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An Approach to the Synthesis of the Phomoidrides

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The phomoidrides are a structurally fascinating family of natural products which possess moderate inhibitory activity against Ras farnesyl transferase and squalene synthase. Since their discovery they have inspired a great deal of attention from synthetic chemists. Our own work, culminating in an efficient synthesis of the fully elaborated tetracyclic core of phomoidrides B and D, is described herein. The synthesis relies on a late stage tandem reaction involving a novel carbonylation reaction that delivers the strained bicyclic pseudoester system, which strain in turn drives a highly efficient silyloxy-Cope rearrangement that delivers the tetracyclic core of phomoidrides B and D. Several examples of this powerful tandem reaction are presented that document its tolerance of significant structural variation. The application of this methodology to the synthesis of a phomoidride D precursor lacking only the maleic anhydride is described, and the prospects for the completion of a total synthesis are discussed.

Introduction

Guided by a screening program carried out with the aim of identifying inhibitors of squalene synthase and Ras farnesyl transferase, researchers at Pfizer isolated and structurally characterized two novel natural products they termed CP-225,917 (phomoidride A) and CP-263,-114 (phomoidride B) (Figure 1).[1] Both compounds were shown to display moderately potent activity against squalene synthase and Ras farnesyl transferase. More recently, Sulikowski has provided evidence that phomoidride B is the primary biosynthetic product and that phomoidride A and the epimeric 7(*R*) compounds phomoidrides C and D are secondary metabolites as well that are derived from phomoidride B.[2]

While the biological activities of the phomoidrides are certainly intriguing, it is also fair to say that the vast attention given these targets by synthetic chemists over the last several years is primarily due to their structural novelty and complexity. Practitioners of natural product synthesis cannot but be intrigued by the bridgehead double bond, the quaternary stereocenter at C(14), the pseudoester ring system of phomoidrides B and D, and the fused maleic anhydride. Indeed, in addition to ourselves[3] no less than thirteen research groups have reported model studies directed toward a synthesis of the phomoidrides,[4] while an additional four—those of Nicolaou,[5] Shair,[6] Fukuyama,[7] and Danishefsky[8]—have completed total syntheses.

Results and Discussion

Synthesis Plan. The Nicolaou, Shair, Fukuyama, and Danishefsky syntheses all established the bicyclic core of the phomoidrides relatively early and then set about the challenging task of parleying functional group transformations into a total synthesis. From the beginning, we were convinced that the density of functionality in the core ring system as well as such seemingly innocuous features as the isolated olefins of the side chains would combine to render ineffective many standard reactions.

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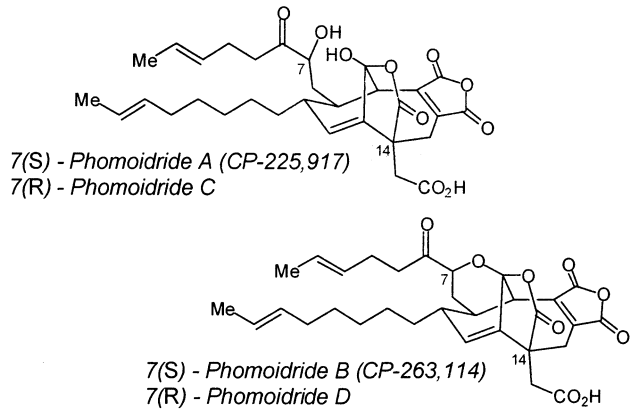
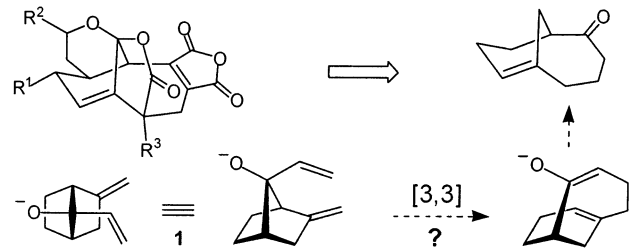


FIGURE 1. Phomoidrides A−D.

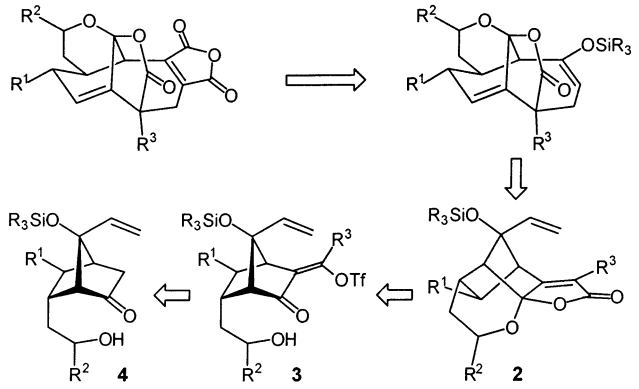
SCHEME 1



A different approach was therefore sought wherein the entire tetracyclic core of phomoidride B would be delivered in a late-stage reaction. In this fashion, functional group transformations following establishment of the ring system might be kept to a minimum. The plan that was developed as described below was guided by this overarching principle.

Stripped of all ancillary rings and side chains, the all-carbon bicyclic core of the phomoidrides reveals the retron for the anionic oxy-Cope rearrangement (Scheme 1).[9,10] At the time we began our work, no such example of the anionic oxy-Cope rearrangement was known,[11] and the question of kinetic feasibility was of concern as

SCHEME 2



inspection of molecular models indicated that the reacting termini of the two olefins of diene **1** are far from ideally oriented for a Cope rearrangement. Indeed, we were sufficiently concerned that we decided from the beginning to eschew the anionic oxy-Cope approach, and instead pursue a less obvious strategy for promotion of this unprecedented rearrangement. In fact, after we began our work Clive and Sgarbi reported just such an anionic oxy-Cope rearrangement, thus establishing the feasibility of the reaction.[4b] However, the reaction conditions (100 °C for 20 h) indicated an unusually sluggish anionic oxy-Cope rearrangement. Furthermore, it was subsequently reported that even seemingly minor changes to the substrate rendered the reaction completely unsuccessful,[4d] a result that was later confirmed by Wood in a closely related system.[4n]

We had sought from the start to build into our Cope rearrangement precursor an extra structural feature designed to promote the rearrangement which, ideally, would be present in the natural product so as not to require additional steps in the synthesis. Analysis of the Cope rearrangement with the pseudoester ring system already built into the starting material reveals that the exo-methylene of **1** would be constrained within the lactone ring as in **2** (Scheme 2). This results in significant strain and twisting in the bicyclic system, and it was proposed that relief of this strain would render the Cope rearrangement substantially more facile, and indeed that this would be the only way to successfully harness this powerful rearrangement for a synthesis of the phomoidrides.[12] It thus became the central tenet of our synthesis plan that the pseudoester ring system would be built into the Cope rearrangement precursor. The problem of establishing the strained pseudoester ring system in **2** therefore required attention, and for this purpose we envisioned a novel carbonylation reaction that would form both rings in a single reaction from enol triflate **3**. Thus, palladium-catalyzed carbonylation of **3** would proceed by way of a palladium-acyl species, which would be trapped by the hemiketal OH group formed from the hydroxy ketone in **3**.[13] Finally, it was envisioned that **3** could arise from ketone **4** by way of a Claisen condensation or aldol addition/oxidation sequence, followed by a regio- and stereoselective *O*-triflation of the resultant *β*-diketone. With these parameters established, we set

(5) (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H. S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669−1675. (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; He, Y.; Yoon, W. H.; Choi, H. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 1676−1678. (c) Nicolaou, K. C.; Jung, J.-K.; Yoon, W. H.; He, Y.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1829−1832. (d) Nicolaou, K. C.; Jung, J.; Yoon, W. H.; Fong, K. C.; Choi, H. S.; He, Y.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 2183−2189. (e) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H. S. *J. Am. Chem. Soc.* **2002**, *124*, 2190−2201. (f) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H. S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211.

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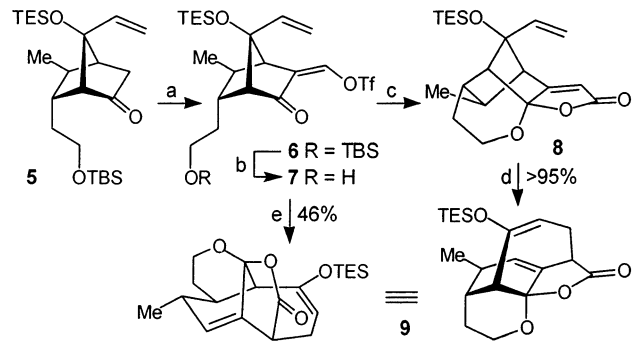
(9) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765−4766.

(10) For reviews on the Cope rearrangement, see: (a) Hill, R. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 5, pp 785−826. (b) Paquette, L. A. *Tetrahedron* **1997**, *53*, 13971−14020.

(11) A related anionic oxy-Cope rearrangement has been employed in an approach to the taxane bridgehead double bond: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190−3192.

(12) As was revealed shortly after our first report (ref 3a), the Clive group reached a similar conclusion. See ref 4d.

SCHEME 3[a]

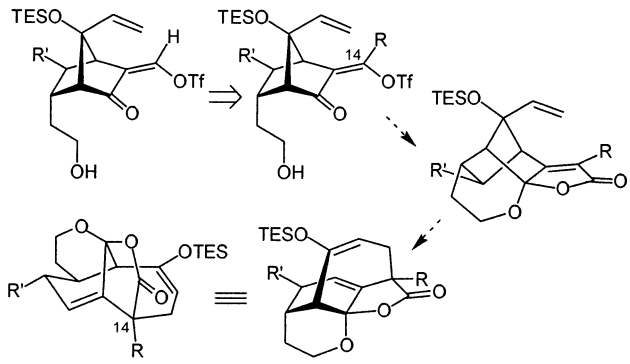


[a] Reagents and conditions: (a) KHMDS, HCO_2Me; 2-[*N*,*N*-bis(trifluoromethyl-sulfonyl)amino]-5-chloropyridine, 48% + 41% **5**. (b) Camphorsulfonic acid, MeOH, 74%. (c) 10 mol % of $Pd(PPh_3)_4$, Et_3N, 600 psi of CO, THF, 60 °C, 19% + 11% **7**. (d) Toluene, reflux, >95%. (e) 10 mol % of $Pd(PPh_3)_4$, Et_3N, 600 psi of CO, PhCN, 75−110 °C, 46%.

out to establish the feasibility of both the carbonylation reaction and the strain-induced oxy-Cope rearrangement.

Model Studies. Ketone **5** (TES = triethylsilyl; TBS = *tert*-butyldimethylsilyl) was envisioned as an appropriate model incorporating all of the key features of **4**, and a straightforward synthesis of **5** was developed.[3a] To install the requisite (*Z*)-configured enol triflate, ketone **5** was subjected to a Claisen condensation with methyl formate and the product was trapped in situ with 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine[14] (Scheme 3). This one-pot procedure provided enol triflate **6** in 48% yield as a >10:1 *Z*:*E* mixture of olefin isomers along with 41% recovered **5**. The selectivity for the (*Z*) isomer may be rationalized by invoking chelation of the potassium enolate product of the Claisen condensation with the ketone. Selective methanolysis of the TBS group then gave the required alcohol **7** in 74% yield. In the first test of the key carbonylation reaction, treatment of **7** with $Pd(PPh_3)_4$ (10 mol %) and Et_3N under 600 psi of CO in THF at 60 °C did indeed proceed to give the desired pseudoester **8** in low yield (19%, plus 11% recovered enol triflate **7**). With the desired system **8** in hand, we elected to investigate the Cope rearrangement prior to optimization of this crucial carbonylation reaction. Gratifyingly, heating a toluene solution of **8** at reflux for 1 h followed by evaporation of the solvent led to an essentially quantitative yield of phomoidride core model **9**. With the ease and efficiency of this rearrangement established, we recognized that isolation of **8** may be unnecessary. Indeed, it was discovered that simply by repeating the carbonylation experiment described above (**7**→**8**, Scheme 3) and raising the temperature to 110 °C that **7** could be converted into **9** in a single step. We then set about optimizing the efficiency of the carbonylation process, and quickly discovered that the proper choice of solvent was critical. Thus, carbonylation of **7** in benzonitrile at 75 °C, and then simply raising the temperature of the reaction to 110 °C, led to the isolation of **9** in 46% yield.[3a]

SCHEME 4



That the neutral silyloxy-Cope rearrangement of **8** to **9** proceeds at 110 °C in 1 h, while the Clive anionic oxy-Cope experiment required 100 °C for 20 h is remarkable. The rate acceleration due to the anion effect has been estimated at $10^{10}-10^{17}$,[9] and we may thus conclude that qualitatively, the strain built into pseudoester **8** results in a similar acceleration. It is noteworthy that this simple thermal rearrangement is not only highly efficient, but also lends itself well to being combined with the carbonylation in a tandem reaction process that would not be possible with the anionic variant of the oxy-Cope rearrangement.

Establishment of the C(14) Quaternary Stereocenter. One of the many difficult challenges posed by these targets—and one that was not addressed in our model study—is the all-carbon quaternary stereocenter at C(14). We were confident that the Cope-based strategy would lend itself well to this task.[15] Thus, it was proposed that the stereoselective synthesis of a tetrasubstituted enol triflate with an acetic acid equivalent as the R group would allow the simple and direct construction of the C(14) quaternary center as shown in Scheme 4.

Before we could investigate methods for the synthesis of the requisite tetrasubstituted enol triflate, it was first necessary to revise the synthesis of ketone **5** both for greater material throughput and for incorporation of the requisite C(17) side chain. This was accomplished as described in Scheme 5. Diels−Alder reaction between (*E*)-3-hexenedioic acid dimethyl ester and the commercially available cyclopentadienone equivalent 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene[16] required prolonged heating at 200 °C, but was reasonably efficient providing adduct **10** in 74% yield. The esters of **10** were reduced with $LiAlH_4$ and the resulting diol **11** was subjected to a one-pot cyclization−reduction sequence. In an adaptation of elegant chemistry developed by Gössinger,[17] treatment of **11** with NaOEt in EtOH at reflux led to an interesting alkoxylative cyclization to an acetal, and was followed by the addition of Na to the reaction mixture to fully

(13) For butenolide syntheses of this type with other traps for the palladium acyl, see: (a) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193−4198. (b) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500−7506. (c) Shimoyama, I.; Zhang, Y.; Wu, G.; Negishi, E.-I. *Tetrahedron Lett.* **1990**, *31*, 2841−2844. (d) Hamaoka, S.-I.; Kawaguchi, M.; Mori, M. *Heterocycles* **1994**, *37*, 167−170.

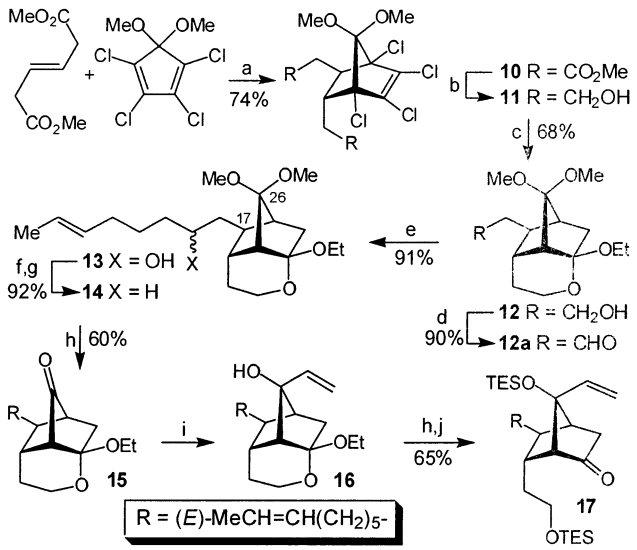
(14) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.

(15) Clive has also established that this silyloxy-Cope rearrangement strategy may be used to establish the C(14) quaternary stereocenter. See ref 4d.

(16) (a) McBee, E. T.; Diveley, W. R.; Birch, J. E. *J. Am. Chem. Soc.* **1955**, *77*, 385−387. (b) Jung, M. E.; Hudspeth, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 5508−5510.

(17) (a) Gössinger, E.; Müller, R. *Tetrahedron* **1989**, *45*, 1377−1390. (b) Aichberger, W. D.; Aigner, J.; Gössinger, E.; Gruber, K.; Menz, G. *Monatsh. Chem.* **1994**, *125*, 991−1010.

SCHEME 5[a]

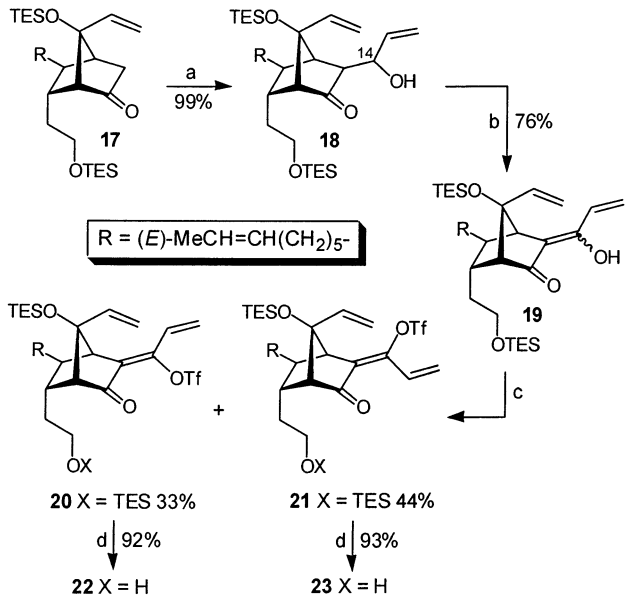


[a] Reagents and conditions: (a) Decalin, 200 °C, sealed tube, 74%. (b) LiAlH4, THF. (c) NaOEt, EtOH, reflux; Na, EtOH, reflux, 68% for 2 steps. (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temperature, 90%. (e) (*E*)-1-Iodo-4-hexene, *t*-BuLi, TMEDA, Et_2O, THF, −78 to 0 °C, 91%. (f) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C to room temperature. (g) $LiAlH_4$, THF, reflux, 92% for 2 steps. (h) TFA, H_2O, MeCN, 60%. (i) Vinyllithium, Et_2O, −78 to −20 °C. (j) TESCl, imidazole, CH_2Cl_2, 65% for 3 steps.

reduce the remaining chlorines to give diacetal **12** in 68% overall yield over the two steps from **10**. C(17) side chain installation was then carried out in four straightforward and efficient steps. Oxidation of alcohol **12** under the conditions of Swern,[18] followed by addition of (*E*)-1-lithio-4-hexene to the resultant aldehyde gave a mixture of alcohols **13** in 82% overall yield. Derivatization of alcohol **13** as its corresponding mesylate was followed by reduction with $LiAlH_4$ to give **14** in 92% overall yield. Moderately selective hydrolysis of the C(26) ketal was achieved by using TFA in $MeCN/H_2O$ to give ketone **15** in 60% yield. Stereospecific addition of vinyllithium to ketone **15** provided tertiary alcohol **16**, and was followed by ketal hydrolysis and protection of the resulting diol as its bis TES ether to produce the target ketone **17** in 65% overall yield from **15**. This efficient 11-step sequence proceeded in 15% overall yield and allowed us to reliably produce multigram quantities of ketone **17**.

After considering several options for the C(14) substituent, we targeted a vinyl group because it was deemed unlikely to interfere with the carbonylation-Cope sequence, and due to its synthetic equivalence to the requisite acetic acid. Attempted Claisen condensation with ketone **17** and acrylate esters under a variety of conditions proved fruitless, and as a result an aldol−oxidation sequence was investigated. Treatment of ketone **17** with lithium diisopropylamide (LDA) and treatment of the resultant enolate with acrolein in THF at −78 °C led to a nearly quantitative yield of aldol **18** as a single diastereomer (Scheme 6). Oxidation according to the Parikh−Doering protocol[19] then delivered *β*-diketone **19** in 76% yield. The critical enol triflate formation was then

SCHEME 6[a]



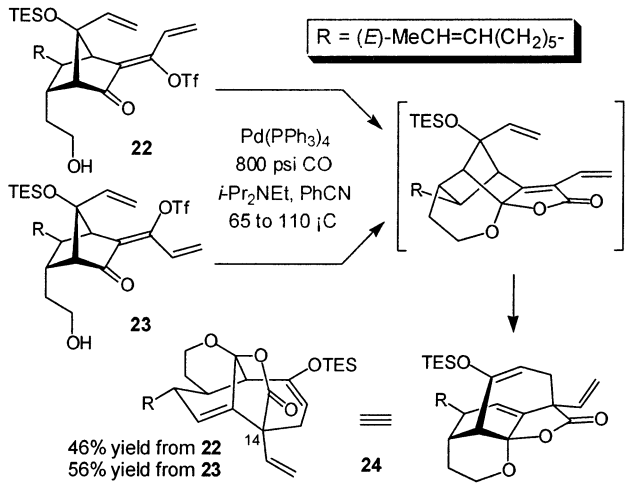
[a] Reagents and conditions: (a) LDA, acrolein, THF, −78 °C. (b) SO_3·pyridine, DMSO, *i*-Pr_2NEt, CH_2Cl_2. (c) KHMDS, HMPA, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, −78 °C. (d) CSA, MeOH, THF.

investigated under a variety of conditions. While the regioselectivity for the exocyclic enol triflate was consistently >10:1 (controlled by the strain in the endocyclic enolate), the stereoselectivity of exocyclic enol triflate formation was found to vary widely with conditions. Enolization of **19** with potassium bis(trimethylsilyl)amide (KHMDS) in the presence of hexamethylphosphoramide (HMPA) in THF at −78 °C and treatment of the resulting anion with Comins' reagent[14] gave a 1:1.3 mixture of (*Z*)- and (*E*)-enol triflates **20** and **21** in 77% yield. Conditions that resulted in a (*Z*)-selective (>10:1) reaction were identified (KHMDS, Tf_2O, Et_2O, −78 °C); however, the yield of **20** was an unacceptable 44%. It is reasonable to ascribe the (*Z*)-selectivity in the latter case to chelation of the potassium enolate with the ketone, an interaction that is presumably disrupted in the presence of HMPA and THF. Lithium bases were tried as well, but were far less efficient in delivering any of either triflate product. Despite our inability to develop an efficient and selective synthesis of the requisite (*Z*)-enol triflate **20**, it was of interest to examine the behavior of both isomers in the carbonylation process, as we anticipated that the "wrong" isomer **21** might be salvaged. In preparation for the tandem carbonylation/oxy-Cope rearrangement, the primary TES ethers of **20** and **21** were removed with catalytic camphorsulfonic acid (CSA) in MeOH/THF, giving **22** and **23** in 92% and 93% yields, respectively.

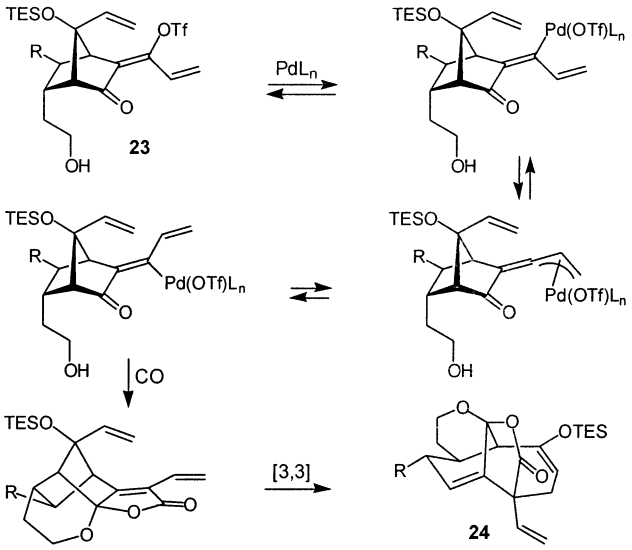
We first examined the carbonylation-Cope rearrangement of enol triflate **22** to confirm that the C(14) vinyl group would not interfere with the reaction. Indeed, subjection of **22** to the tandem carbonylation-oxy-Cope conditions developed previously resulted in the isolation of the Phomoidride core fragment **24** in 46% yield (Scheme 7). We then turned our attention to the "wrong" (*E*)-enol triflate **23**. Remarkably, subjection of **23** to the same carbonylation conditions led to the isolation of **24** in 56% yield.[3b]

(18) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.
(19) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

SCHEME 7



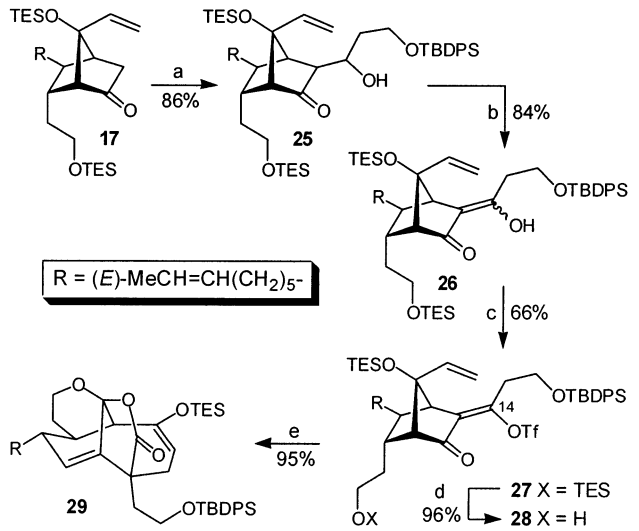
SCHEME 8



Mechanistically, we have proposed the scenario depicted in Scheme 8.[3b] Following insertion of Pd(0) into the (*E*)-enol triflate **23**, CO migratory insertion would be expected to be facile. However, this should be a mechanistic dead-end in that the only potential trap for the palladium-acyl is an *intermolecular* reaction with the primary alcohol. Thus, the initially formed (*E*)-vinylpalladium species may be expected to isomerize via the indicated π-allyl palladium complex to the (*Z*)-vinylpalladium complex. From there, CO insertion and trapping of the resultant palladium-acyl with the hemiketal formed from the ketone and primary alcohol lead to the illustrated unsaturated lactone, which then rearranges to give the observed product **24**.

The generation of allenic π-allyl palladium complexes of the type proposed here from buta-2,3-dien-1-ols and their derived acetates, carbonates, and phosphates is well-precedented.[20] Various traps have been used (alkyl Zn and Mg, sodium ethylmalonate, CO/MeOH, CO/H_2O, organoboranes) and with the exception of the malonate reaction the products are 2-substituted-1,3-butadienes. 1,3-Diene syntheses involving similar intermediates but starting from 2-butyne-1,4-diol dicarbonates are known as well.[21] The present work constitutes the first example

SCHEME 9[a]



[a] Reagents and conditions: (a) LDA, 3-(*tert*-butyldiphenylsilyloxy)propanal, THF, −78 °C. (b) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 to 23 °C. (c) KHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, Et_2O, −78 to 23 °C. (d) CSA, MeOH, THF. (e) 20 mol % of $Pd(PPh_3)_4$, *i*-Pr_2NEt, 800 psi of CO, PhCN, 75−110 °C.

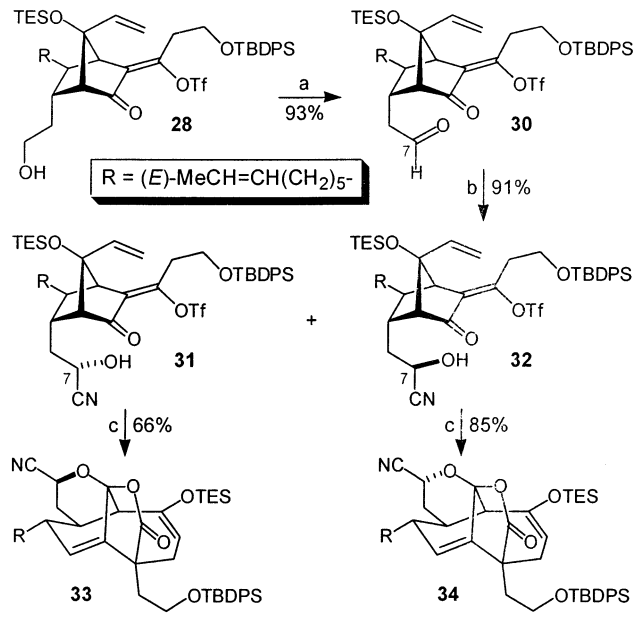
of the isomerization of one geometric isomer of a 2-substituted-1,3-butadiene to the other. Synthetically this discovery has important ramifications in that the need for a relatively difficult stereospecific synthesis of the (*Z*)-enol triflate has been obviated. In essence, a stereospecific synthesis of the C(14) quaternary stereocenter has been "paid for" with a nonselective synthesis of the tetrasubstituted enol triflate.

Despite this interesting observation in palladium chemistry, the vinyl group ultimately proved unsuitable for the purposes of a synthesis of the phomoidrides. Various attempts to hydroborate the hindered vinyl group of **24** resulted in either no reaction or chemistry at the remote olefin of the side chain and/or the strained lactone. This route was therefore ultimately abandoned, and a new acetic acid surrogate for the C(14) substituent was sought. A protected two-carbon primary alcohol seemed most straightforward, and aldol addition of the lithium enolate derived from ketone **17** to 3-(*tert*-butyldiphenylsilyloxy)propanal proceeded in 86% yield to give aldol **25** (Scheme 9). In this series, the oxidation was best accomplished with use of DMSO/trifluoroacetic anhydride (TFAA)/Et_3N to provide β-diketone **26** in 84% yield.[18] Since we could no longer make use of the isomerization chemistry outlined above (Scheme 7), a (*Z*)-selective enol triflate synthesis was required. Using the "chelation-maximized" conditions mentioned above (KHMDS, Et_2O,

(20) (a) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 378−380. (b) Djahanbini, D.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 203−206. (c) Nokami, J.; Maihara, A.; Tsuji, J. *Tetrahedron Lett.* **1990**, *31*, 5629−5630. (d) Ni, Z.; Padwa, A. *Synlett* **1992**, 869−870. (e) Piotti, M. E.; Alper, H. *J. Org. Chem.* **1994**, *59*, 1956−1957. (f) Moriya, T.; Furuuchi, T.; Miyaura, N.; Suzuki, A. *Tetrahedron* **1994**, *50*, 7961−7968. (g) Imada, Y.; Vasapollo, G.; Alper, H. *J. Org. Chem.* **1996**, *61*, 7982−7983. (h) Uemura, K.; Inoue, Y. *Appl. Organomet. Chem.* **2000**, *14*, 8−13.

(21) (a) Kiji, J.; Okano, T.; Fujii, E.; Tsuji, J. *Synthesis* **1997**, 869. (b) Bohmer, J.; Grigg, R. *Tetrahedron* **1999**, *55*, 13463−13470. See also: (c) Gevorgyan, V.; Kadowaki, C.; Salter, M. M.; Kadota, I.; Shinichi, S.; Yamamoto, Y. *Tetrahedron* **1997**, *53*, 9097−9106.

SCHEME 10[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 23 °C. (b) NaCN, CSA, THF, H_2O, 0 °C. (c) 20 mol % of $Pd(PPh_3)_4$, *N*-methylmorpholine, 800 psi of CO, PhCN, 70−110 °C.

Comin's reagent), the desired (*Z*)-enol triflate **27** could be obtained in an acceptable 66% yield, along with 5% of the undesired (*E*) isomer and 26% of recovered **26**. Methanolysis of the TES group was carried out as before (CSA, MeOH, THF) to provide alcohol **28** in 96% yield. While the stage was now set for introduction of the C(1)−C(6) side chain, the performance of hydroxy enol triflate **28** in the tandem carbonylation/oxy-Cope rearrangement protocol was first investigated. We were delighted to find that in this case the reaction proceeded highly efficiently to give phomoidride core system **29** in 95% yield. It is not clear why the carbonylation is so much more efficient in this case, but a plausible hypothesis is that the steric bulk of the C(14) silyloxyethyl group renders the key strained pseudoester ring forming step (attack of the hemiketal OH on the palladium acyl) more facile by pushing the palladium acyl closer to the hemiketal OH trap than does a C(14) hydrogen (**7**) or a C(14) vinyl group (**22** and **23**).

Installation of the C(1)−C(6) Side Chain. The synthesis of the C(1)−C(6) side chain required an expedient solution and, in principle, was a simple matter of adding a six-carbon acyl anion equivalent to a C(7) aldehyde. The issue of relative stereochemistry at C(7) was a complicating factor, but evidence has now been provided that suggests that both diastereomers are natural products.[2] We therefore sought a maximally flexible solution that could provide either the 7(*S*) (phomoidrides A and B) or 7(*R*) (phomoidrides C and D) stereochemistry.[22] Oxidation of alcohol **28** under the conditions of Swern provided aldehyde **30** in 93% yield,[18] and set the stage for side chain incorporation (Scheme 10). Treatment of aldehyde **30** with NaCN/CSA in THF/H_2O resulted in a smooth hydrocyanation to give a 1:1 mixture of cyanohydrins **31** and **32** in 91% overall yield. It was further found that **31** and **32** were easily separable, and that either could be recycled back to aldehyde **30** in good yield (>90%) by treatment with aqueous NaOH. Due to the ease and efficiency of these transformations this was viewed as a potentially excellent solution to the issue of C(7) stereochemistry. However, alkylation of the nitrile and, for the first time, performing the tandem carbonylation/oxy-Cope sequence with a secondary alcohol at C(7) loomed as the difference between potential and reality. Examining the latter issue first, both **31** and **32** were separately subjected to the standard conditions for the carbonylation reaction, and both failed to give meaningful amounts of the desired rearrangement products **33** and **34**. Reasoning that *i*-Pr_2NEt was too basic and was simply promoting dehydrocyanation, we employed the less basic *N*-methylmorpholine, and were gratified to find that under these conditions phomoidride core systems **33** and **34** could be obtained in 66% and 85% yields, respectively. That a cyanohydrin at C(7) performs admirably in the key strained pseudoester forming carbonylation attests to the robustness of this transformation.

Incorporation of C(1)−C(5) through alkylation of the nitrile or by reduction of the nitrile to an aldehyde and alkylation of this aldehyde were some of the options considered at this stage. Nitriles **31**, **32**, **33**, and **34** were all examined in this context. In no case could a successful alkylation (alkyllithiums, alkyl Grignards) or reduction of the nitrile group be achieved. Extensive decomposition always accompanied these reactions, and it is not difficult to rationalize the sensitivity of these molecules. We were thus forced to abandon the hydrocyanation approach.

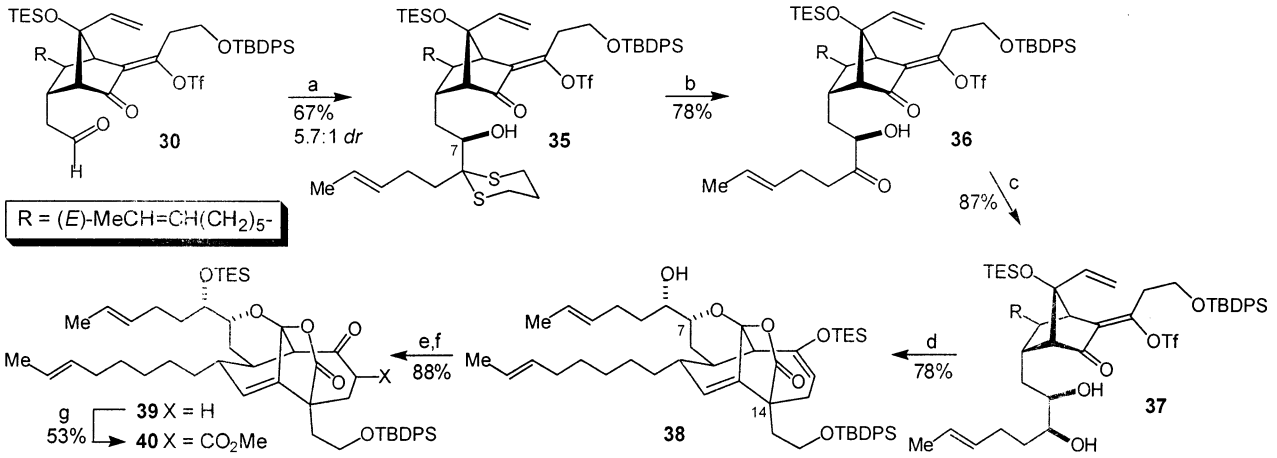
This was not necessarily problematic as the addition of a fully elaborated C(1)−C(6) acyl anion equivalent to aldehyde **30** would represent a more direct—if potentially less flexible—solution. Addition of 2-lithio-2-pent-*trans*-3-enyl-[1,3]-dithiane to aldehyde **30** proceeded to give a mixture of two diastereomeric products from which the major diastereomer, identified as **35** possessing the 7(*S*) stereochemistry[22] of the phomoidride C and D series, could be isolated in 57% yield (Scheme 11). The minor product, the C(7) diastereomer, was isolated in 10% yield. All attempts to alter the diastereoselectivity of this reaction (solvent, additives (e.g. HMPA)) either failed or resulted in drastically reduced yields. Both Nicolaou[5a] and Danishefsky[8b] have employed this same dithiane addition with drastically different stereochemical outcomes that were dependent on changes in the neighboring functional groups. In our case, no chelation of the lithium counterion may be invoked, and the moderate diastereoselectivity must be ascribed to more subtle conformational factors. Because it was anticipated that the dithiane functionality might be incompatible with the conditions of the palladium-catalyzed carbonylation reaction, dithiane **35** was transformed into ketone **36** in 78% yield.[23] Chelation-controlled reduction of ketone **36** employing $Zn(BH_4)_2$ proceeded to give diol **37** stereospecifically in 87% yield.[24] In the most complex tandem carbonylation-Cope reaction we have yet performed, we were delighted to find that **37** could be smoothly transformed into phomoidride core

(22) The compounds discussed here are racemic. In this context, we are using the descriptors 7(*S*) and 7(*R*) to indicate relative stereochemistry with respect to the illustrated (natural) enantiomer.

(23) (a) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382−383. (b) Takano, S.; Hatakeyama, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1977**, 68.

(24) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.

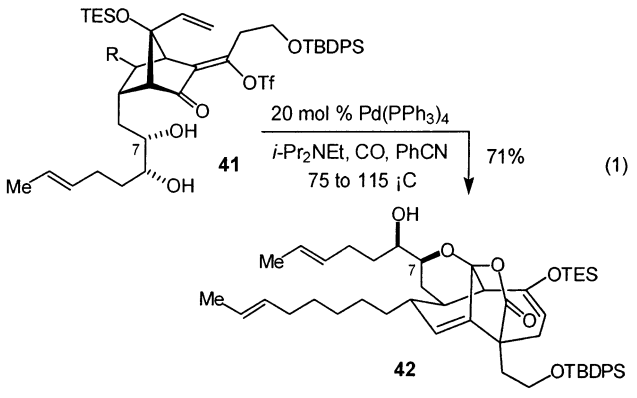
SCHEME 11[a]



[a] Reagents and conditions: (a) 2-Pent-*trans*-3-enyl-[1,3]-dithiane, *n*-BuLi, THF, toluene, −78 °C. (b) MeI, $NaHCO_3$, MeCN, acetone, H_2O, reflux. (c) $Zn(BH_4)_2$, Et_2O, −10 °C. (d) 20 mol % of $Pd(PPh_3)_4$, *i*-Pr_2NEt, 800 psi of CO, PhCN, 70−115 °C. (e) CSA, MeOH, THF, reflux. (f) TESCl, imidazole, CH_2Cl_2. (g) LDA, MeO_2CCN, Et_2O, −78 to 23 °C.

system **38** (78% yield) lacking only the maleic anhydride. This reaction further serves to illustrate the robustness of the tandem reaction sequence and effectively differentiates the two alcohols. We note as well that hydroxy ketone **36** may be successfully subjected to the tandem carbonylation-Cope sequence, but that the presence of the C(6) ketone in the product was expected to be incompatible with the chemistry required for installation of the maleic anhydride. Selective desilylation of the silyl enol ether of **38**, followed by silylation of the C(6) alcohol provided ketone **39**. Ketone **39** represents a fully elaborated phomoidride precursor with the C(14) quaternary stereocenter and both side chains installed. Only the synthesis of the maleic anhydride remains for a total synthesis. To set the stage for the anhydride synthesis, ketone **39** was carbomethoxylated by treatment of the derived lithium enolate with Mander's reagent (MeO_2CCN)[25] to give *β*-keto ester **40** in 53% yield.

It was also of interest to investigate the minor 7(*R*) diastereomer[22] from the dithiane addition to aldehyde **30** (**30**→**35**, Scheme 11). This compound was subjected to the same sequence of functional group manipulations as was **35** (dithiane hydrolysis and ketone reduction with $Zn(BH_4)_2$, 34% yield overall, unoptimized) to deliver diol **41**. Similar to diol **37**, **41** performed admirably in the tandem carbonylation/silyloxy-Cope reaction to provide phomoidride B core system **42** in 71% yield (eq 1). Combined with



the results for cyanohydrins **31** and **32**, it may thus be concluded, significantly, that the carbonylation reaction is tolerant of either diastereomer of the C(7) alcohol. Our access to the phomoidride B series will be limited only by our ability to access the 7(*R*) alcohol diastereomer in the installation of the C(1)−C(6) side chain.

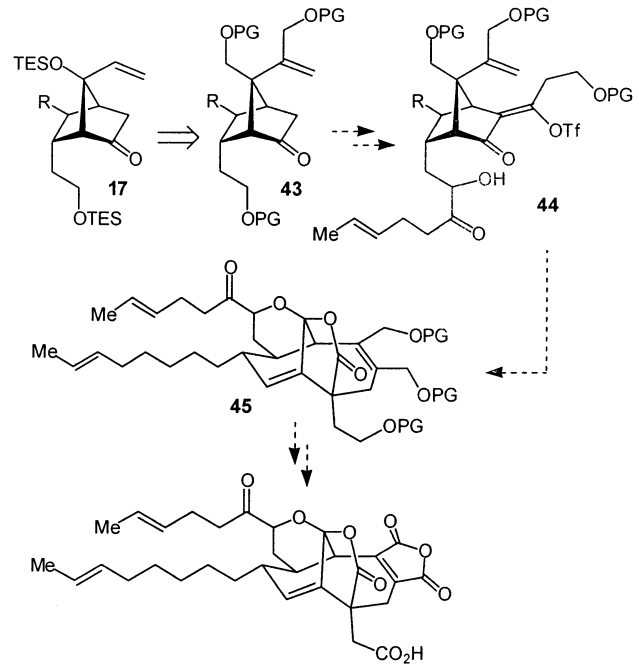
With *β*-keto ester **40** in hand, we were well-positioned, in principle, to marshall the chemistry developed by Shair for the synthesis of the maleic anhydride.[6b] That work entailed conversion of a similar *β*-keto ester to its derived enol triflate, followed by palladium-catalyzed carbonylation. The success of this extremely difficult carbonylation, which failed in the expert hands of others,[5d] was found to lie uniquely in the use of $P(OMe)_3$ as the ligand for the palladium catalyst. While we were able to convert *β*-keto ester **40** into its derived enol triflate, two attempts to carbonylate this enol triflate employing the Shair conditions failed to deliver detectable amounts of any carbonylated material. It is possible that further experimentation could reverse this misfortune, and it is also possible that the seemingly subtle differences between Shair's enol triflate and ours are indeed the difference between the success and failure of this key reaction. What is clear is that this carbonylation is a highly sensitive reaction. For this reason, and other reasons described below, and despite the fact that we were seemingly only a few steps from a synthesis of Phomoidride D, we decided to revise the synthesis plan to incorporate the maleic anhydride in what we hoped would be an efficient and graceful fashion. Thus, compounds **39** and **40** represent our furthest points of progress under the original synthesis plan toward a synthesis of the phomoidrides.

Conclusion

A novel, efficient, and quite general carbonylation reaction that delivers the strained pseudoester ring system required for our synthetic approach to the phomoidrides has been developed. In addition it may be performed in tandem with a highly facile strain-driven silyloxy-Cope

(25) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425−5428.

SCHEME 12



rearrangement that smoothly and reliably delivers the complete core ring system of phomoidrides B and D. This tandem reaction sequence has been demonstrated in several contexts (**7** → **9**, **22** and **23** → **24**, **28** → **29**, **31** → **33**, **32** → **34**, **37** → **38**, and **41** → **42**), and has been shown to be perfectly suited to the incorporation of the two side chains and the challenging C(14) quaternary stereocenter. Indeed, as regards the latter issue, the four total syntheses reported thus far rely either on a one-carbon homologation of a C(14) carboxylic acid that proceeds at best with moderate efficiency[5−7] or on a highly imaginative multistep sequence that takes place following establishment of the core ring system.[8,26] The present approach easily allows the highly efficient incorporation of an appropriate two-carbon fragment requiring only an alcohol to carboxylic acid oxidation following establishment of the core ring system.

(26) Meng, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1485−1488.

Notwithstanding the difficulty we encountered during our attempts to synthesize the maleic anhydride from ketone **39**, it is certainly reasonable to expect that a total synthesis could be achieved using the route described in this article. We were, however, scientifically far more intrigued by the possibility that both carbons of the maleic anhydride might be incorporated early in the synthesis. Thus, ketone **43** has become the initial target as a new generation version of ketone **17** (Scheme 12). Such a change is certainly not trivial in that the planned conversion of **44** to **45** would entail a Cope rearrangment as opposed to a silyloxy-Cope rearrangement. But it is the very central finding of our investigations that the silyloxy-Cope rearrangement, driven by the strain induced by the pseudoester ring system, is a highly efficient solution to this Cope-based approach to the synthesis of the phomoidrides, and indeed is a superior solution to the traditional anionic oxy-Cope approach. Free from the requirement of the alkoxide for acceleration of the rearrangement, it is reasonable to project that a Cope rearrangement will be effective in this context. Once again, the Clive group has independently reached the same conclusion, and they have recently reported that a Cope rearrangement of the type discussed here is indeed feasible in a model system.[4y] What remains is the development of an effective synthesis of a system corresponding to **43**. Current efforts are focused on a concise solution to this problem and in turn on a total synthesis of the phomoidrides.

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Supporting Information Available: Full experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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