obtained on an authentic sample of sphondin provided by H. Shimomura.[20]

**6-Methoxy-2-oxo-(2*H*)-furo[2,3-*h*]benzopyran [Sphondin (4)] from 6-Methoxy-2-oxo-3-(phenylthio)-(2,3,4*H*)-furo[2-3-*h*]-1-benzopyran (29).** A mixture of 20 mg of compound **29** (0.061 mmol) and 250 mg of powdered anhydrous $Na_2CO_3$ in 1.5 mL of toluene was cooled to −78 °C. To this mixture was added a solution of 13 mg of MCPBA (0.061 mmol, 85% purity) in 2 mL of 1:1 toluene/$CH_2Cl_2$ over a period of 5 min. This mixture was warmed to 20 °C, and 10 mL of toluene was added. The $CH_2Cl_2$ was then distilled off, and the resulting toluene solution was heated to reflux for 10 h. The reaction mixture was filtered through silica gel with acetone as the eluant to obtain 19.5 mg (85%) of a material that had spectral properties identical with those reported above for sphondin.

**Reaction of [(2-Thiofuryl)(methoxy)carbene]pentacarbonylchromium (31) with Methyl 4-Pentynoate (13a).** A solution of 5.3 g of complex **31**[24] (16.6 mmol) and 4.1 mL (24.9 mmol) of methyl 4-pentynoate in 100 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and then heated to 85 °C for 10 h under argon. The THF was removed folllowed by immediate purification by chromatography (silica gel, 1:10 EtOAc/hexane) to provide phenol **33** and its corresponding lactone **32** in a 1:7 ratio in a total yield of 42% (1.477 g) and, in addition, the furan **34** in 30% yield (1.2 g). Furan **34** is unstable and was observed to decompose at room temperature after a few hours. The following data were collected for furan **34**: $^1$H NMR ($CDCl_3$) δ 2.55 (t, 2 H, *J* = 7 Hz, $CH_2CO_2CH_3$), 2.64 (t, 2 H *J* = 7 Hz, $CH_2CH_2CO_2CH_3$), 3.68 (s, 3 H, $CO_2CH_3$), 3.95 (s, 3 H, ArOC$H_3$), 6.26 (s, 1 H, 3-C*H*), 6.96 (t, 1 H, *J* = 4 Hz, 3′-C*H*), 7.07 (d, 1 H, *J* = 3 Hz, 4′-C*H*), 7.10 (d, 1 H, *J* = 5 Hz, 5′-C*H*); $^{13}$C NMR ($CDCl_3$) δ 18.6 (t), 34.0 (t), 51.3 (t), 59.6 (q), 99.3 (s), 107.5 (q), 120.7 (d), 122.6 (d), 127.3 (s), 133.7 (d), 139.5 (s), 155.3 (s), 173.1 (s); IR (neat) 1734 s, 1647 m, 909 s cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 266 M$^+$ (100), 251 (95), 237 (20), 219 (25), 193 (100), 165 (55), 111 (100), 86 (50).

The mixture of phenol **33** and the lactone **32** was dissolved in toluene and heated to reflux in the presence of a catalytic amount of *p*-toluenesulfonic acid (20 mg, 0.05 equiv) and the condensate passed over activated 4-Å molecular sieves to remove the generated methanol. This reaction mixture was then neutralized with $NaHCO_3$ (aqueous), washed with brine, and dried over $MgSO_4$. Solvent removal and purification by flash chromatography on silica gel with a 10:1 mixture of benzene/acetone as eluant provided 1.4 g (90%) of the lactone **32** as a colorless solid: $^1$H NMR ($CDCl_3$) δ 2.86 (t, 2 H, *J* = 7.0 Hz, $CH_2CO_2CH_3$), 3.10 (t, 2 H, *J* = 7.0 Hz, $CH_2CH_2CO_2CH_3$), 3.97 (s, 3 H, ArOC$H_3$), 6.53 (s, 1 H, 5-C*H*), 7.43 (d, 1 H, *J* = 5 Hz, 9-C*H*), 7.48 (d, 1 H, *J* = 5 Hz, 8-C*H*); $^{13}$C NMR ($CDCl_3$) δ 23.8 (t), 29.2 (t), 55.7 (q), 103.3 (s), 117.4 (d), 119.6 (s), 127.3 (s), 128.6 (s), 130.5 (s), 140.4 (s), 150.5 (d), 168.5 (s); IR ($CCl_4$) 1758 s cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 234 M$^+$ (100), 206 (35), 192 (100), 163 (43), 149 (45), 134 (60), 121 (40), 91 (42). Anal. Calcd for $C_{12}H_{10}O_3S$: C, 61.54; H, 4.27; S, 13.67. Found: C, 61.65; H, 4.20; S, 13.35.

**Dehydrogenation of 6-Methoxy-2-oxo-(2,3,4*H*)-thiofuro[2,3-*h*]-1-benzopyran (32) to 6-Methoxy-2-oxo-(2*H*)-thiofura[2,3-*h*]-1-benzopyran [Thiospondin (35)].** A mixture of 1.1 g of **32** (4.7 mmol) and 2.13 g of DDQ (9.4 mmol) in 50 mL of toluene was heated to reflux for 4 h until none of the starting material remained. The reaction mixture was filtered through silica gel (benzene eluant) and then chromatographed on silica gel (1:10 benzene/acetone) to provide 750 mg (69%) of **35** as a light pink solid which was crystallized from benzene to give colorless needles: mp 189–189.5 °C; $^1$H NMR ($CDCl_3$) δ 4.04 (s, 3 H ArOC$H_3$), 6.43 (d, 1 H, *J* = 9.5 Hz, 4-C$H_3$), 6.71 (s, 1 H, 5-C*H*), 7.54 (d, 1 H, *J* = 5 Hz, 9-C*H*), 7.77 (d, 1 H, *J* = 5.4 Hz, 8-C*H*), 7.78 (d, 1 H, *J* = 9.4 Hz 3-C*H*); $^{13}$C NMR ($CDCl_3$) δ 56.0 (q) 100.7 (d), 114.8 (d), 115.1 (s), 120.7 (d), 128.2 (d), 130.1 (s), 133.6 (s), 144.2 (s), 144.6 (d), 150.9 (s), 160.9 (s); IR (neat) 3054 m, 1726 s, 1266 m cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 232 M$^+$ (100), 217 (99), 189 (99), 161 (85), 145 (15),

133 (25), 111 (25), 89 (50). Anal. Calcd for $C_{12}H_8O_3S$: C, 62.07; H, 3.44; S, 13.79. Found: C, 62.06; H, 3.31; S, 13.47.

**Reaction of [(3-Furyl)(methoxy)carbene]pentacarbonylchromium (10a)[6] with Methyl 4-Pentynoate (13a).** This reaction was run in methanol and worked up with tri-*n*-butylphosphine as described for the reaction of complex **8** with **13b**. Flash chromatography (silica gel, 18% EtOAc/hexane) provided phenol **36a** (51%) and lactone **36** (8%). Closure of **36a** to **36** was achieved in 90% yield by treatment with catalytic (0.05 equiv) of *p*-toluenesulfonic acid in refluxing benzene with removal of methanol in a Dean–Stark trap. Methyl 7-hydroxy-4-methoxy-8-benzo[*b*]furanpropionate (**36a**): $^1$H NMR ($CDCl_3$) $\delta$ 2.80 (t, 2 H, $J$ = 6.7 Hz, $CH_2CO_2CH_3$), 3.07 (t, 2 H, $J$ = 6.7 Hz, $CH_2CH_2CO_2CH_3$), 3.75 (s, 3 H, $OCH_3$), 3.77 (s, 3 H, $OCH_3$), 6.52 (s, 1 H, 5-C*H*), 6.95 (d, 1 H, $J$ = 2.1 Hz, 3-C*H*), 7.17 (s, 1 H, Ar-O*H*), 7.66 (d, 1 H, $J$ = 2.1 Hz, 2-C*H*); mass spectrum, *m/e* (relative intensity) 250 $M^+$ (37), 218 (70), 190 (12), 176 (100), 147 (08), 91 (08); *m/e* calcd for $C_{13}H_{14}O_5$ 250.2481, measd 250.0482; colorless solid. 4-Methoxy-8-oxo-(6,7,8*H*)-furo[3,2-*h*][1]benzopyran (**36**): $^1$HMR ($CDCl_3$) $\delta$ 2.86 (dd, 2 H, $J$ = 6.4, 8.0 Hz, 7-$CH_2$), 3.10 (br dt, 2 H, $J$ = 7.4 Hz, 6-$CH_2$), 3.91 (s, 3 H, $ArOCH_3$), 6.41 (s, 1 H, 5-CH), 6.85 (d, 1 H, $J$ = 2.0 Hz, 3-C*H*), 7.55 (d, 1 H, $J$ = 2.0 Hz, 2-C*H*); mass spectrum, *m/e* (relative intensity) 218 $M^+$ (71), 176 (100), 147 (9), 119 (12), 105 (3), 91 (12); *m/e* calcd for $C_{12}H_{10}O_4$ 218.0589, measd 218.0584; colorless prisms from benzene/hexane, mp 127–128 °C.

**[(2-Furyl)(3-methyl-2-butenoxy)carbene]pentacarbonylchromium (37).** A solution of 2.1 g of tetramethylammonium [(2-furyl)(oxido)carbene]pentacarbonylchromium (**24**)[15,17] (0.56 mmol) in 50 mL of $CH_2Cl_2$ was treated with 0.78 mL of prenyl bromide (6.2 mmol) at 20 °C under an argon atmosphere. This mixture was allowed to stir for 3 h, filtered through glass wool, and then stripped of solvent. Some unreacted **24** remained in the glass wool and was eluted with $CH_2Cl_2$ and treated with another portion of prenyl bromide for an additional 3 h. Filtration of this second fraction, solvent removal, and extraction of the combined residues into hexane followed by filtration through Celite gave a red solution that provided purple prisms upon cooling. Flash chromatography (silica gel, hexane) of the concentrated mother liquors followed by crystallization from hexane provided a second crop of crystals, with a combined yield of 72.5%. Alternatively, treatment of the acyloxy complex obtained from the reaction of **24** and acetyl chloride with prenyl alcohol according to the procedure for the preparation of **10e** afforded lower yields of **37** (55%). The following data was obtained for complex **37**: $^1$H NMR ($CDCl_3$) $\delta$ 1.83 (s, 3 H, allyl $CH_3$), 1.87 (s, 3 H, allyl $CH_3$), 5.57 (d, 2 H, $J$ = 7.1 Hz, allyl $CH_2$), 5.62 (m, 1 H, vinyl C*H*), 6.56 (dd, 1 H, $J$ = 1.5, 3.3 Hz, 4-C*H*), 6.98 (d, 1 H, $J$ = 3.6 Hz, 3-C*H*), 7.82 (br s, 1 H 5-C*H*); mass spectrum, *m/e* (relative intensity) 356 $M^+$ (6), 300 (4), 288 (9), 287 (7), 272 (5), 260 (6), 259 (9), 244 (8), 232 (6), 216 (10), 203 (20), 175 (29), 148 (69), 120 (41), 119 (45), 52 (100); *m/e* calcd for $C_{15}H_{12}O_7Cr$ 355.9988, measd 355.9988; purple prisms from hexane, mp 58–60 °C; yield, 72.5%.

**Reaction of [(2-Furyl)(3-methyl-2-butenoxy)carbene]pentacarbonylchromium (37) with Methyl 4-Pentynoate (13a).** A solution of 100 mg of complex **37** (0.28 mmol) and 35 μL of methyl pentynoate (**13a**; 281 mmol) in 3 mL of methanol was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and heated to 85 °C for 2 h, at which time the red color of the starting carbene complex **37** was gone. The reaction was filtered repeatedly through silica gel (methanol eluant) until the greenish chromium residue was removed and either chromatographed (silica gel, 3:10:10 EtOAc/hexane/benzene) to provide a mixture of the lactone **38** and its corresponding uncyclized phenol (combined yield 30–40%) or cyclized under acidic conditions (refluxing benzene, catalytic $ZnCl_2$, or $Cl_3CO_2H$, Dean–Stark trap) to convert all the material to lactone **38** (35% from **37**). 6-(3-Methyl-2-butenoxy)-2-oxo-(2-oxo-(2,3,4*H*)-furo[2,3-*h*][1]benzopyran (**38**): $^1$H NMR ($CDCl_3$) $\delta$ 1.76 (br s, 3 H, allyl $CH_3$), 2.84 (dd, 2 H, $J$ = 6.1, 7.9 Hz, methylene $CH_2$), 3.04 (br t, 2 H, $J$ = 7.3 Hz, methylene $CH_2$), 4.69 (d, 2 H, $J$ = 6.7 Hz allyl $CH_2$), 5.56 (triplet of heptets, 1 H, $J$ = 6.7, 2.0 Hz, vinyl *H*), 6.58 (s, 1 H, 5-C*H*), 6.88 (d, 1 H, $J$ = 1.6 Hz, 9-C*H*), 7.58 (d, 1 H, $J$ = 1.6 Hz, 8-C*H*); mass spectrum, *m/e* (relative intensity 272 $M^+$ (2), 204 (100), 176 (28), 162 (81), 147 (6), 119 (5), 95 (4), 69 (31). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.31; H, 6.04. Colorless needles from benzene/hexane, mp 105–106 °C.

**6-(3-Methyl-2-butenoxy)-2-oxo-(2*H*)-furo[2,3-*h*]-1-benzopyran [Heratomin (5)].** A solution of 10 mg of 6-(3-methyl-2-butenoxy)-2-oxo-(2,3,4*H*)-furo[2,3-*h*]benzopyran (**38**; 37 μmol) and 40 mg of DDQ (0.18 μmol) in 1 mL of toluene was refluxed for 20 h, after which time no starting **38** remained (TLC monitoring). Flash chromatography (dry loaded silica gel column, 5:20:15 EtOAc/hexane/benzene) followed by preparative TLC (silica gel, same solvent) provided 12% (1 mg ) of a material that was tentatively identified as heratomin (**5**) and 5 mg of an unidentified colorless oil. The use of chloranil instead of DDQ resulted only in the slow destruction of **38**. The minor component was identified as heratomin on the basis of the following: $^1$H NMR ($CDCl_3$) $\delta$ 1.79 (s, 3 H, allyl $CH_3$), 1.82 (s, 3 H, allyl $CH_3$), 4.75 (br t, 2 H, $J$ = 6.8 Hz, allyl $CH_2$-O), 5.52 (triplet of heptets, 1 H, $J$ = 6.8, 1.5 Hz, vinyl C*H*), 6.36 (d, 1 H, $J$ = 9.5 Hz, 4-C*H*), 6.80 (s, 1 H, 5-C*H*), 7.13 (d, 1 H, $J$ = 2.5 Hz, 9-C*H*), 7.69 (d, 1 H, $J$ = 2.5 Hz, 8-C*H*), 7.73 (d, 1 H, $J$ = 9.5 Hz, 3 C*H*). The $^1$H NMR spectral data obtained from the synthetic material is nearly identical with that reported for the natural material.[10]

**Table I.** Products Identified from Thermolysis of Complex **43**

| compound | identification method[a] |
|---|---|
| diphenylacetylene (**44**) | NMR, GC, MS |
| *cis*-stilbene (**46**) | NMR, GC, MS |
| *trans*-stilbene (**45**) | NMR, GC, MS |
| biphenyl (**47**) | NMR, GC, MS |
| phenylacetophenone (**48**) | NMR, GC |
| acetoxystilbene (**49**) | mol ion |
| $\eta^6$-diphenylacetylenetricarbonylchromium (**50**) | mol ion |

[a] MS, comparison of published mass spectra[38] with GC–MS of the crude reaction mixture.

**Preparation of [(Acetoxy)(3-furyl)carbene]pentacarbonylchromium (41) and Reaction with 3-Hexyne.** To a solution of 0.25 g of tetramethylammonium [3-furyl)(oxido)carbene]pentacarbonylchromium (**25**; 0.69 mmol) in 40 mL of $CH_2Cl_2$ that was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) was added 40 μL of acetyl chloride (0.69 mmol) at −20 °C under an argon atmosphere. This mixture was stirred for 10 min at −20 °C, and formation of a dark red color was noted. Then 62 μL of 3-hexyne (0.72 mmol) was added at this same temperature, and the mixture allowed to warm to 20 °C and stirred for 1 h. After this time the mixture had changed from red to brown, and no further change was apparent from TLC after an additional 9 h of stirring. The reaction mixture was oxidized with 10.5 mL of a solution of CAN (0.5 M CAN/0.1 N $HNO_3$); the TLC remained unchanged after this treatment. The absence of the expected 5,6-diethyl-4,7-dioxo-(4,7*H*)-benzo[*b*]furan (**20**) was established by coelution on TLC with an authentic sample. Filtration of the crude reaction mixture through silica gel with $CH_2Cl_2$ followed by preparative TLC (silica gel, 3:10 EtOAc/hexane) allowed isolation of a small amount (3%) of an acetylene tentatively identified as **40**. The bulk of the reaction mixture was an intractable brown oil composed of many compounds. The following spectral data were collected for compound **40**: $^1$H NMR ($CDCl_3$) $\delta$ 6.48 (d, 2 H, $J$ = 1.9 Hz, 4-C*H*), 7.38 (t, 2 H, $J$ = 1.6 Hz, 5-C*H*), 7.61 (br s, 2 H, 2-C*H*); mass spectrum, *m/e* (relative intensity) 158 $M^+$ (100), 129 (58), 102 (33), 75 (53), 50 (24).

**Preparation and Thermolysis of [(3-Furyl-)(4-pentynoyloxy)carbene]pentacarbonylchromium (39).** Complex **39** was prepared at −20 °C in methylene chloride by the addition of 4-pentynoyl chloride (**13c**)[36] to tetramethylammonium [(3-furyl)(oxido)carbene]pentacarbonylchromium (**25**) as in the preparation of [(acetoxy)(3-furyl)carbene]pentacarbonylchromium (**41**) above. Slow warming to 20 °C produced a brown complex mixture of polar compounds, from which only a trace amount of acetylene **40** was eluted on preparative TLC (silica gel, 3:10 EtOAc/hexane). The same result was obtained from the reaction of **25** with 5-(trimethylsilyl)-4-pentynoyl chloride (**13d**).

**Preparation of [(Acetoxy)(phenyl)carbene]pentacarbonylchromium (43) and Reaction with 3-Hexyne.** A solution of 0.50 g of tetramethylammonium [(oxido)(phenyl)carbene]pentacarbonylchromium (**42**)[37] (1.35 mmol) in 20 mL of $CH_2Cl_2$ was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and treated with 75 μL of acetyl chloride (1.35 mmol) at −20 °C to generate in situ the purple acyloxy complex **43**.[25] The mixture was stirred for 5 min, the solvent was removed under high vacuum at −20 °C and then the residue was extracted with degassed hexane that was precooled to −20 °C. The solvent was removed from the hexane-soluble material under high vacuum at −20 °C and replaced with 10 mL of THF that had been precooled to −20 °C. After 0.3 mL of 3-hexyne (2.6 mmol) was added, the mixture was deoxygenated by the freeze–thaw method (−196 to −20 °C, 3 cycles), warmed to 20 °C, and stirred in the dark for 15 h. A yellow-brown mixture resulted, which was opened to the air with rapid formation of a green suspension of oxidized chromium compounds. Filtration through activity IV alumina provided a complex mixture of small quantities (1–5% each) of products, a few of which were identified as those shown in Table I. These products arise from the reaction of two carbene

(36) Grotjahn, D. B.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 2091.
(37) Fischer, E. O.; Maasböl, A. *Chem. Ber.* **1967**, *100*, 2445.

ligands; no products incorporating the alkyne were found. The identities of these materials were established by the combination of the following methods indicated in Table I: (1) NMR, $^1$H NMR of sample purified by preparative GC; (2) GC, coinjection with authentic samples on a $^1/_8$ in. × 6 ft OV-101 packed GC column; (3) MS comparison of published mass spectra[38] with GC–MS of the crude reaction mixture; (4) mol ion, identification of component in the crude reaction mixture by GC–MS by molecular ion. The same mixture of products was obtained if 3-hexyne was deleted from the reaction.

**Preparation and Intramolecular Reaction of [(3-Furyl)(4-pentynyloxy)carbene]pentacarbonylchromium (10b).** A solution of 300 mg of tetramethylammonium [(3-furyl)(oxido)carbene]pentacarbonylchromium (**25**; 0.83 mmol) in 35 mL of $CH_2Cl_2$ was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and cooled to 0 °C under an argon atmosphere. To this mixture was added 59 μL of acetyl chloride (0.83 mmol), and after the resultant mixture was stirred for 15 min, 350 μL of 4-pentyn-1-ol (40 mmol) was added and stirring continued at −20 °C for 2.5 h. The methylene chloride was removed, and the resulting brownish mixture was flash chromatographed (silica gel, hexane) to provide a 54% yield (146 mg) of **10b** as a red oil. A solution of complex **10b** in 4 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and heated at 75 °C for 14 h. The solvent was removed, the residue was dissolved in 20 mL of acetone, and 350 μL of tri-*n*-butylphosphine[13] (1.78 mmol) was added. This mixture was stirred at 50 °C for 5 h, and then the excess phosphine was destroyed by the addition of methanol (2 mL) and carbon tetrachloride (2 mL) followed by stirring for 16 h. Flash chromatography (silica gel, 3:10 EtOAc/hexane) provided dihydropyran **53** in 14% yield (12 mg) as a colorless solid which crystallized from benzene/hexane to give colorless needles, mp 120.5–121.5 °C. 6-Methoxy-(2,3,4*H*)-furo[2,3-*H*][1]benzopyran (**53**): $^1$H NMR ($CDCl_3$) δ 2.05 (m, 2 H, 3-C$H_2$), 2.80 (t, 2 H, $J$ = 6.5 Hz, 2-C$H_2$), 4.24 (br t, 2 H, $J$ = 5.2 Hz, 4-C$H_2$), 4.81 (br s, 1 H, ArO$H$), 6.51 (s, 1 H, 5-C$H$), 6.80 (d, 1 H, $J$ = 2.1 Hz, 9-C$H$), 7.50 (d, 1 H, $J$ = 2.1 Hz, 8-C$H$); $^{13}$C NMR ($CDCl_3$) δ 22.8 ($CH_2$), 24.8 ($CH_2$), 66.6 ($CH_2$), 104.6 (CH), 115 (CH), 115.1 (Q), 118.7 (Q), 134.7 (Q), 141.7 (Q), 143.1 (Q), 144.0 (CH); mass spectrum, *m/e* (relative intensity) 190 $M^+$ (98), 175 (7), 162 (100), 147 (14), 134 (16); *m/e* calcd for $C_{11}H_{10}O_3$ 190.06302, measd 190.0631. A study of the effect of the starting concentration of **10b** on the yield of **53** produced the following results: 0.5 M, 13%, 0.05 M, 12%, 0.005 M, 14%.

**Preparation and Intramolecular Reaction of [(3-Furyl)[[5-(trimethylsilyl)-4-pentynyl]oxy]carbene]pentacarbonylchromium (10c).** Complex **10c** was prepared and reacted in the same fashion as described above for complex **10b** except that 5-(trimethylsilyl)-4-pentyn-1-ol[29] was used instead of 4-pentyn-1-ol. The yields of complex **10c** ranged from 56 to 82%, and the yields of **53** ranged from 60 to 76% (the TMS group was cleaved from the product during the phosphine workup).

**Preparation and Intramolecular Reaction of [(3-Furyl)[[2-(phenylthio)-5-(trimethylsilyl)-4-pentynyl]oxy]carbene]pentacarbonylchromium (10e).** A solution of 20.0 g of tetramethylammonium [(3-furyl)(oxido)carbene]pentacarbonylchromium (**25**; 57.5 mmol) in 260 mL of a 1:1 mixture of $CH_2Cl_2$ and DMF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles), treated at −20 °C with 3.95 mL of acetyl chloride (57.5 mmol, freshly distilled), and stirred at this temperature for 45 min. To this mixture was added 14.6 g (57.5 mmol) of 2-(phenylthio)-5-(trimethylsilyl)-4-pentynol (**13f**), and after being stirred for 2 h at −20 °C, the mixture was allowed to warm to room temperature for an additional hour. The reaction mixture was poured into hexane/brine, and the phases were partitioned. The aqueous phase was extracted with hexane, and the combined hexane phases were washed with aqueous saturated $NaHCO_3$ and then dried over $MgSO_4$. Flash chromatography on silica gel (hexane/EtOAc, 20:1) provided 22.5 g (78%) of **10e** as a red oil: $^1$H NMR ($CDCl_3$) δ 0.15 (s, 9 H, Si(C$H_3$)$_3$), 2.76 (dd, 1 H, $J$ = 9, 14 Hz, propargyl $H$), 2.84 (dd, 1 H, $J$ = 6, 14 Hz, propargyl $H$), 3.73 (m, 1 H, methine C$H$), 5.24 (m, 2 H, O-C$H_2$), 6.76 (dd, 1 H, $J$ = 0.8, 2 Hz, 3-C$H$), 7.33 (m, 3 H, S-Ph), 7.41 (br t, 1 H, $J$ = 2 Hz, 4-C$H$), 7.52 (m, 2 H, S-Ph), 8.23 (dd, 1 H, $J$ = 0.8, 2Hz, 5-C$H$); $^{13}$C NMR ($CDCl_3$) δ −0.14, 23.9, 47.4, 79.5, 88.4, 101.6, 107.5, 128.3, 129.3, 132.2, and 133.8, 142.1, 143.6, 150.2, 216.6, 222.7, 326.3. This reaction was carried out on six different scales between 1 and 20 g, and the yields ranged from 78 to 82%.

A solution of 4.0 g (7.6 mmol) of complex **10e** in 60 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and then heated to 80 °C for 8 h or until the starting complex was consumed (TLC). The THF was removed and replaced with acetone, and the resulting solution was filtered through Celite and then methylated by refluxing the solution in the presence of excess methyl iodide and excess powdered anhydrous $K_2CO_3$ for 8 h. The reaction mixture was filtered through Celite, and the acetone was removed from the filtrate. This residue was dissolved in 50 mL of $CCl_4$, then 45 mL of a 1.5:1 (v/v) mixture of $CF_3CO_2H$ and $CH_3CO_2H$ was added, and the mixture was stirred for 10 min. The mixture was then diluted with 30 mL of $CCl_4$, and saturated aqueous sodium bicarbonate solution was added until the pH was ~7. The phases were then separated, and the organic phase was dried over $MgSO_4$. For small-scale reactions (<1 g), the reaction mixture was fairly clean at this point and could be chromatographed directly. On larger scales, a considerable amount of chromium remained complexed to the product; the solvent was replaced by 20 mL of THF, an excess (>7 equiv) of $FeCl_3$–DMF complex[40] was added, and the solution was stirred from 30 min. The solvent was removed and the residue chromatographed (silica gel, 2:10 EtOAc/hexane) to give 1.43 g (60%) of the desired dihydropyran **60** which was crystallized from $CH_2Cl_2$/hexane to give colorless needles, mp 101.5–103 °C. 6-Methoxy-3-(phenylthio)-(2,3,4*H*)-furo[2,3-*h*][1]benzopyran (**60**): $^1$H NMR ($CDCl_3$) δ 2.88 (dd, 1 H, $J$ = 10.1, 15.9, 2-C(H)$H$), 3.17 (ddd, 1 H, $J$ = 1.8, 5.4, 15.9 Hz, 2-C(H)$H$), 3.68 (m, 1 H, 3-C$H$), 3.94 (s, 3 H, ArOC$H_3$), 3.97 (dd, 1 H, $J$ = 9.8, 10.7 Hz, 4-C(H)$H$), 4.41 (ddd, 1 H, $J$ = 1.9, 3.4, 10.7 Hz, 4-C(H)$H$), 6.44 (s, 1 H, 5-C$H$), 6.76 (d, 1 H, 2.1 Hz, 9-C$H$), 7.31 (m, 3 H, S-Ar), 7.49 (m, 2 H, S-Ar), 7.52 (d, 1 H, $J$ = 2.1 Hz, 8-C$H$); $^{13}$C NMR ($CDCl_3$) δ 31.6 ($CH_2$), 40.8 (CH), 56.7 ($CH_3$), 69.3 ($CH_2$), 104.1 (CH), 107.6 (CH), 112.7 (Q), 118.9 (Q), 127.6 (CH), 129.1 (CH), 132.4 (CH), 133.4 (Q), 140.1 (Q), 141.2 (Q), 144.2 (CH); IR ($CH_2Cl_2$) 2855 w, 1620 m, 1584 m, 1496 s, 1352 m, 1071 s, 980 w cm$^{-1}$. Anal. Calcd for $C_{18}H_{16}O_3S$: C, 69.20; H, 5.17; S, 10.26. Found: C, 68.84; H, 5.19; S, 10.00. This reaction was carried out on seven different scales from 0.2 to 12.0 g with yields in the range of 56–94%.

**6-Methoxy-(2*H*)-furo[2,3-*h*]-1-benzopyran (61).** A solution of 2.8 g of 6-methoxy-3-(phenylthio)-(2,3,4*H*)-furo[2,3-*h*]-1-benzopyran (**60**; (8.9 mmol) in 100 mL of a 1:1 mixture of $CH_2Cl_2$ and toluene was slurried with 2.5 g of powdered anhydrous $K_2CO_3$, cooled to −78 °C, and treated with 1.98 g of MCPBA (11.5 mmol, purified by washing an ethereal solution with saturated aqueous $NaHCO_3$) as a solution in 2 mL of $CH_2Cl_2$. The mixture was allowed to warm to room temperature over a period of 30 min. Analytical TLC (silica gel, 3:10 EtOAc/hexane) showed complete conversion of **60** into the desired sulfoxide ($R_f$ = 0.2, 3:10 EtOAc/hexane) and a trace of another compound that was isolated and identified as the sulfone ($R_f$ = 0.4). The sulfoxide was not isolated and characterized, but was converted into the desired pyran **61** by distillative removal of the $CH_2Cl_2$ after the addition of ~50 mL of toluene followed by heating in refluxing toluene for 7 h. The reaction mixture was filtered through a bed of Celite, and after the volatiles were removed, the residue was chromatographed (silica gel, 1:10 EtOAc/hexane) to provide 1.29 g (75%) of the pyran **61** as a colorless oil. This material was markedly unstable and darkened upon standing at ambient temperature and even in the solid state at lower temperatures under argon. The substance was stored as a frozen benzene solution. The starting sulfide **60** is chromatographically very similar to the pyran **61**, and it is thus more desirable to overoxidize slightly to produce a small amount of the sulfone instead of attempting to separate the pyran **61** from unreacted sulfide **60**. 6-Methoxy-1(2*H*)-furo[2,3-*h*]-1-benzopyran (**61**): $^1$H NMR ($CDCl_3$) δ 3.86 (s, 3 H, ArOC$H_3$), 4.86 (dd, 2 H, $J$ = 3.7, 1.8 Hz, 2-C$H_2$), 5.71 (dt, 1 H, $J$ = 9.6, 3.6 Hz, 3-C$H$), 6.45, (dt, 1 H, $J$ = 9.8, 1.8 Hz, 4-C$H$), 6.46 (s, 1 H, 6-C$H$), 6.78 (d, 1 H, $J$ = 2.2 Hz, 9-C$H$), 7.52 (d, 1 H, $J$ = 2.1 Hz, 8-C$H$); $^{13}$C NMR ($CDCl_3$) δ 56.6 ($CH_3$), 65.5 ($CH_2$), 104.1 (CH), 105.5 (CH), 115.9 (Q), 118.6 (Q), 119.3 (CH), 125.1 (CH), 140.1 (Q), 141.3 (Q), 144.6 (CH), 145.3 nQ); IR (thin film) 3121 w, 3048 w, 2959 m, 2832 m, 1605 m, 1539 m, 1485 s, 1736 s, 1326 s, 1306 s, 1219 s, 1162 s, 1049 s, 989 m, 878 m, 836 m, 806 m, 773 m, 732 s cm$^{-1}$; *m/e* calcd for $C_{12}H_{10}O_3$ 202.0630, measd 202.0620. This reaction has been run on eight different scales between 0.1 and 3.1 g with yields in the range of 70–90%.

**6-Methoxy-2-oxo-(2*H*)-furo[2,3-*h*]-1-benzopyran [Sphondin (4)] from 6-Methoxy-(2*H*)-furo[2,3-*h*]-1-benzopyran (61).** To a solution of 8.0 g (0.1 mol) of pyridine in 80 mL of $CH_2Cl_2$ at 0 °C was added 5.0 g (0.05 mol) of chromium trioxide. The reaction mixture was allowed to stir at room temperature for 15 h. A solution of 1.6 g (7.8 mmol) of **61** in 10 mL of $CH_2Cl_2$ was added dropwise, and after the addition, the reaction mixture was stirred for another 7 h, filtered through Celite, and evaporated to dryness. The residue was chromatographed on silica gel (benzene/acetone, 8:2) to provide 0.889 g (52%) of sphondin (**4**). The synthetic sphondin obtained by this procedure had spectral data identical with those of the material obtained from the dehydrogenation of lactone **26** described above.

(38) Stenhagen, E.; Abrahamson, S.; McClafferty, F. W. *Registry of Mass Spectral Data*; Wiley: New York, NY, 1974.

(39) Bunce, R. A.; Hertzler, D. V. *J. Org. Chem.* **1986**, *51*, 3451.

(40) Tobinaga, S.; Kotani, E. *J. Am. Chem. Soc.* **1972**, *94*, 309.

The yields of this oxidation were not sensitive to scale, at least in the range of 0.02–1.6 g. A 50% yield on a 1.5-g scale was possible with PDC in the presence of molecular sieves and acetic acid.[28] Oxidation of **61** only with PDC or PCC at ambient or elevated temperatures produced low yields of sphondin (10–15%) after reaction times of several days.[29] Attempted oxidation of **61** with chromium carbonyl and *tert*-butyl hydroperoxide failed.[30]

**Deprotonation of 6-Methoxy-(2*H*)-furo[2,3-*h*]-1-benzopyran (61).** A solution of 31.5 mg of pyran **61** (0.15 mmol) and 0.1 mL of HMPA in 2 mL of THF was cooled to −20 °C and treated with 85 μL of 1.7 M *tert*-butyllithium/hexane (0.15 mmol) under an argon atmosphere. This mixture was stirred at −20 °C for 5 min, then quenched with $D_2O$, allowed to warm to room temperature, and finally poured into a pH 7 buffer solution. Extraction with diethyl ether, drying over $MgSO_4$, and solvent removal provided a colorless oil which was chromatographed (silica gel, 3:10 EtOAc/hexane) to provide 18.3 mg (55%) of the deuteriated furan labeled in the 8-position. This material had a $^1$H NMR spectrum identical with that of the unlabeled **61** except that the furan resonance at 7.52 ppm was absent and that the furan resonance at 6.68 ppm was a singlet (instead of a doublet as exhibited by the perprotiated **61**).

**Oxidation of 6-Methoxy-(2*H*)-furo[2,3-*h*]-1-benzopyran (61) with Benzeneseleninic Anhydride.** A mixture of 30 mg of pyran **61** (0.15 mmol) and 53 mg of benzeneseleninic anhydride[23] (0.15 mmol) in 4 mL of benzene was heated to 65 °C for 3 h. The solution was washed with pH 7 buffer solution, dried over $MgSO_4$ and, after concentration, was chromatographed (silica gel, 3:10 EtOAc/hexane) to provide 50.8 mg (94%) of a material tentatively identified as 6-methoxy-4-(phenylseleninoxy)-(4*H*)-furo[2,3-*h*]-1-benzopyran (**63**) on the basis of the following spectral data: $^1$H NMR (benzene $d_6$) δ 3.33, (s, 3 H, Ar-OC*H*$_3$), 3.78 (dd, 1 H, *J* = 3.5, 5 Hz, 4–C(H)*H*), 4.11 (dd, 1 H, *J* = 11.0, 3.5 Hz, 4-C(H)*H*), 4.24 (dd, 1 H, *J* = 11,5 Hz, 3-C*H*), 6.56 (d, 1 H, *J* = 2 Hz, 8-C*H*), 6.93 (m, 3 H, Se-Ar), 7.54 (s, 1 H, 5-C*H*), 7.59 (m, 3 H, Se-Ar), IR (thin film) 3680 w, 3600 w, 1678 s, 1605 m, 1485 m, 1355 m, 1085 m, 1060 m, 1040 w, 860 w (brd) cm$^{-1}$; colorless oil.

**Oxidation of 6-Methoxy-4-(phenylseleninoxy)-(4*H*)-furo[2,3-*h*]-1-benzopyran (64) with PCC.** PCC was slowly added to a mixture of 50 mg of **63** (0.15 mmol) in 5 mL of $CH_2Cl_2$ over 30 min with stirring at 20 °C until **63** was consumed (TLC monitoring). The reaction mixture was filtered through Celite and the reaction flask rinsed with benzene which was used to wash the Celite. The combined benzene fractions were concentrated and chromatographed (silica gel, 5:20:15 EtOAc/hexane/benzene) to provide 9.6 mg (32%) of a colorless solid which was tentatively identified as chromanone **64** on the basis of the following spectral data: $^1$H NMR ($CDCl_3$) δ 4.11 (s, 3 H, ArOC*H*$_3$), 6.40 (d, 1 H, *J* = 5.9 Hz, 2-C*H*), 7.11 (d, 1 H, *J* = 2.1 Hz, 9-C*H*), 7.52 (s, 1 H, 5-C*H*), 7.74 (d, 1 H, *J* = 2.2 Hz, 8-C*H*), 7.91 (d, 1 H, *J* = 5.9 Hz, 3-C*H*); $^{13}$C NMR ($CDCl_3$) δ 56.6, 100.2, 104.9, 113.0, 119.1, 121.3, 144.5, 146.1, 154.2, 177.4, 198.4.

**6-Hydroxy-3-(phenylthio)-(2,3,4*H*)-furo[2,3*h*]-1-benzopyran (72).** A solution of 7.11 g of **10e** (13.6 mmol) in 120 mL of THF was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and heated to 80 °C for 8 h until the starting complex was consumed (TLC). Excess ferric chloride–DMF complex[40] (>7 equiv) was added at room temperature and the mixture stirred for 20 min. The reaction mixture was filtered through Celite and the THF was removed. The residue was dissolved in 60 mL of $CCl_4$, and then 40 mL of a 1.5:1 (v/v) mixture of $CF_3CO_2H$ and $CH_3CO_2H$ was added and the mixture stirred for 15 min. This solution was then quenched with an aqueous $NaHCO_3$ solution until the pH was ~7. The organic phase was dried over $MgSO_4$. Solvent removal and chromatography (silica gel, 3:10 EtOAc/hexane) gave a 51% (2.03 g) yield of the desired phenol **72**: $^1$H NMR ($CDCl_3$) δ 2.84 (dd, 1 H, *J* = 16, 10 Mz, 2-C(CH)*H*), 3.14 (ddd, 1 H, *J* = 2, 5.5, 16 Hz, 2-C(H)*H*), 3.66 (m, *J* = 1 Hz, 3-C*H*), 3.97 (t, 1 H, *J* = 10 Hz, 4-C(H)*H*), 4.51 (ddd, 1 H, *J* = 10, 4, 2 Hz, 4C(H)*H*), 4.96 (s, 1 H, ArO*H*), 6.49 (s, 1 H, 5-C*H*), 6.68 (d, 1 H, *J* = 2 Hz, 9-C*H*), 7.41 (m, 3 H, S-Ph), 7.50 (m, 3 H, S-Ph, 8-C*H*); $^{13}$C NMR ($CDCl_3$) δ 31.1 ($CH_2$), 40.6 (CH) 69.2 ($CH_2$), 104.5(CH), 110.9(CH), 113.3(Q), 118.3(Q), 127.6(CH), 129.1(CH), 132.3(CH), 133.1(Q), 135.1(Q), 140.8(Q), 143.1(Q), 144.1(CH); mass spectrum, *m/e* (relative intensity) 298 M$^+$ (96), 189 (100), 175 (14), 161 (33), 147 (17), 133 (20), 123 (24), 105 (12), 91 (11), 77 (20); *m/e* calcd for $C_{17}H_{14}O_3S$ 298.0663, measd 298.0663; colorless needles from benzene/hexane, mp 130.5–131 °C. This reaction was not optimized and was carried out only once. Indications are that the yield of **72** could be improved with an oxidant milder than the $FeCl_3$–DMF complex or with oxidation for shorter periods of time or at temperatures below room temperature since TLC of the crude reaction mixture indicated the presence of a second compound suspected of being the quinone that would result from the overoxidation of **72**.

**6-[(Trifluoromethyl)sulfonyl]-3-(phenylthio)-(2,3,4*H*)-furo[2,3-*h*]-benzopyran (73).** Triflic anhydride (4.5 mL, 30 mmol) was added slowly at 0 °C to a stirred solution of 6-hydroxy-3-(phenylthio)-(2,3,4*H*)-furo-[2,3-*h*]benzopyran (**72**; 1.65 g, 5.53 mmol) in 180 mL of methylene chloride and 4.2 mL of triethylamine and the resulting solution stirred for 10 min. The reaction mixture was poured into aqueous $NaHCO_3$, and the organic layer was separated, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 10:1) to give the desired triflate **73** (2.2 g, 93%) as a colorless oil: $^1$H NMR ($CDCl_3$) δ 2.9 (dd, 1 H, *J* = 10, 16 Hz, 2-C(H)*H*), 3.20 (ddd, 1 H, *J* = 2, 5.5, 16 Hz, 2-C(H)*H*), 3.65 (m, 1 H, 3-C*H*), 4.05 (br t, 1 H, *J* = 10 Hz, 4-C(H)*H*), 4.50 (ddd, 1 H, *J* = 2, 4, 10 Hz, 4C(H)H), 6.85 (d, 1 H, *J* = 2 Hz, 9-C*H*), 6.9 (d, 1 H, *J* = 2 Hz, 6-C*H*), 7.35 (m, 3 H, S-Ph), 7.5 (m, 2 H, S-Ph), 7.6 (d, 1 H, *J* = 2 Hz, 8-C*H*); $^{13}$C NMR ($CDCl_3$) δ 30.9 ($CH_2$), 39.9 (CH), 69.4 ($CH_2$), 104.5 (CH), 113.7 (Q), 118.3 (CH), 118.8 ($CF_3$, *J* = 319 Hz), 119.8 (CH), 127.7 (Q), 128.0 (CH), 129.2 (CH), 132.4 (Q), 132.8 (CH), 145.2 (Q), 145.3 (CH), 146.9 (Q); mass spectrum, *m/e* (relative intensity) 430 M$^+$ (55), 299 (65), 187 (100), 123 (45); *m/e* calcd for $C_{18}H_{13}S_2O_5F_3$ 430.0157, measd 429.9741.

**3-(Phenylthio)-(2,3,4*H*)-furo[2,3-*h*]-1-benzopyran (74).** To a mixture of 6-hydroxy-3-(phenylthio)-[(2,3,4*H*)-furo[2,3-*h*][1]benzopyran (**73**; 2.0 g, 4.6 mmol), tri-*n*-butylamine (5.4 mL, 22.6 mmol), bis(triphenylphosphine)palladium acetate (69.6 mg, 0.09 mmol) and DMF (7.0 mL), was added 99% formic acid (0.4 mL, 10.0 mmol).[31,32] The mixture was deoxygenated by the freeze–thaw method (−196 to 25 °C, 3 cycles) and stirred at 70 °C for 2.5 h under argon. Ethyl acetate and water were added, and the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 10:1.2) to give 1.159 g (89%) of 3-(phenylthio)-(2,3,4*H*)-furo[2,3*h*]-1-benzopyran (**74**) as a colorless oil: $^1$H NMR ($CDCl_3$) δ 2.90 (dd, 1 H, *J* = 10, 16 Hz, 2-CH)*H*), 3.20 (ddd, 1 H, *J* = 5.5, 2.0, 1.6 Hz, 2-(H)*H*), 3.65 (m, 1 H, 3-C*H*), 4.00 (br t, 1 H, *J* = 10 Hz, 4-C(H)*H*), 4.45 (ddd, 1 H, *J* = 10, 4, 2 Hz, 4 C(H)*H*), 6.78 (d, 1 H, *J* = 2 Hz, 9-CH), 6.92 (dd, 1 H, *J* = 2, 8 Hz, 5-CH), 7.05 (dd, 1 H, *J* = 8, 2 Hz, 6-CH), 7.30 (m, 3 H, S-Ph), 7.50 (m, 3 H, S-Ph, 8-CH); $^{13}$C NMR ($CDCl_3$) δ 31.0 ($CH_2$), 40.4 (CH), 69.2 ($CH_2$), 103.6 (CH), 104.4 (CH), 112.9 (Q), 116.9 (Q), 125.5 (CH), 127.5 (CH), 129.0 (CH) 132.3 (CH), 133.0 (Q), 143.8 (CH), 147.1 (Q), 155.0 (Q); IR ($CH_2Cl_2$) (thin film) 3400 m, 1600 s, 1080 s, 1060 m cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 282 M$^+$ (100), 262 (15), 173 (78), 159 (25), 145 (23); *m/e* calcd for $C_{17}H_{14}SO_2$ 282.0715, measd 282.0700.

**(2*H*)-Furo[2,3-*h*]-1-benzopyran (75).** A solution of 3-(phenylthio)-(2,3,4*H*)-furo[2,3-*h*]-1-benzopyran (**74**); 1.69 g, 5.7 mmol) in 120 mL of a 1:1 mixture of $CH_2Cl_2$ and toluene was slurried with 2.0 g of powdered anhydrous $K_2CO_3$, and cooled to −78 °C, and treated with 1.28 g of MCPBA (7.4 mmol) as a solution in 10 mL of $CH_2Cl_2$. The reaction mixture was allowed to warm to room temperature, and the $CH_2Cl_2$ was removed by distillation. After the addition of 40 mL of toluene, the resulting solution was heated at reflux for 7 h. The reaction mixture was filtered through a bed of Celite, stripped of volatiles, and chromatographed (silica gel, 10:1 hexane/EtOAc) to provide 0.785 g (80%) of the pyran **75** as a colorless oil: $^1$H NMR ($CDCl_3$) δ 4.92 (dd, 2 H, *J* = 3.4, 1.8 Hz, 2-C*H*$_2$), 5.67 (dt, 1 H, *J* = 9.8, 3.5 Hz, 3-C*H*), 6.49 (dt, 1 H, *J* = 8.2, 1.6 Hz, 4-C*H*), 6.77 (d, 1 H, *J* = 2.0 Hz, 9-C*H*), 6.90 (d, 1 H, *J* = 8.0 Hz, 5-C*H*), 7.00 (d, 1 H, *J* = 8.0 Hz, 6-C*H*), 7.49 (d, 1 H, *J* = 2.0 Hz, 8-C*H*); $^{13}$C NMR ($CDCl_3$) δ 65.7 ($CH_2$), 103.6 (CH), 104.3 (CH), 115.8 (Q), 116.7 (Q), 118.6 (CH), 123.2 (CH), 124.9 (CH), 144.2 (CH), 147.5 (Q), 156.4 (Q); IR ($CH_2Cl_3$) (thin film) 1720 s, 1580 s, 1020 m, cm$^{-1}$; mass spectrum, *m/e* (relative intensity: 172 M$^+$ (95), 144 (10), 115 (35), 85 (100); *m/e* calcd for $C_{11}H_8O_2$ 171.0446, measd 171.0439.

**2-Oxo-(2*H*)-furo[2,3-*h*]-1-benzopyran [Angelicin (2)].** To a solution of 181 mg (1.05 mmol) of **75** and 685 mg (1.84 mmol) of PDC in 10 mL of $CH_2Cl_2$ were added 460 mg of freshly activated powdered 3-Å molecular sieves and 100 μL of anhydrous acetic acid at room temperature.[28] The reaction was stirred for 2 h and then filtered through Celite, and the reaction flask was rinsed with ethyl acetate. A small amount of silica gel was added to the filtrate, and the solvent was then evaporated. The residue was chromatographed (silica gel, 1:10 EtOAc/hexane to 100% EtOAc) to provide a 50% yield of angelicin (**2**; 98 mg): $^1$H NMR ($CDCl_3$) δ 6.38 (d, 1 H, *J* = 9.5 Hz, 4-C*H*), 7.11 (d, 1 H, *J* = 2.0 Hz, 9-C*H*), 7.36 (d, 1 H, *J* = 8.5 Hz, 5-C*H*), 7.40 (d, 1 H, *J* = 8.5 Hz, 6-C*H*), 7.67 (d, 1 H, *J* = 2.0 Hz, 8-C*H*), 7.79 (d, 1 H, *J* = 9.5 Hz, 3-C*H*); $^{13}$C NMR ($CDCl_3$) δ 104.1 (CH), 108.7 (CH), 113.5 (Q), 114.1 (CH), 116.8 (Q), 123.8 (CH), 144.5 (CH), 145.8 (CH), 148.4 (Q), 157.3 (Q), 160.8 (Q); IR ($CH_2Cl_2$) (thin film) 3400 m, 1720 s, 1628 s, 1581 m; mass spectrum, *m/e* (relative intensity) 186 M$^+$ (65), 158 (100), 102 (30); *m/e* calcd for $C_{11}H_6O_3$ 186.0317, measd 186.0309; mp 137–137.5

°C. The synthetic angelicin had an $R_f$ value and $^1H$ and $^{13}C$ NMR spectra identical with those of a natural sample kindly provided by Professor Berenbaum. A mixed melting point was found to be within 0.5 °C of the individual samples.

**Acknowledgment.** This work was supported by a grant from the National Science Foundation (CHE-8517103). We thank the Dow Chemical Co. for a predoctoral fellowship (J.S.M.). The NMR instruements used were funded in part by the NSF Chemical Instrumentation Program and by the NCI via the University of Chicago Research Center (CA 14599).

# Total Synthesis of Octosyl Acid A. Intramolecular Williamson Reaction via a Cyclic Stannylene Derivative

**Samuel J. Danishefsky,*,† Randall Hungate,† and Gayle Schulte‡**

*Contribution from the Department of Chemistry and Yale Chemical Instrumentation Center, Yale University, New Haven, Connecticut 06511.* *Received December 21, 1987*

**Abstract:** The total synthesis of the title compound has been achieved. The key features involved (i) the construction of a carbon-linked furanoside–pyranoside by a cyclocondensation reaction of compound **8**, (ii) the use of the pyran matrix to elaborate the required stereochemistry at carbon 7′ of a nucleoside (see compound **34**), and (iii) cyclization via a 2′,3′-stannylene derivative (see transformation **35** to **36**).

**Background and Synthetic Plan.** One of the primary concerns of our laboratory since 1984 has been the development of totally synthetic routes to a class of compounds known as complex or "higher" monosaccharides (**1**). Elsewhere, we have catalogued this interesting group of saccharides and summarized some of the salient points of interest concerning their biological activity.[1] In this presentation, we provide a full account of the synthesis of a member of this family, i.e., octosyl acid A.[2a-c]

The octosyl acids were isolated from *Streptomyces cacaoi*.[3] They are part of a broader group of polyoxin antifungal nucleosides.[4] It was the novel chemical structures of the octosyl acids that first engaged our attentions. A key element of our proposal for a synthesis involved the challenge of chirality extension from carbohydrate matrices.[5] Moreover, the novel biological profile of a congener of octosyl acid A (**1**) (Figure 1), namely, the modified nucleoside **2**, served to augment interest in achieving synthetic progress in the area. Semisynthetic **2** inhibits the action of cyclic AMP phosphodiesterases from a variety of animal tissues. It is possible that the phosphodiesterase enzyme recognizes compound **2** as a "carba" version of 3′,5′-cyclic nucleotides [cf. cyclic AMP, (**3**)].[6a-c]

Our approach called for the use of the aldehyde **5**, derivable from ribose,[7] as our starting material. A total synthesis of racemic **5** from a sequence that started with formaldehyde and diene **4** has been achieved.[8a,b] This demonstration sufficed to establish *in principle* a fully synthetic route to goal systems derived from **5**. As a practical matter, the material derived from naturally occurring D-ribose served as our starting material.

The strategy called for elongation of **5** to reach, eventually, a system of the type **6** (Figure 2). Examination of conformer **6c** (c = chair) suggests the possibility of displacement of the OL (leaving) from $C_{7'}$ by some nucleophilic version of a $C_{3'}$ hydroxyl function. Of course, in our plan inversion of configuration at $C_{7'}$ was anticipated. Accordingly, access to the $C_{5'}$(R), $C_{7'}$(R) diastereomer would be necessary.

While suggestive of the possibilities for establishing the trans-fused pyranofuran system, conformational figure **6c** shows that *for cyclization through a chairlike transition state to occur, the OL (leaving) and OP (protected alcohol) functions at $C_{7'}$ and $C_{5'}$ respectively, must be in a pre-1,3-diaxial state.* There was little in the way of precedent to deal with the feasibility of such a reaction.

Continuing in the retrosynthetic vein, it was presumed that reduction of the keto group of the dihydropyrone moiety in compound **7** would afford the equatorial alcohol shown in **8**. Excision of $C_1$ fragment (carbon 9′) from the system with appropriate functional group management might then lead to the required series **6**.

Given this recognition, a viable strategy presented itself. Compound **7** could itself be synthesized in one step from a Lewis acid catalyzed cyclocondensation reaction of diene **4a** with aldehyde **5**. Crucial to the success of the enterprise was the facial control that would be exerted by aldehyde **5** in such a cyclocondensation process.

It was hoped that the reactive conformer of **5** would be the one depicted. Elsewhere[9,10] we have reported that this is in fact the case and that cyclocondensation of this aldehyde with dienes **4a** or **4b** under Lewis acid catalysis occurs in the indicated $\alpha$ sense (i.e., anti to the ribosyl framework) with high stereoselectivity. This type of reaction, which provides a route to carbon-linked disaccharides, was extremely useful in providing access to the higher monosaccharides.

† Department of Chemistry.
‡ Yale Chemical Instrumentation Center.

(1) Danishefsky, S.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.
(2) (a) For a preliminary account of a portion of this work, see: Danishefsky, S.; Hungate, R. *J. Am. Chem. Soc.* **1986**, *108*, 2486. (b) For the only other synthesis of octosyl acid, which appeared concurrently with our submission, see: Hanessian, S.; Kloss, J.; Sugawara, T. *Ibid.* **1986**, *108*, 2758.
(3) Isono, K.; Crain, P. F.; McCloskey, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 943, and references therein.
(4) (a) Sakate, K.; Sakurai, A.; Tumura, S. *Agric. Biol. Chem.* **1973**, *37*, 694. (b) Sakata, K.; Sakurai, A.; Tamura, S. *Ibid.* **1974**, *38*, 1983. (c) Sakata, K.; Sakurai, A.; Tumura, S. *Tetrahedron Lett.* **1974**, *15*, 4327. (d) Sakata, K.; Sakurai, A.; Tamura, S. *Ibid.* **1975**, *16*, 3191.
(5) Danishefsky, S.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. *Tetrahedron* **1986**, *42*, 2809.
(6) (a) Azuma, I.; Isono, K. *Chem. Pharm. Bull.* **1977**, *25*, 3347. (b) Bloch, A. *Biochem. Biophys. Res. Commun.* **1975**, *64*, 210. (c) Suhadolnik, R. J. *Nucleosides as Biological Probes*; Wiley: New York, 1979; p 295.
(7) Jones, G. H.; Moffatt, J. G. *Methods Carbohydr. Chem.* **1979**, *7*, 315.
(8) (a) Webb, R. R.; Danishefsky, S. *J. Org. Chem.* **1984**, *49*, 1955. (b) The synthesis of racemic **5** was achieved by J. Y. Lee of Yale University.
(9) Danishefsky, S.; Maring, C.; Barbachyn, M.; Seemuller, B. *J. Org. Chem.* **1984**, *49*, 4564.
(10) Danishefsky, S.; Barbachyn, M. *J. Am. Chem. Soc.* **1985**, *107*, 7761.

0002-7863/88/1510-7434$01.50/0 