same results are obtained from the controlled-potential reductive electrolysis of H_2O_2 in pyridine.[114] Recent experiments[19] confirm that O_2^- can also be produced in good yield through reduction of O_2 by the dianions of either *p*-hydroquinone (H_2Q) or ascorbic acid in aprotic media (eq 39).

$$Q^{2-} + O_2 \rightarrow O_2^- + Q^-\cdot \qquad (39)$$

How Super?

Superoxide clearly is not "superreactive" in the sense that many investigators have assumed. It is not a reactive electron-transfer oxidant of organic or inorganic substrates unless the resulting peroxide anion is somehow stabilized, for example, by coordination to a metal. Superoxide will oxidize certain basic reductants such as reduced flavins by a hydrogen atom transfer mechanism, but such substrates are not common.

Although superoxide contains an odd number of electrons, its reactivity does not resemble that of typical organic radicals. The principal example of such reactivity for superoxide is the formation of a superoxide adduct with reduced methylviologen via a radical–radical coupling mechanism. Under aprotic conditions, O_2^- is a strong nucleophile, but such reactivity is not observed in aqueous solutions. In this property, superoxide resembles small anions such as fluoride, which are powerful nucleophiles only in non-hydrogen-bonding media. Superoxide also can act as a ligand to metal ions and complexes. The most dominant characteristic of O_2^-, by far, is its ability to act as a strong Brønsted base. It readily removes protons from water and weakly acidic substrates such as 1-butanol, and in so doing it rapidly disproportionates to become a source of peroxide and dioxygen. Because these products of the disproportionation of superoxide are strong oxidants, addition of superoxide to a protic substrate frequently results in overall oxidation; however, the true oxidant is H_2O_2 or O_2 rather than O_2^-. Superoxide also is a moderate one-electron reducing agent (about as effective as dithionite). When O_2^- is oxidized by strong one-electron oxidants with closed coordination spheres, singlet oxygen ($^1O_2$) is formed via a singlet transition state.

We conclude that the "super" in superoxide should not be taken to imply exceptional reactivity for that species based on the chemistry that is now known. Nevertheless, superoxide has been and will continue to be an interesting species for study because of the multiplicity of its chemical reactions and because of its importance as an intermediate in reactions that involve dioxygen and hydrogen peroxide.

The material of this Account results primarily from the efforts of graduate students, postdoctoral associates, and colleagues as indicated by the citations. Their contributions are gratefully acknowledged, as is the support of the National Science Foundation under Grant No. CHE79-22040 (D.T.S.) and CHE78-08122 (J.S.V.) and the U.S. Public Health Service, National Institutes of Health, Grant No. GM-22761 (D.T.S.) and GM-28222 (J.S.V.).

(113) Roberts, J. L., Jr.; Morrison, M. M.; Sawyer, D. T. *J. Am. Chem. Soc.* **1978**, *100*, 329.
(114) Morrison, M. M.; Roberts, J. L., Jr.; Sawyer, D. T. *Inorg. Chem.* **1979**, *18*, 1971.

Siloxy Dienes in Total Synthesis†

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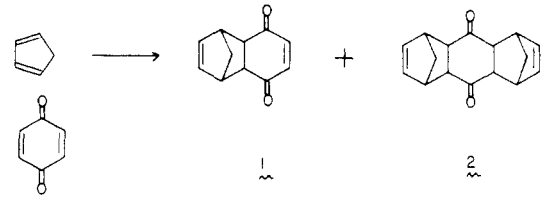
Early research around the turn of this century identified an unusual reaction, whereby certain "conjugated" dienes, upon thermolysis, undergo dimerization.[1] Albrecht[2] described an investigation into the reaction of cyclopentadiene with *p*-benzoquinone and noted the formation of 1:1 as well as 2:1 (diene:quinone) products. A major step forward in this field was achieved in 1928 by Diels and Alder who determined the structures of Albrecht's adducts to be of the type **1** and **2**.[3] Moreover, in a classic series of logical and comprehensive investigations, they demonstrated the generality and elucidated the basic regiochemical and stereochemical principles of this reaction which now



bears their names. The synthetic applications of the Diels–Alder reaction, as well as the very subtle mechanistic issues which it raises, are of such import that the continuing attention it has received is entirely justified.

Understandably, the Diels–Alder reaction has been extensively discussed in the review literature.[4] Al-

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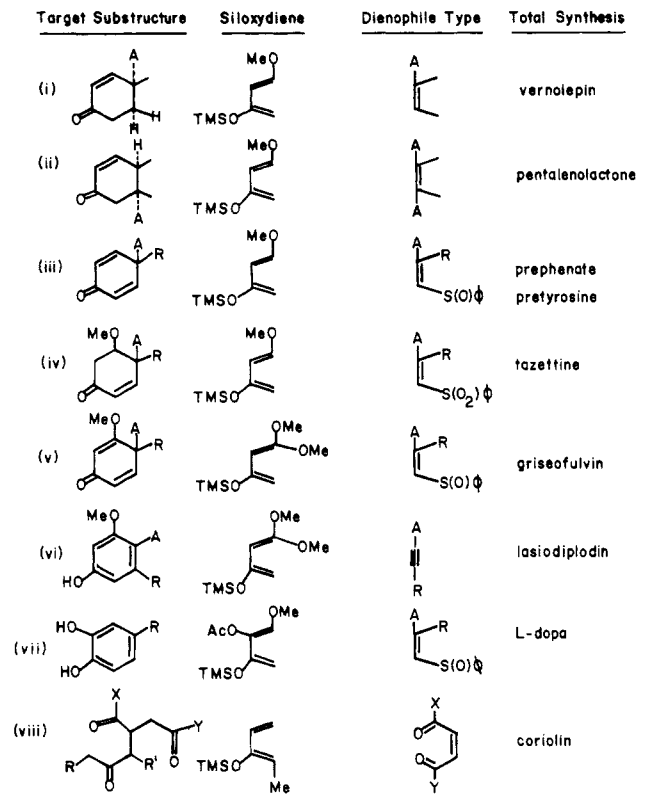
† I am pleased to dedicate this Account to Professor Gilbert Stork on the occasion of his recent receipt of the Roussel, Nichols, and Cope Awards.

(1) For an example, see: Wieland, H. *Chem. Ber.* **1906**, *39*, 1492.
(2) Albrecht, W. *Ann.* **1906**, *348*, 31.
(3) Diels, O; Alder, K. *Ann.* **1928**, *460*, 98.

0001-4842/81/0114-0400$01.25/0

Chart I



though there is a continuing need to update such secondary source material, this Account is not offered in that spirit. Here, we attempt to provide a description of our personal involvement in the Diels–Alder reaction. These investigations arose from our interest in the total synthesis of natural products. The reader should not read into this paper an Account of the realization of a clearly formulated plan by which the role of siloxy dienes in total synthesis was envisioned. In practice, what occurred was rather less dramatic. Each successful application of the method generated new feasibility studies. As a result of these cumulative experiences, it is now clear that Diels–Alder reactions using siloxy dienes can be a major source of simplification in total synthesis.

In this Account, we shall demonstrate how this extended Diels–Alder methodology was crucial to our successes[5] in a variety of adventures in total synthesis. The emphasis will not be on recapitulation of the total syntheses; these are all duly recorded in the primary literature. What we hope to convey in the Account is in each case, the emergence of a synthetic problem and the realization of a solution via the Diels–Alder reactions of various siloxy dienes with suitable dienophiles. In some cases, it was necessary to develop a new type of dienophile whose properties might mesh with the siloxy diene to provide our solution.

To help guide the reader through this Account, we offer the following synopsis of our findings (Chart I).

There follows a series of discussions in which these problems and solutions are provided in the context of the natural products syntheses in which they were investigated. We include enough information for each synthesis to provide the reader with a sense of the terrain in which our explorations were conducted.

Discussion

The Use of Diene 10. Applications to Vernolepin, Pentalenolactone, and Prephenate. In furtherance of a proposed synthesis of vernolepin[6] (**3**), we sought rapid access to systems of the type **4**. Given the cis junction, a possible "Diels–Alder connection" was considered. It was hypothesized that **4** might result from the unravelling of **5** which might have arisen from a Diels–Alder reaction of **6** + **7**. (Compound **6** itself could be fashioned from a Diels–Alder reaction of butadiene and methyl propiolate.) The diene would have to be readily available, since this reaction was to be but the first step in a long journey of uncertain course. Moreover, it should be sufficiently reactive to overcome the predictably[7a] serious dienophilic sluggishenss of **6**.

From a reactivity standpoint, a 1,3-dialkoxybutadiene such as **8** appeared to be of interest. The synergism of the two oxygens could well provide the margin of dienic activity necessary for reaction with **6**. Indeed, compound **8** was known, and a single Diels–Alder reaction (with methyl glyoxylate) had been described.[7b] However, the published preparation of **8** involves the acid-catalyzed cracking of the bis acetal of formylacetone. Since **8** is itself unstable to acid, its synthesis in this way was far from a simple matter. Several attempts on our part to prepare **8** in bulk were unsuccessful.

The emergence of silyl enol ethers in organic synthesis was largely a consequence of the ground-breaking research of Stork and Hudrlik.[8] These workers recognized the pertinence of such systems to the generation of site-specific enolates. New protocols for the preparation of silyl enol ethers and new developments in the attainment of kinetic and thermodynamic control in the preparation of such systems from nonsymmetric precursors were described by House.[9] Another major event was the discovery of the Mukaiyama school[10] that, under catalysis by titanium tetrachloride, silyl enol ethers could engage in a variety of processes (aldol condensations, Michael reactions, etc.) heretofore generally associated with enolates.

Given the fact that the conversion of ketones to their silyl enol ether derivatives is much simpler[8,9] than the corresponding synthesis of enol ethers, a study of the usefulness of such systems in cycloaddition reactions seemed to be warranted. In fact, at the inception of our study there were two recorded examples of very simple Diels–Alder reactions of the parent 1- and 2-[(trimethylsilyl)oxy]-1,3-butadiene.[11]

(4) Wollweber, H. "Diels–Alder reakton"; Verlag, G. T., Stuttgart, **1972**, and references therein.

(5) The reader will, of course, recognize that for every positive result recorded here there were encountered many adversities. A more balanced rendering of our experiences can be obtained from the full papers describing the individual syntheses.

(6) Danishefsky, S.; Kitahara, T.; Schuda, P. F.; Etherredge, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3028. Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *Ibid.* **1976**, *98*, 6715. Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etherredge, S. J. *Ibid.* **1977**, *99*, 6066. For the first synthesis of vernolepin, see: Grieco, P. A.f Nishizawa, M.; Burke, S. D.; Marinovic, M. *Ibid.* **1976**, *98*, 1612. Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, M. *Ibid.* **1977**, *99*, 5773.

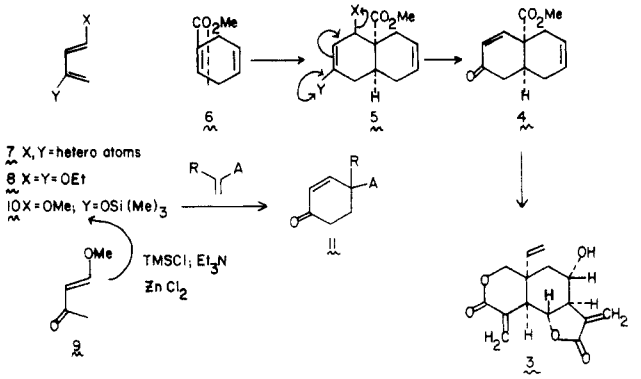
(7) (a) Cf: Kronenthal, R. L.; Becker, E. I. *J. Am. Chem. Soc.* **1977**, *79*, 1095. (b) Shavrygena, O.; Makin, Sn. M. *Khim. Farm. Zh.* **1969**, *3*, 17.

(8) Stork, G.; Hudrlik, P. *J. Am. Chem. Soc.* **1968**, *90*, 4462.

(9) (a) House, H. O.; Dzuba, L.; Gall, M.; Olmstead, H. J. *J. Org. Chem.* **1969**, *34*, 2324. House, H. O.; Gall, M.; Olmstead, H. D. *Ibid.* **1971**, *36*, 2361.

(10) Mukaiyama, T.; Banno, K.; Narasaka, K. J. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

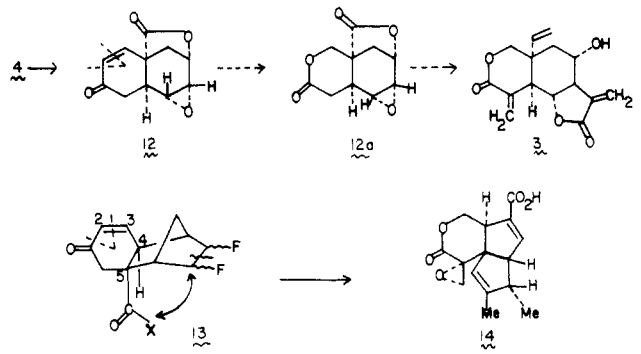
Happily, enol silylation of the readily available methoxyenone **9** with trimethylchlorosilane using triethylamine and zinc chloride afforded a 60–70% yield of **10**.[12,13] Compound **10** undergoes Diels–Alder reactions with a wide variety of dienophiles to give products of the type **11**. Included among these successful re-



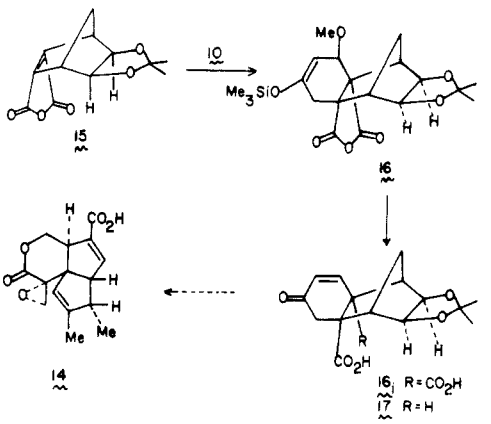
actions of **10** was that with dienophile **6** to give a 60% yield of **4**. A route to vernolepin was available.[6]

A key element of this total synthesis was the convertability of cyclohexenones to δ-lactones. The groundwork for such a transformation had been carefully secured in model systems.[14] In the vernolepin synthesis it was utilized in the conversion of **12** → **12a**.

In our studies of the total synthesis of the microbially derived tumor inhibitor, pentalenolactone (**14**), some new and interesting issues were confronted.[15,16] If we were to exploit our enone → lactone capability, there would be required access to a 5-acylcyclohexenone such as **13**. The Diels–Alder reaction using siloxy diene **10** leads to a 4-acylcyclohexenone (cf. **11** and **12**).

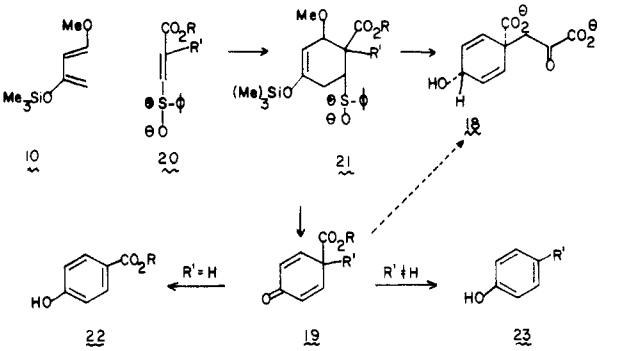


A pleasing solution to this problem presented itself. We demonstrated the solution in the context of the synthesis **15** + **10** → **16** → **17**. By the use of symmetrical anhydride **15**, the regiochemical issue is avoided. Presumably the action of barium hydroxide ion on **16** leads, at some stage, to **16$_i$**, whereupon the extraneous carboxyl group, now appearing as a vinylogous β-keto acid, sulfur decarboxylation. Ketonization in the expected way leads to **17** in which all of the backbone



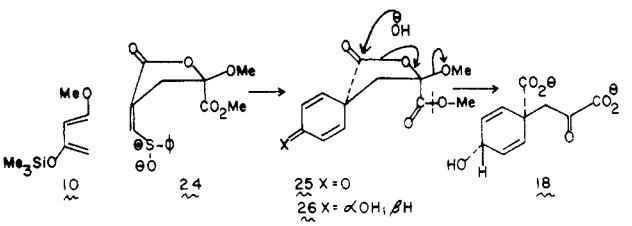
stereochemistry has been arranged. Eventually the total synthesis of **14** was achieved.

Our next objective was the highly labile biosynthetic intermediate, prephenic acid (**18**).[17,18] In this connec-



tion, access to a 4,4-disubstituted cyclohexadienone of the general type **19** would be helpful. For this purpose we developed a new type of dienophile, **20**, wherein the phenylsulfinyl function activates the double bond toward Diels–Alder reactions, yet does not compete with the ester group for regiochemical control. Elimination of phenylsulfenate at some stage of the unravelling of adduct **21** leads to **19**. From **19** one can proceed to two different kinds of phenols. For the case R′ = H, the product is phenol **22**. Alternatively, the R′ substituent can be retained and the acyl function eliminated, leading to **23**. Both of these formulations were reduced to practice in our studies[19,20] (vide infra).

For the synthesis of prephenate, we used compound **24** as the Diels–Alder dienophile. Difficulty manageable functionally was contained in a methoxy lactone arrangement. Cycloaddition of **24** with **10** gave, upon workup, the dienone **25**. As a consequence of its in-



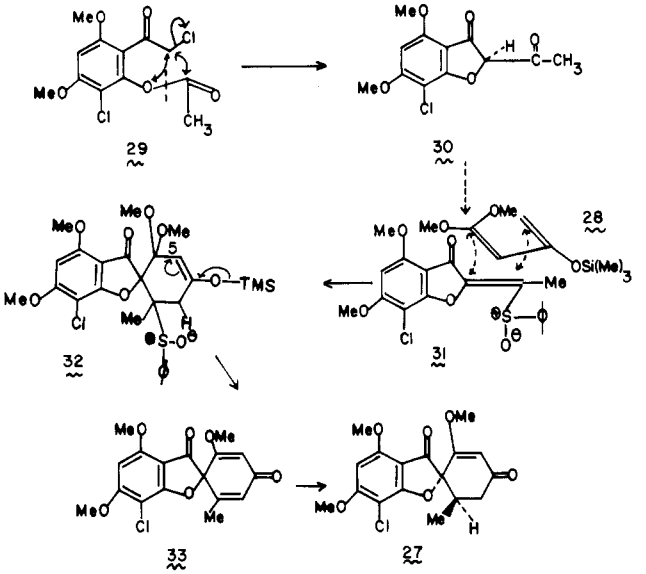
stability to chromatographic purification, the isolated

(11) Cazeau, P.; Frainnet, E. F. *Bull. Chim. Soc. Fr.* **1972**, 1658.
(12) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.
(13) Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. *J. Am. Chem. Soc.* **1979**, *101*, 6996.
(14) Danishefsky, S.; Schuda, P.; Kato, K. *J. Org. Chem.* **1976**, *41*, 1081.
(15) Danishefsky, S.; Hirama, M.; Gombatz, K.; Harayama, T.; Berman, E.; Schuda, P. *J. Am. Chem.* **1978**, *100*, 6536.
(16) Danishefsky, S.; Hirama, M.; Gombatz, K.; Berman, E.; Schuda, P. F. *J. Am. Chem. Soc.* **1979**, *101*, 7020.
(17) Danishefsky, S.; Hirama, M. *J. Am. Chem. Soc.* **1977**, *23*, 7740.
(18) Danishefsky, S.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 7013.
(19) Danishefsky, S.; Singh, R. K.; Harayama, T. *J. Am. Chem. Soc.* **1977**, *99*, 5810.
(20) Danishefsky, S.; Harayama, T.; Singh, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 7008.

yield of crystalline **25** was only 31%. Reduction (nonstereospecific) of **25** with 9-BBN gave **26**. Treatment of the latter with alkali afforded, for the first time, homogeneous disodium perphenate (18).

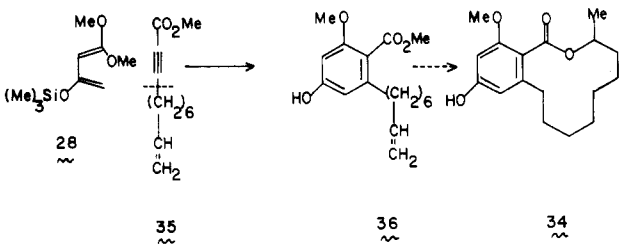
The Use of Diene 29. Applications to Griseofulvin, Lasiodiplodin, and Tazettine. Our expeditious total synthesis of griseofulvin (**27**) involved further evolution of these concepts. In this case we exploited the 1,1,3-trioxygenated diene **28**. The chemistry of the diene had been previously investigated.[21,22] It was shown that at least in its Diels–Alder reactions with simple dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate, **28** is more reactive then **10**.

The 2-acylcoumaranone **30** was obtained smoothly from the action of sodium hydride on the *o*-chloroacetyl phenolic acetate, **29**. Compound **30** could be converted



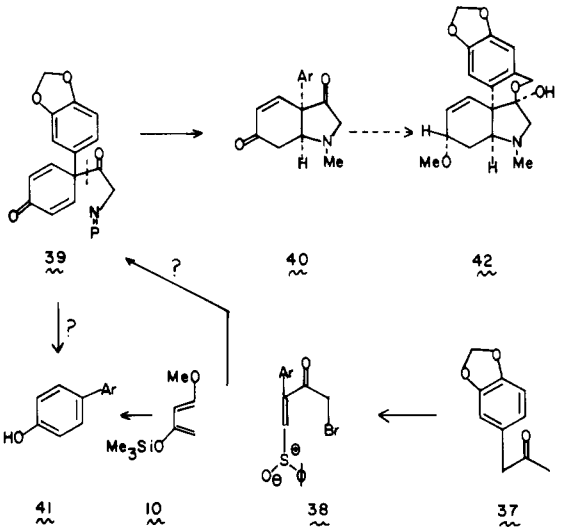
into dienophile **31** by application of standard methods. Cycloaddition of **31** with **28** afforded, on workup, *dl*-dehydrogriseofulvin (**33**) which upon catalylic reduction afforded *dl*-griseofulvin (**27**).[23,24]

Diels–Alder reactions of **28** with acetylenic dienophiles provide a new and rapid route to aromatic rings of otherwise difficulty accessible functionality patterns. This possibility was exploited in our synthesis of the antibiotic lasiodiplodin (**34**).[25] The dienophile **35** was



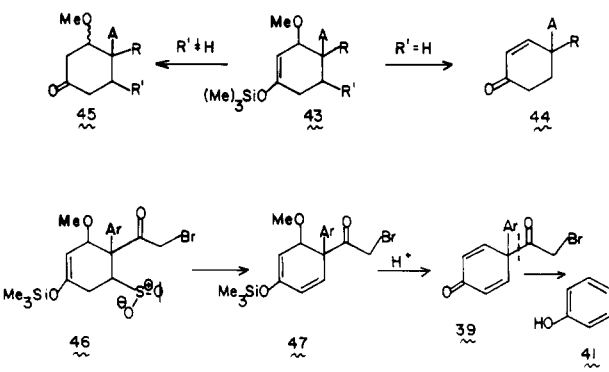
obtained by alkylation of the dianion of propiolic acid with 8-bromo-1-octene followed by esterification. Cycloaddition of **35** with **28** gave, in one step, the differentiated resorcinol, **36**.

In our studies directed to the total synthesis of the alkaloid tazettine (**42**)[26] a different sort of problem emerged during the experimentation. Our original proposal for the total synthesis envisioned the scenario shown below. A central feature of the plan was the cyclization reaction **39** → **40**, wherein N=P was to ei-



ther a protected version of a methylamino group or a precursor thereof. Following the logic of the prephenate synthesis, it was anticipated that **39** would arise from a Diels–Alder cycloaddition of dienophile **38** with diene **10**. Indeed, compound **38** (R = CH_2Br) was preparable by standard reactions, starting with **37**. Unfortunately, several efforts to obtain **39** (NP = bromide) from **10** and **38** were uniformly unsuccessful. In each case there was isolated the biphenyl derivative **41** (Ar = 3,4-(methylenedioxy)phenyl). Thus it seemed that the Diels–Alder, elimination, and hydrolysis steps leading to **39** were, in fact, occurring. However, in our hands and under our treatments, compound **39** (unlike compound **25**) was not surviving its formation. Apparently the combination of the 4-aryl and 4-acyl functions, undermines the stability of the cyclohexadienone to the point where it is no longer viable relative to aromatization.

We had noted[12,13] that the hydrolytic fate of Diels–Alder adducts of the type **43** was much influenced by the nature of the substituent R′. In the case of R′ = H, formation of **44** could be expected. When R′ is a

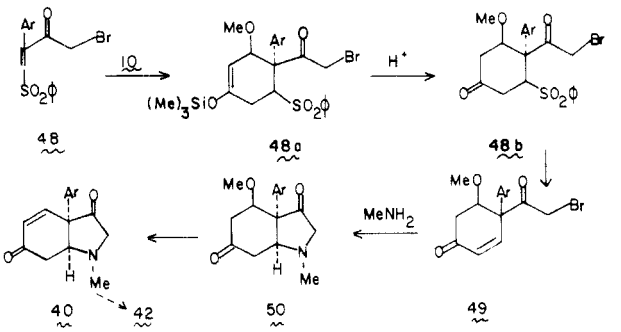


substituent (or ring residue), hydrolysis is more likely to result in retention of the methoxyl function (**45**).[27]

(21) Banvillea, J.; Brassard, P. *J. Chem. Soc., Perkin Trans. 1*, **1976**, 1852.
(22) Danishefsky, S.; Singh, R. K.; Gammill, R. B. *J. Org. Chem.* **1978**, *43*, 379.
(23) For an earlier approach which afforded *dl*-epigriseofulvin; see: Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1978**, *43*, 4604.
(24) Danishefsky, S.; Walker, F. *J. Am. Chem. Soc.* **1979**, *101*, 7018.
(25) Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1979**, *44*, 4716.
(26) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838.

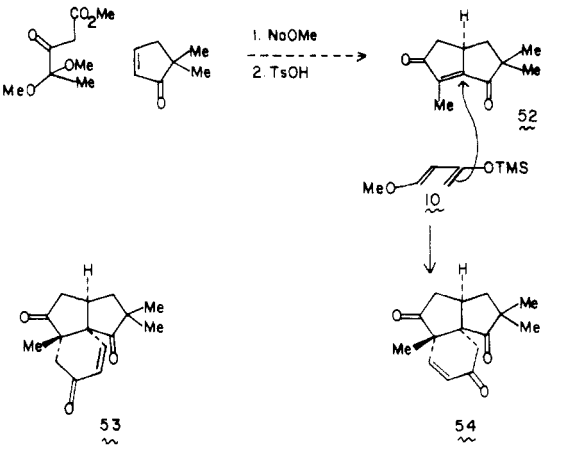
In the case of a dienophile of the type **38** (R = CH_2Br), Diels–Alder reaction with **10** would afford **46**. Under the conditions of the reaction, pyrolytic elimination of the homoallylic sulfoxide would lead to **47** which, upon acidic treatment, would lead to **39**. While ordinarily (cf. the prephenate, griseofulvin, and arogenate syntheses) such a result would have been ideal for our purposes, in the case at hand, **39** appeared to suffer unavoidable decomposition to afford **41**. If this formulation is accepted, the shape of the required response was clear. It was necessary to reach a functional equivalent of **39** which would be sufficiently stable for purposes of isolation and subsequent handling, yet would undergo conversion to **40**.

The solution in practice involved the use of the dienophile **48**. Its Diels–Alder reaction with **10** affords **48a**, wherein the phenylsulfonyl (in contrast to the



phenylsulfinyl) grouping has been retained. Thus, standard acidic treatment afforded **48b**. *It is only after the ketonic group is exposed that the phenylsulfonyl function is lost* via β elimination. There is thus obtained **49** wherein the β-methoxy ketone array provides the needed stabilization against aromatization. Happily, reaction of **49** with methylamine afforded **50**. At this point, the methoxy group can be caused (SiO_2) to suffer β elimination, providing the long-sought **40**. From this compound, a stereoselective route to tazettine (**42**) was realized.

Cycloadditions of Siloxy Dienes 10 and 56 with an Enedione Dienophile. Applications to the Coriolin Problem. Our total synthesis of the complex tumor inhibitor coriolin (**51**) again involved some painful, experimentally imposed, changes of course.[28,29] It was our initial intention to achieve the synthesis of **53** *via* a Diels–Alder reaction of **52** with **10**. Compound **52** was constructed through a new annulation reaction sequence, as shown. In practice, Diels–Alder reaction of **52** with **10** did indeed afford a single tricyclic trione, but its structure was unfortunately the undesired **54**. With hindsight now available to guide our theory, it emerged that, of the two keto groups in enedione **52**, *the one which is β to the bridgehead (i.e., s-trans to the double bond)* was more influential in determining its dienophilicity. This Diels–Alder tendency of **52**[30a]



which may be the consequence of the faborable energetics associated with early rehybridization of the strained bridgehead carbon from the sp^2 to the sp^3 level, was also mirrored in its Michael reactions[30b] with a variety of nucleophiles.

Two solutions presented themselves. One[30a] involved recourse to an alternate type of diene wherein this tendency of **52** could be relied upon to produce the desired result. The elegant research of Trost carried in it an implicit solution to our problem. Thus cycloaddition of **52** with Trost diene **55**[31] followed by hydrolysis, oxidation, and elimination indeed afforded **53**. Given the results of Trost, which clearly indicate that the sulfur is the more potent regiocontrol element in **55** relative to acetoxyl, the observed result, leading to **53**, was also in keeping with dienophilic regiocontrol which was being exercised by the s-*trans* ketone of **52**.

The other approach which we used for the total synthesis[28,29] of coriolin was to take advantage of the aforedescribed tendency of **52**, still within the context of a siloxy diene solution. In this connection, we found it advantageous to use siloxy diene **56**. Careful analysis of literature precedents[32] suggested that in Diels–Alder reactions of a diene such as **56** with enediones *which are electronically closely balanced* the effect of the 1-methyl group could well override the counterdemand exerted by the 2-(trimethylsilyl)oxy function.

In the event, Diels–Alder reaction of **52** with **56** gave an adduct which was, without purification, subjected to the action of phenylselenyl chloride. Oxidative deselenylation afforded directly the enone **57**, wherein the inclusion of the additional C–C bond (see asterisk for emphasis) as part of the Diels–Alder dynamic, was most helpful in the late stages of the synthesis. From **57** a route to coriolin was soon developed.

Siloxy Dienes 10 And 67. Applications to the Synthesis of Optically Pure Amino Acids. Recently,[33] we have successfully completed the total synthesis of pretyrosine ("arogenate", **66**) drawing upon methodology which was developed in connection with several of the aforedescribed pursuits. Pretyrosine is an extremely labile amino acid which is isolated in a variety of microorganisms. Its biosynthesis involves transamination of prephenate, and it is enzymically converted to the crucial aromatic amino acids, tyrosine

(27) For the moment, the stereochemical dependence of this effect has not been established with certainty. It might well be assumed that a cis relationship between the R′ and methoxyl functions might be most influential in avoiding elimination (see mechanistic rationale advanced in ref 13).

(28) (a) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. (b) Danishefsky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, 3439.

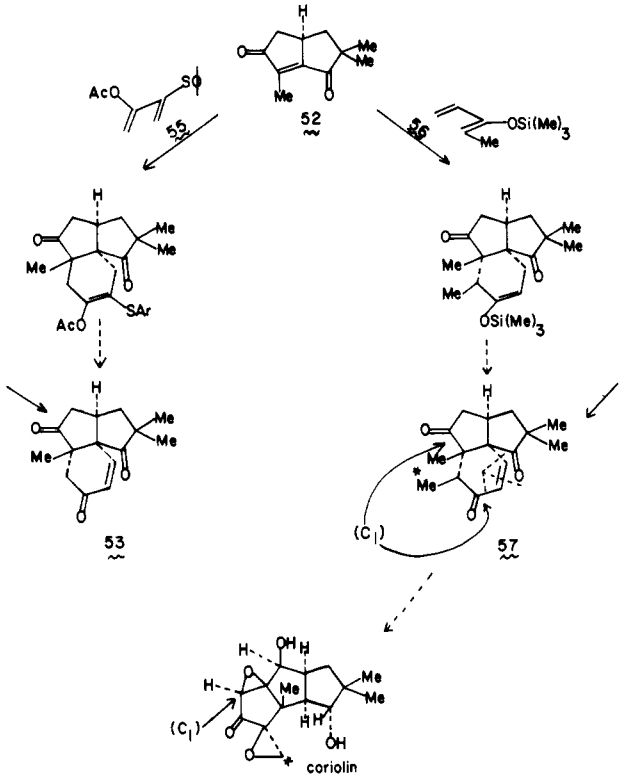
(29) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460.

(30) (a) Danishefsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, 489. (b) Dansihefsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, 485.

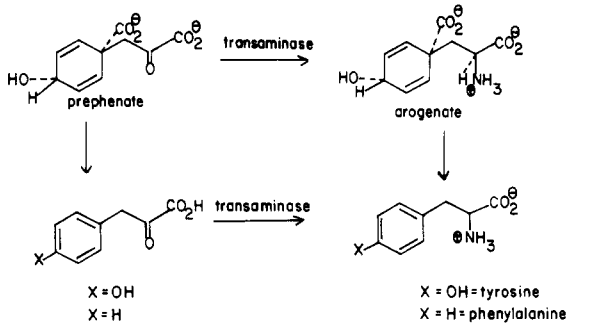
(31) Trost, B. M.; Vladuchick, W. C.; Bridges, A. *J. Am. Chem. Soc.* **1980**, 3548, 3554.

(32) See ref 30a, footnote 14, for a compilation of these cases.

(33) Danishefsky, S.; Morris, J.; Clizbe, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 1602.



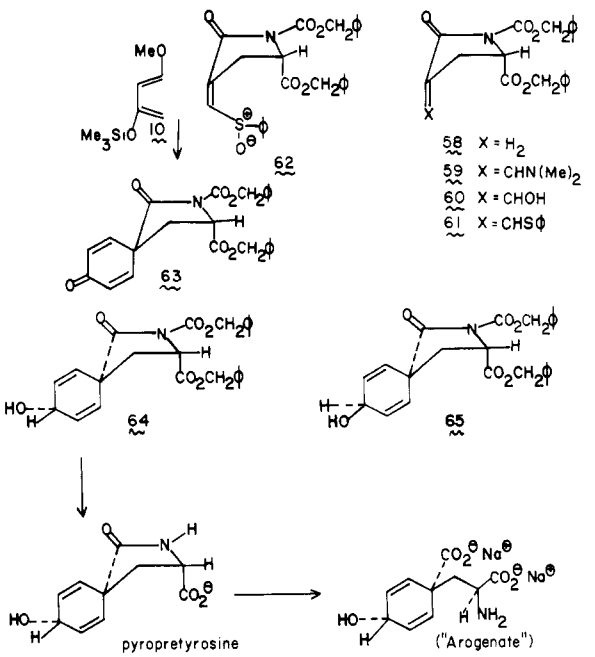
and phenylalanine. Alternatively, in a more well-es-



tablished pathway, the aromatic amino acids arise from transamination of the aryl pyruvates which are generated from prephenate.

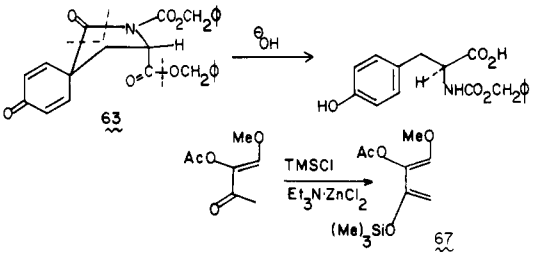
Accordingly, we undertook the assignment of preparing "arogenate" by total synthesis. If our synthetic studies were to have useful implications for biosynthesis, the arogenate which we would furnish must be optically pure. Happily, this additional boundary condition could be realized.

The dienophile **62** was prepared from L-glutamic acid via the previously described[34] pyroglutamate derivative **58**. Reaction of **58** with Bredereck reagent afforded **59** which upon hydrolysis gave the hydroxymethylene derivative **60**. The later was converted (Ph_3P; PhSSPh) to the sulfide **61** and thence, on oxidation, to the optically pure sulfoxide **62**. Cycloaddition of **62** with diene **10** gave a 57% yield of the crystalline dienone **63**. This underwent reduction with DIBAH to give **64** (56% isolated yield) and **65** (24% isolated yield). Under very carefully defined conditions, **64** could be converted by alkaline hydrolysis (NaOH–MeOH, room temperature) first to **66** ("pyropretyrosine") which suffers subsequent ring opening under more stringent (NaOH, ethanol, 70

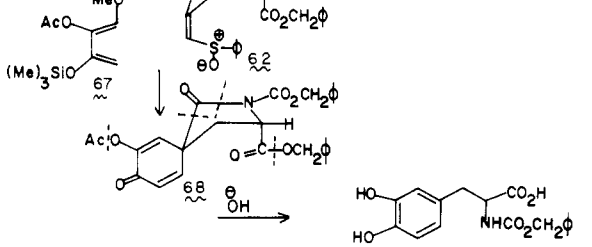


°C) circumstances. After ion-exchange chromatographic purification, there was isolated fully homogeneous disodium pretyrosinate (**67**). The synthetic material was optically pure, as shown by its conversion to L-phenylalanine methyl ester by acidification and esterification (diazomethane). Moreover, the synthetic material suffers enzymic conversion to tyrosine.[35]

With dienophile **62** in hand, a synthesis of the medicinally important amino acid L-Dopa could scarcely be resisted. A key model reaction was the synthesis of *N*-Cbz-tyrosine *via* the reaction of dienone **63** with alkali.[36] For application of this novel type of construction of aromatic rings to the L-Dopa problem, without necessity for post-Diels–Alder oxidations, a new siloxy diene, **67** was synthesized and its chemistry was explored.



Cycloaddition of **62** with **67** affords, after acidic workup, the acetoxy diene **68** (48% yield). Reaction



(34) Danishefsky, S.; Berman, E.; Clizbe, L.; Hirama, M. *J. Am. Chem. Soc.* **1979**, 101, 4385.

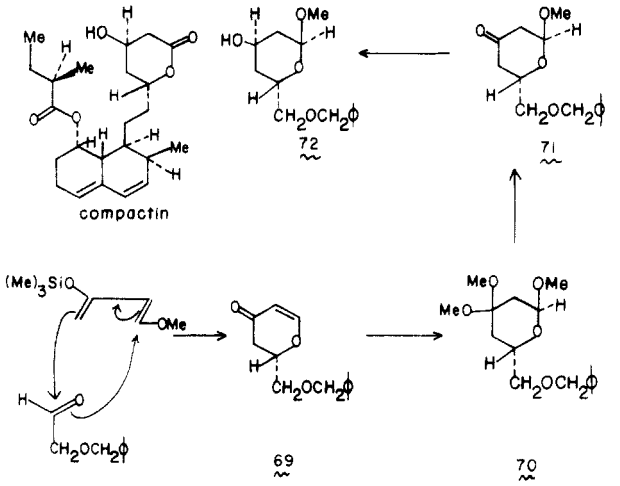
(35) Private communication, Professor L. Zamir, Department of Chemistry, State University of New York at Binghamton.

(36) Danishefsky, S.; Morris, J.; Clizbe, L. A. *Heterocycles* **1981**, *15*, 1205.

of **68** with hydroxide affords L-Dopa as its *N*-Cbz derivative. A variety of other less demanding Diels–Alder reactions of **67** were successfully carried out in higher yield. This diene will clearly be of importance in providing additional functionality to Diels–Alder adducts.[37]

Cyclocondensations of Siloxy Diene 10 with Aldehydes. A New Horizon. Finally, we describe the application of compound **10** to the synthesis of pyranone systems of relevance to carbohydrates.[38] We first became interested in this possibility in connection with a possible route to the pyranone portion of the hypocholestemic agent compactin (**73**).[39] We have already noted that the carbonyl group of a glyoxylate ester functions as a heterodienophile in an apparent Diels–Alder reaction with diene **8**.[7] There were some indications in the literature[40] that the feasibility of using a formyl function as a heterodienophile might well extend beyond the highly activated aldehyde of a glyoxylate.

In the event, cycloaddition of **10** with benzyloxyacetaldehyde under catalysts by zinc chloride occurred at room temperature to afford **69** (85% yield). Mi-



chael-like addition of methanol to **69** was accompanied by ketalization. There was isolated a 75% yield of the trimethoxy compound **70**. Deketalization afforded **71**, which, upon reduction (L-Selectride) followed by acetylation, afforded **72**. Thus a solution to one of the several key stereochemical issues of the compactin problem is in hand.

The possibilities of extending the cycloaddition[41] of various polyoxygenated butadienes with other heterodienophiles to achieve the synthesis of highly functionalized heterocycles are currently being evaluated in our laboratory, and the results are most encouraging.[42]

Conclusion

When we began this program, it was already known that silyl enol ethers could be prepared more readily than the corresponding alkyl enol ethers.[8-10] Our research demonstrated that this ease of preparation extends to multiply oxygenated systems. Furthermore the siloxybutadienes so produced exhibit excellent reactivity with a broad range of electrophilic dienophiles. It would appear that the Diels–Alder reactivity exhibited from the combination of highly "nucleophilic" dienes with highly "electrophilic" dienophiles (cf. **28** + **31** and **10** + **52**) overrides what would otherwise be perceived to be very serious steric encumberances to reaction. We also note the emergence of several new types of dienophiles (the β-phenylsulfinylacrylate[18] and even the aldehyde group[41]) which, in combination with the silyloxy dienes, afford difficultly accessible functionality patterns.

These methodological advances have found application to the total synthesis of structurally diverse and biologically important natural products. In this Account, we have confined ourselves to feasibility demonstrations which arose from our own investigations. More noteworthy is the increasingly widespread use, in other laboratories, of highly functionalized dienes, particularly those bearing silyloxy substituents. It seems clear that siloxy dienes are now staples in the household of organic synthesis.

The research described above was brought to fruition by the planning and experimentation of many postdoctoral and graduate student colleagues. Their intellectural excellence, professionalism, and selflessness will always be an inspiration to me. Support was provided by NIH Grants CA 48408, AI 48702, and HL 48136. Additional assistance from Merck Inc. is gratefully acknowledged.

(37) Craig, T. *Tetrahedron*, in press.
(38) Danishefsky, S.; Kerwin, J. F., Jr. manuscript in preparation.
(39) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165.
(40) Aben, R. W.; Scheeren, H. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3132.
(41) It will be recognized that the term cyclization is used here in a structural rather than mechanistic sense. The pathway for these interesting reactions remains to be delineated.
(42) Kerwin, J. R., Jr.; Kobayashi, S.; Kato, N., unpublished Results.