Intramolecular Cyclohexadienone Annulations of Fischer Carbene Complexes: Model Studies for the Synthesis of Phomactins
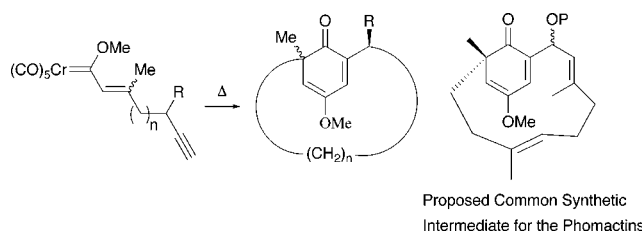
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ABSTRACT

Proposed Common Synthetic
Intermediate for the Phomactins

The intramolecular cyclohexadienone annulation of chromium carbene complexes is examined as a method to provide general access to the Phomactin family of natural products. The importance of the stereochemistry of the carbene complex and the number of carbons in the tether connecting the carbene complex and the alkyne are probed. Additionally, the degree of the 1,4-asymmetric induction is examined.

Since the discovery[1] of the phomactins in the early to mid 1990s, their unusual carbon skeleton combined with attractive bioactivity as PAF antagonists has prompted much interest among synthetic organic chemists.[2–4] The structures of the phomactins share a common bicyclo[9.3.1]pentadecane ring system featuring a highly substituted cyclohexane bearing a quarternary center and a 12-membered macrocycle (Figure 1).

The phomactins and members of the taxol family share a common biosynthetic pathway (Figure 2).[2,5] Cyclization of geranylgeranyl diphosphate gives rise to the verticillenyl carbocation **13**, which can lead to verticilllene **12** by simple

proton loss or to taxadiene **11** via an intramolecular proton transfer and subsequent intramolecular cyclization. Alternatively, it has been shown that cation **13** is the precursor to

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(3) For studies directed at the synthesis of phomactins, see: (a) Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275. (b) Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 1776. (c) Seth, P. P.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 8750. (d) Seth, P. P.; Totah, N. I. *Org. Lett.* **2000**, *2*, 2507. (e) Kallan, N. C.; Halcomb, R. L. *Org. Lett.* **2000**, *2*, 2687. (f) Chemler, S. R.; Danishefsky, S. J. *Org. Lett.* **2000**, *2*, 2695. (g) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Org. Lett.* **2000**, *56*, 10185. (h) Foote, K.; John, M.; Pattenden, G. *Synlett* **2001**, 365. (i) Mi, B.; Maleczka, R. *Org. Lett.* **2001**, *3*, 1491. (j) Chemler, S. R.; Iserloh, U.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2949. (k) Houghton, T.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615. (l) Mohr, P. J.; Halcomb, R. L. *Org. Lett.* **2002**, *4*, 2413. (m) Cole, K.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4843. (n) Balnaves, A. S.; McGowan, G.; Shapland, P. D. P.; Thomas, E. J. *Tetrahedron Lett.* **2003**, *44*, 2713. (o) Foote, K. M.; Hayes, C. J.; John, M. P.; Pattenden, G. *Org. Biomol. Chem.* **2003**, *1*, 3917. (p) Cheing, J. W. C.; Goldring, W. P. D.; Pattenden, G. *Chem. Commun.* **2003**, 2788. (q) Cole, K. P.; Hsung, R. P. *Chem. Commun.* **2005**, 5784. (r) Ryu, K.; Cho, Y.-S.; Jung, S.-I.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343.

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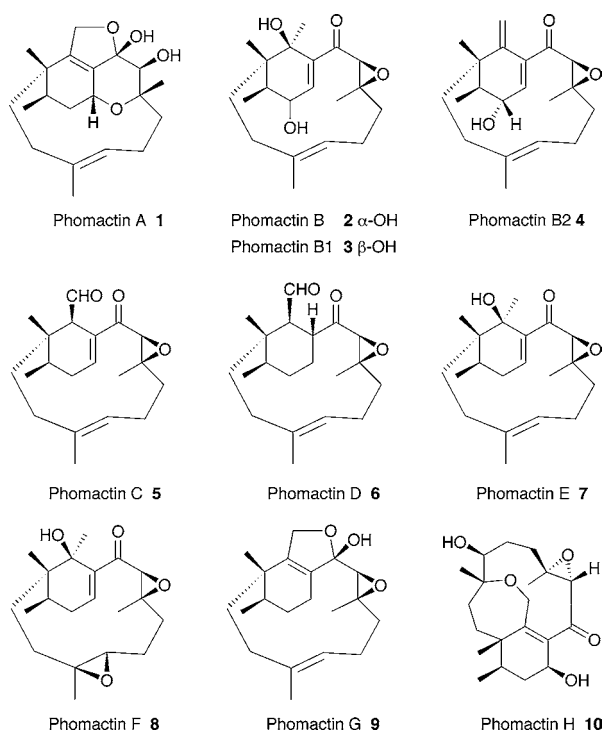
Figure 1. Phomactin family of natural products.

phomactatriene **14** via a series of 1,2-hydrogen and 1,2-methyl shifts.[5a] Phomactatriene **14** is also a natural product and has been isolated from Phoma sp. and its stereochemistry recently corrected.[5b] It has been suggested by Pattenden that the last common intermediate in the biosynthesis of all the phomactins is the keto epoxide **15**, which results from oxidations of phomactatriene.[2]
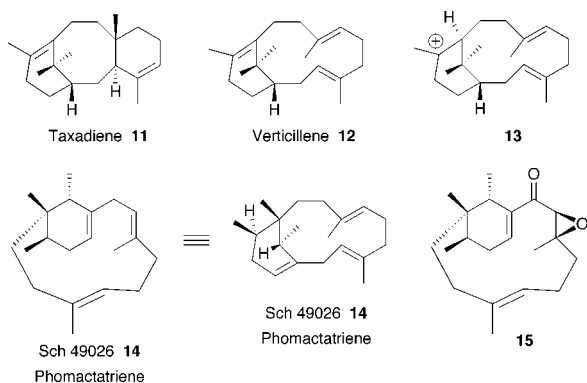

Figure 2. Biosynthesis of phomactins and taxol.

We envisioned that the bicyclic cyclohexadienone **16** could also serve as a common intermediate for the synthesis of all

(5) (a) Tokiwano, T.; Endo, T.; Tsukagoshi, T.; Goto, H.; Fukushi, E.; Oikawa, H. *Org. Biomol. Chem.* **2005**, *3*, 2713. (b) Tokiwano, T.; Fukushi, E.; Endo, T.; Oikawa, H. *Chem. Commun.* **2004**, 1324.

of the phomactins in much the same way that the epoxy ketone **15** has been proposed to be the biosynthetic precursor to all of the phomactins.[2] All of the previous synthetic approaches[3] and total syntheses[4] of the phomactins have constructed the six-membered ring before the macrocycle is closed. Closure of the macrocycle has been effected by a number of different tactical methods including NHK coupling,[3i,4b,d,e] Suzuki coupling,[4c,3e] Stille coupling,[3k] sulfone coupling to an allyic halide,[4a,3n] and oxa[3+3] cycloaddition.[3m,q] Our retrosynthesis for the phomactins involves the intramolecular cyclohexadienone annulation of the carbene complex **17** (Scheme 1). Thermolysis of **17** would be

Scheme 1. Retrosynthetic Analysis for the Phomactins
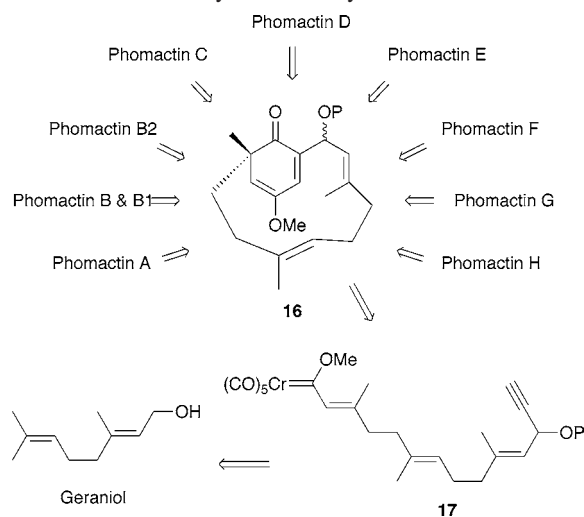
anticipated to lead to the formation of 6-membered and 12-membered rings in the same event.

The benzannulation reaction of α,β-unsaturated carbene complexes with alkynes is one of the most important methods for the synthesis of phenols (Scheme 2). This reaction was discovered in 1975 by Dötz and since that time[6] the reaction has been extensively studied and widely applied in organic

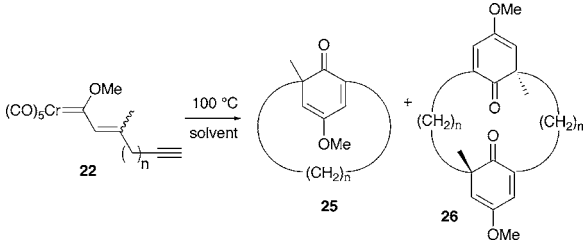**Scheme 2.** Cyclohexadienone Annulation and Benzannulation
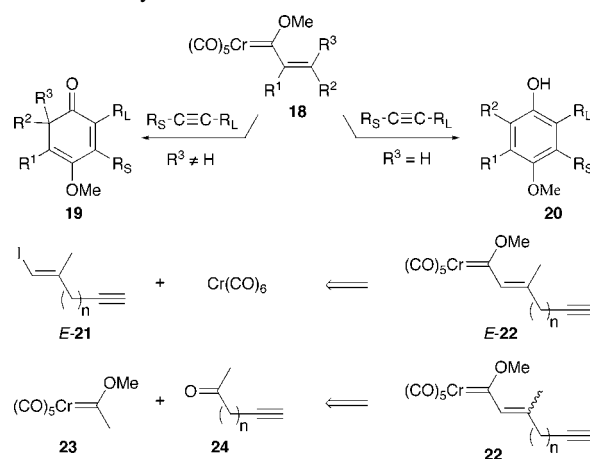
synthesis.[7] We reported the cyclohexadienone annulation in 1985, which involves the reaction of carbene complexes of the type **18** where both substituents of the β-carbon are non-hydrogen.[8] The reaction of such complexes with alkynes is general and allows for rapid entry to cyclohexadienones bearing a quaternary carbon.[7] The intramolecular variant of the benzannulation reaction has been known[9,10] for quite some time and has been utilized in the total synthesis of deoxyfrenolicin,[9b,c,g] angelicin,[9d,e] sphondin,[9e] and arnebinol.[9h] The intramolecular version of the cyclohexadienone annulation is unknown and is the subject of the present work.

The retrosynthesis of the phomactins shown in Scheme 1 requires the carbene complex **17** and thus as model systems we chose to prepare a family of carbene complexes of the type **22** (Scheme 2) in which the alkyne is tethered to the β-carbon of the alkenyl substituent of the carbene complex. It was anticipated that it would be important not only to include complexes of the type **22** with different tether lengths in the initial screen of the intramolecular cyclohexadienone annulation but also to include complexes with both cis and trans double bonds in the carbene complex. It is known[11] that β,β-disubstituted alkenyl carbene complexes are configurationally stable under the conditions of the cyclohexadienone annulation and thus it is certainly possible that cis and trans isomers of **22** could behave differently during the intramolecular process involving the carbene complex and the tethered alkyne unit. The E-isomer of complex **22** was prepared from the E-vinyl iodide precursor E-**21** via the standard Fischer method involving the addition of the vinyllithium derived from E-**21** with chromium hexacarbonyl followed by methylation. The Z-isomer of **22** was prepared from the corresponding Z-isomer of the vinyl iodide **21** (not shown) and the details can be found in the Supporting Information. More rapid entry to these carbene complexes is possible via the aldol reaction[12] of the methyl carbene complex **23** with the ketone **24** (Scheme 2); unfortunately,

this route produces a mixture of the Z- and E-isomers of **22** which proved to be inseparable.

The intramolecular cyclohexadienone annulation of carbene complex **22** was examined with complexes of four different tether lengths and the results are presented in Table 1. The yield of the desired bicyclic cyclohexadienone **25**

Table 1. Intramolecular Cyclohexadienone Annulation of Complex **22**[a]

entry	complex	n	solvent	% yield of **25**[b]	% yield of **26**[b]	anti-**26**: syn-**26**[c]
1	E-**22a**	6	THF[d]		18	1.3:1.0
2	E-**22a**	6	MeCN[e]		22	1.8:1.0
3	E-**22a**	6	benzene[f,g]		46	1.1:1.0
4	E-**22b**	8	THF	45		
5	E-**22b**	8	MeCN	45		
6	E-**22b**	8	benzene	10		
7	Z-**22c**	10	THF	15	[h]	
8	$Z+E$-**22c**[i]	10	THF	37	14	1.0:1.0
9	E-**22c**	10	THF	43		
10	E-**22c**	10	MeCN	64		
11	E-**22c**	10	benzene	36		
12	E-**22d**	13	THF	64		
13	E-**22d**	13	MeCN	51		
14	E-**22d**	13	benzene	32		

[a] Unless otherwise specified, all reactions were carried out at 0.005 M in **22** at 100 °C for 24 h. [b] Isolated yields after chromatography on silica gel. [c] The anti isomer is shown and was characterized by X-ray diffraction. [d] 6% yield of trimer isolated. [e] 4% yield of trimer isolated. [f] 13% yield of trimer observed. [g] Yields were calculated from the weight of a mixture of compounds and ratios determined by HPLC. [h] Five additional compounds were observed in the crude reaction which were not separated and characterized. [i] 71:29 ratio of E:Z isomers.

increases with increasing tether length until $n = 10$ and then appears to level off. The phomactins have nine carbons in the larger bridge and the results in Table 1 are encouraging since reasonable yields of the cyclized product **25** can be realized with both eight and ten methylene tethers. However, none of the desired cyclized product **25** is seen with the complex **22a** with six methylene spacers. In this case, depending on solvent, up to a 46% yield of the dimeric cyclohexadienone **26** was observed as a 1.1:1.0 mixture of diastereomers along with smaller amounts of the corresponding trimeric product (not shown). In acetonitrile the ratio of the dimers was formed in a 1.8:1.0 ratio and the stereochemistry of the major diastereomer was confirmed by an X-ray diffraction study. This study of intramolecular cyclohexadienone annulation of complexes **22** also clearly reveals that the stereochemistry of the double bond of the carbene

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complex is very important. The *Z*-isomer of complex **22** gives a 15% yield of **25**, whereas, the *E*-isomer gives a 43% yield (entries 7 vs 9). Interestingly, a 79:21 mixture of *E*:*Z* isomers of **22c** was prepared by the aldol reaction indicated in Scheme 2 and the thermolysis of this mixture gave a 37% yield of **25** (Table 1, entry 8). On the basis of the data for the pure *E*- and *Z*-isomers (entries 7 and 9), the expected yield would have been 35%.

We have previously shown that high levels of 1,4-asymmetric induction could be achieved in the intermolecular cyclohexadienone annulations with propargyl ethers.[11] For example, the reactions of the carbene complex **27** with the trityl propargyl ether **28** are stereospecific (Scheme 3). It is

Scheme 3. 1,4-Asymmetric Induction in Intermolecular Cyclohexadienone Annulation
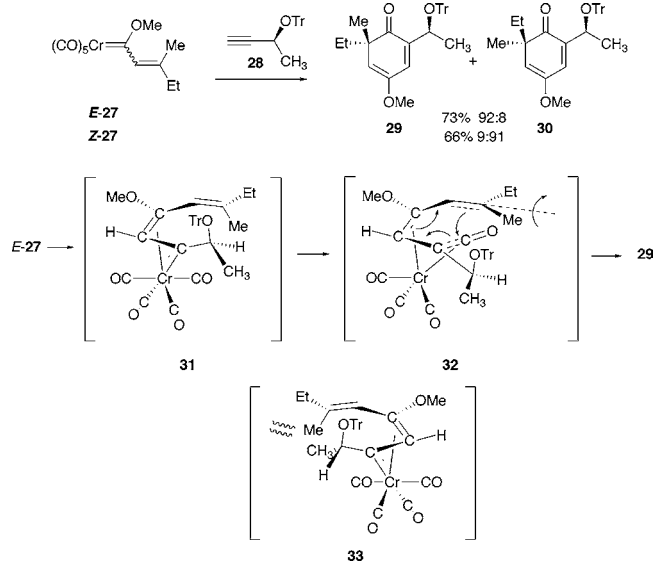
thought that the origins of this stereoselectivity derives from a stereoelectronic preference for the propargyl oxygen to be anti to the chromium in the η^1,η^3-vinyl carbene complexed intermediate, which can exist as the two diastereomeric forms **31** and **33** when *E*-**27** was cylized. Of the two, intermediate **31** is expected to be the more stable for steric reasons. Insertion of a CO ligand gives the vinyl ketene complex **32** and then an electrocyclic ring closure with upward movement of the methyl would be expected to avoid close contacts of the methyl group with the chromium and its CO ligands to provide **29** as the major product. Thus cyclization of *Z*-**27** gave the opposite selectivity favoring formation of **30**.

A series of carbene complexes **34** were prepared which had ten carbons in the tether and which had a variety of propargyl substituents to determine the extent of 1,4-asymmetric induction in the intramolecular cyclohexadieneone annulation (Table 2). It was no surprise that carbon substituents gave 1:1 mixtures of isomers since this had also been found to be the case for intermolecular benzannulations.[13] However, oxygen substiutents were found to give

Table 2. 1,4-Asymmetric Induction in Intramolecular Cyclohexadienone Annulation[a]
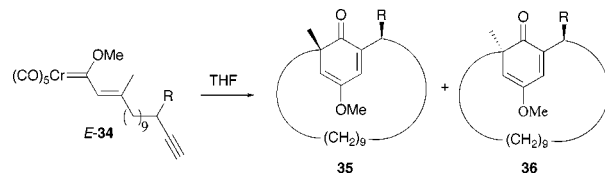
entry	complex	R	temp (°C)	% yield of **35** + **36**[b]	**35**:**36**[c]
1	*E*-**34a**	OTr	55	65	1.0:1.1
2			100	52	1.2:1.0
3	*E*-**34b**	OTIPS	55	45	3.0:1.0
4			100	47	2.0:1.0
5	*E*-**34c**	OMe	55	66	2.1:1.0
6			100	69	1.6:1.0
7	*E*-**34d**	OMOM	55	44	1.0:1.1
8			100	36	1.0:1.0
9	*E*-**34e**	*t*-Bu	100	66	1.0:1.0
10	*E*-**34f**	Me	100	94	1.0:1.2
11	*E*-**34g**	Ph	100	54	1.0:1.0

[a] Unless otherwise specified, all reactions were carried out at 0.005 M in **34** in THF for 16−24 h. [b] Isolated yields after chromatography on silica gel. [c] Ratio determined by ^{1}H NMR. Assignment of relative stereochemistry was made on the basis of an X-ray structure of **35b**.

high selectivity in the intermolecular benzannuation[13] and cyclohexadienone annulations.[11] Clearly, from the data in Table 2, the intramolecularity of the reaction leads to very low stereoselectivities with propargyl oxygen substituents. This is not necessarily a surprise given the geometrical constraints that can be associated with intramolecular processes. The best selectivity of 3:1 was observed with a siloxy group and this is consistent with the increased electron releasing ability of a siloxy group.[13,14] This result is significant since it provides for an asymmetric entry to the phomactins via carbene complex **17**. The introduction of the proper configuration at the alcohol carbon in **17** would allow for 1,4-asymmetric induction in **16** and thus to asymmetric syntheses of the phomactins.

The success of these model systems is quite encouraging for the development of an approach to the phomactins involving a double cyclization of an alkyne tethered carbene complex. Thermolysis of these complexes generates macrocyclic embedded cyclohexadienones and work directed to the synthesis of the phomactins utilizing this process will be reported in due course.

Supporting Information Available: Experimental procedures, compound characterization, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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