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C–C Bond Cleavage Approach to Complex Terpenoids: Development of a Unified Total Synthesis of the Phomactins

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ABSTRACT: The rearrangement of carbon-carbon (C–C) single bonds in readily available carbocyclic scaffolds can yield uniquely-substituted carbocycles that would be challenging to construct otherwise. This is a powerful and often non-intuitive approach for complex molecule synthesis. The transition metal-mediated cleavage of C–C bonds has the potential to broaden the scope of this type of skeletal remodeling by providing orthogonal selectivities compared to more traditional pericyclic and carbocation-based rearrangements. To highlight this emerging technology, a unified, asymmetric, total synthesis of the phomactin terpenoids was developed, enabled by the selective C–C bond cleavage of hydroxylated pinene derivatives obtained from carvone. In this full account, the challenges, solutions, and intricacies of Rh(I)-catalyzed cyclobutanol C–C cleavage in a complex molecule setting is described. In addition, details of the evolution of strategies that ultimately led to the total synthesis of phomactins A, K, P, R, and T, as well as the synthesis and structural reassignment of Sch 49027, are detailed.

INTRODUCTION

Terpenoids have long held the fascination of the chemical community, in no small part due to their varied and intriguing molecular architectures and the challenge they pose to de novo chemical synthesis.¹ Terpenoid natural products primarily consist of a hydrocarbon skeleton, punctuated by varying degrees of oxidation/oxygenation. Because of their inherent carbocyclic nature, the synthesis of terpenoids has been dominated by methods for the precise construction of carbon-carbon (C-C) bonds. In this context, C-C bond construction can either begin from acyclic isoprene-derived units which proceed through bioinspired polyene cyclizations,² or in a step-wise manner by substitution around the periphery of a readily available carbocyclic starting material to introduce target-relevant structural complexity (Figure 1A). The latter strategy can be effective, particularly when readily available carbocycles with the requisite functional handles are embedded within a larger natural product framework.³ However, a large number of terpenoid natural products contain densely functionalized carbocycles that do not directly correspond to an easily accessible precursor carbocycle.

Many significant advancements in terpenoid total synthesis can be traced to the rearrangement of abundant carbocyclic feedstocks. The skeletal or peripheral remodeling of "chiral pool" compounds (e.g., Figure 1B) involving C-C bond forming and cleavage is a particularly valuable approach to access new enantioenriched scaffolds that might otherwise be difficult to build from classical C-C bond forming processes that functionalize only the periphery of a ring (as in Figure 1A).⁴ The possibility of C-C bond formation/cleavage sequences often enables non-intuitive retrosynthetic disconnections that can greatly simplify a synthesis if used strategically. While various pericyclic and carbocation-based rearrangements have been successfully enlisted in this regard, the toolbox of rearrangement reactions for carbocyclic skeletons remains relatively limited and is often driven by the stereoelectronic effects inherent to the substrate carbocycle.⁵ In contrast, transition metalmediated C–C bond cleavage processes provide promising new avenues for remodeling carbon scaffolds that often proceed with selectivities orthogonal to "classical" rearrangements (i.e., those catalyzed by Brønsted or Lewis acids, or thermally driven).⁶ When combined with or initiated by a bond-forming process, transition metal-mediated C–C bond cleavage has the potential to access novel carbocyclic scaffolds and provide non-intuitive approaches to complex molecule synthesis.⁷



Figure 1. (A) A sequential bond formation strategy. (B) A strategy of bond formation followed by C–C bond cleavage to access rearranged carbocycles.

In this Article, we report our studies on the underutilized potential of metal-mediated C–C bond cleavage processes of hydroxylated pinene derivatives derived from (+)-carvone to form uniquely-substituted cyclohexenones. This skeletal remodeling process has been applied in the asymmetric and unified total synthesis of the phomactin terpenoids.



Figure 2. (A) Representative members of the phomactin family of natural products. (B) Yamada's synthesis of (+)-phomactin D. (C) Pattenden's synthesis of (±)-phomactin A. (D) Halcomb's synthesis of (+)-phomactin A.

Structural Features of the Phomactins

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The phomactin natural products are a small class of terpenoids exemplified by phomactin A (1), the first of the secondary metabolites to be discovered in this class (Figure 2A).⁸ Phomactin A was first isolated from a *Phoma* species of marine fungus in 1991 during a search for fungal metabolites that display platelet-activating-factor receptor (PAFR) antagonism.⁹ Further investigation into this *Phoma* species resulted in the isolation of additional phomactin natural products including phomactin B2 (2), phomactin G (3), and several other congeners.¹⁰ More recently in 2018, Berlinck and coworkers disclosed six new phomactin terpenoids including phomactin R (4) and phomactin T (5), which were isolated from the fungus *Biatriospora* sp. CBMAI 1333.¹¹ To date, there have been 27 distinct phomactin natural products isolated and disclosed by various groups.¹²

The phomactin terpenoids are characterized by an unusual bicyclo[9.3.1]pentadecane core that comprises their carbocyclic framework (highlighted in green for phomactin P (**6**), Figure 2A). As a result, each natural product contains a densely functionalized cyclohexyl ring, bridged by a macrocyclic "strap". Phomactin A (**1**), the flagship molecule in this terpenoid class, is arguably the most structurally complex congener. It contains an oxadecalin framework embedded in its core structure as well as a highly sensitive hydroxylated dihydrofuran structural motif, which is also present in phomactin G (**3**) and Sch 49027 (**7**).

<u>Previous Synthetic Studies</u>

The phomacin natural products have garnered much attention from the synthetic community over the past 30 years.⁸ In addition to the total syntheses of several members (**1**, **2**, **3** and **8**) that had been completed prior to our studies, there exists over 25 "progress toward" studies, featuring diverse strategies for the construction of either the common bicyclo[9.3.1]pentadecane core or the reduced furanochroman functional grouping that is unique to phomactin A (1).¹³ The sheer number of studies toward the syntheses of these natural products highlights the synthetic challenge associated with preparing these molecules. In particular, formation of the densely functionalized cyclohexyl core in enantioenriched form has proven surprisingly difficult.

The first completed total synthesis of a phomactin congener was of (+)-phomactin D (8), which was reported by Yamada and coworkers in 1996 (Figure 2B).¹⁴ This synthesis of the enantioenriched natural product set an important precedent for future approaches by independently constructing the functionalized cyclohexyl system (13) and the linear "strap" portion (14), then effecting a convergent coupling to forge the macrocycle at a late-stage. As is described within, our own strategy for a unified synthesis of the phomactins benefitted immensely from many principles first highlighted by Yamada. However, the Yamada synthesis also revealed the difficulty in building the cyclohexane fragment (see 13; highlighted in blue), requiring 25 steps and many functional group interconversions to prepare this complex piece.

In 2002, Pattenden and coworkers were the first to complete a total synthesis of (±)-phomactin A (Figure 2C).¹⁵ Although this was a racemic synthesis, the unique strategy employed by Pattenden et al. to introduce the "strap" motif (**16**) early in the route led to a relatively short total synthesis (19 steps longest linear sequence). Furthermore, deoxygenation of an intermediate compound prior to reaching **17** in the Pattenden route led to the racemic synthesis of (±)-phomactin G (**3**).¹⁶ Shortly thereafter, in 2003, the first asymmetric synthesis of (+)-phomactin A (**1**) was reported by Halcomb and coworkers (Figure 2D).¹⁷ The Halcomb synthesis utilized a convergent strategy that brought together cyclohexyl core **20** and the linear "strap" **21**, which had been prepared separately. However, a sequential bond formation strategy was employed, and elaboration of the initial

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"chiral pool" compound (+)-pulegone (**18**) to cyclohexene **20** was remarkably challenging, requiring 18 steps.

In the intervening years before our own studies of the phomactins, an inventive 22-step synthesis of (±)-phomactin B2 (2) was accomplished by Wulff and coworkers,¹⁸ as well as a 37-step synthesis of (±)-phomactin A (1) by Hsung and coworkers that was highly illuminating in pointing out many of the hidden challenges in approaching the syntheses of these molecules.¹⁹ Recently, a formal synthesis of (+)phomactin A (1) was disclosed by Lee and coworkers that intercepts a late-stage intermediate in the Halcomb route.²⁰ While there have been many creative strategies developed to synthesize phomactin-type terpenoids, we recognized that there still existed an unmet synthetic challenge, namely, an efficient strategy that could provide a unified route to numerous phomactin congeners in enantioenriched form. Our solution to this problem was published in 2018, enabling the asymmetric total synthesis of six phomactin congeners from a common late-stage synthetic intermediate and showcasing the power of a C-C bond formation/cleavage strategy in terpenoid synthesis.¹¹ Here, we provide both a full account of the evolution of our synthetic strategy as well as a demonstration of the intricacies of metal-mediated C-C bond cleavage on complex substrates, discovered over the course of our total synthesis endeavor.

RESULTS AND DISCUSSION

<u>Retrosynthetic Considerations</u>

Our synthetic strategy was built on the recognition that the central cyclohexyl ring of the phomactins could be accessed efficiently from abundant "chiral pool" compound (+)-carvone (22, Figure 3A). While the intact carvone skeleton does not map directly onto the phomactin terpenoid framework, we pictured a "rearranged" skeleton such as 24 as an ideal synthetic partner. In order to achieve the requisite carvone rearrangement, we sought to build on earlier methodology studies from our research group on C-C bond cleavage/functionalizations. Specifically, (+)-carvone can be converted into dihydroxylated pinene derivative 23 using a previously reported two-step procedure involving epoxidation of 22 with mCPBA followed by reductive coupling of the epoxide and carbonyl moieties with in situ generated Cp₂TiCl.²¹ Subjecting cyclobutanol 23 to substoichiometric amounts of [Rh(cod)OH]2 results in scission of the C4-C5 bond of the cyclobutanol, thus effecting the skeletal rearrangement of carvone into cyclohexenone 24.22 The cleavage of the cyclobutanol C-C bonds occurs selectively and results in the cleavage of the stronger C4-C5 bond over the weaker C2-C5 bond.23

Cyclohexenone **24** readily maps onto the congested cyclohexene core structure of the phomactin natural products, leading to the enantiospecific formation of this stereochemically demanding portion of the phomactins in just three steps from carvone. Furthermore, elaboration of cyclohexenone **24** into a late-stage common synthetic intermediate (**25**) could be accomplished by the addition of a simple linear polyene such as **26** (Figure 3B), similar to the pioneering work showcased by Yamada and coworkers.¹⁴ This common synthetic intermediate bears functionality common to all the phomactin congeners and contains key orthogonal functional handles for further late-stage diversification into a wide variety of natural products.



Figure 3. (A) Skeletal rearrangement of carvone into substituted cyclohexenone **24**. (B) Generalized synthetic strategy. (C) Initial retrosynthesis of common synthetic intermediate **25** involving delayed cyclobutanol fragmentation.

Key to the success of our carvone skeletal remodeling strategy would be tactical manipulations of not just the functional groups of cyclohexenone 24, but also those of intermediate cyclobutanol 23. In fact, we first envisioned several potential benefits of delaying C-C bond cleavage until after macrocyclization (Figure 3C). Here, the common synthetic intermediate (25) could arise from enone 27 via methylenation and selective oxidation at the bis-allylic C2 position. Enone 27 in turn could arise from cyclobutanol 28, first through intramolecular sulfone alkylation to close the macrocycle (in line with the precedent of ref. 14 and 13l), followed by selective cleavage of the cyclobutanol to establish the syn disposed vicinal methyl groups of enone 27. We hypothesized that by delaying the cyclobutanol opening, the potentially challenging macrocyclization step²⁴ would be facilitated by the rigid scaffold of the bicyclo[3.1.1] system.²⁵ Indeed, examination of 3D models indicated that cyclobutanol 28 was locked in a productive conformation for cyclization, placing the methylene sulfone moiety in an axial position (see Figure 3C). Additionally, delaying cyclobutanol fragmentation would provide a rigid template to exploit in a hydroxy group-directed C-H functionalization of the allylic methyl group of cyclobutanol 23.

Initial Strategy: π -allyl Stille Fragment Coupling

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Initial studies were undertaken to exploit the tertiary hydroxy group in cyclobutanol 23 as a directing group for C(sp³)-H functionalization. After TBS protection of the primary hydroxy group of 23, the one-pot procedure developed by Hartwig and coworkers for silvlation of alcohol groups followed by dehydrogenative C-H silvlation gave oxasilolane 29 in 80% yield (Scheme 1).²⁶ Importantly, this reaction is completely chemoselective toward functionalization at the allylic methyl position over the alkyl methyl group. This selectivity arises from both the slight activating ability of the neighboring π -system as well as a favorable dihedral angle between the allylic methyl group and the silyloxy group, which is close to 0°. In our envisioned ideal scenario, the allyl silane functionality of 29 would be utilized in a Hiyama-type coupling to achieve direct vinylation at C2. However, with isobutenyl bromide as a model crosscoupling partner, the desired skipped diene (30) was not observed. Instead, cyclohexenone 31 was formed as the sole product, presumably through an Uemura-type C-C cleavage/ cross-coupling sequence.²⁷ Unfortunately, any type of direct coupling at C2 from oxasilolane **29** or its derivatives was unsuccessful, prompting us to investigate a polarity-reversal strategy. In preparation for these studies, Tamao-Fleming oxidation of oxasilolane 29 yielded the corresponding free diol, which was selectively acetylated to give allylic acetate 32. Allylic acetate 32 proved competent as a coupling partner with a range of vinyl nucleophiles.²⁸

Scheme 1. Dehydrogenative C-H Silylation of Cyclobutanol 23



For the purposes of the total synthesis, prior to exploring vinyl cross-couplings of allylic acetates related to **32** en route to the phomactins, primary alcohol **23** was converted to phenyl sulfide **33** (Scheme 2) to provide a future handle for macrocyclization and avoid the use of the TBS protecting group that would be required otherwise. Iridium-catalyzed dehydrogenative silylation was effected on **33** to functionalize the allylic position, however, a subsequent Tamao-Fleming oxidation proved challenging and led to non-specific decomposition. Fortunately, selenium dioxide proved capable of directly effecting allylic oxidation of **33** to provide allylic acetate **34** after mono-acetylation. Oxidation of phenyl sulfide **34** to sulfone **35** with ammonium heptamolybdate and hydrogen peroxide proceeded smoothly. Interestingly, this sulfide to sulfone conversion was found to be uniquely successful on this particular substrate. Attempted sulfide oxidation on compound **33** resulted in substantial rearrangement to [2.2.1]bicycle **36** caused by the nucleophilic alkene engaging the oxidant. It appears that in **34**, the acetate group effectively suppressed this unwanted reactivity because of its electron-withdrawing nature, leading to clean oxidation to sulfone **35**.

Allylic acetate **35** served as an excellent substrate for a π allyl Stille reaction²⁹ with vinyl stannane **38**³⁰ to form coupled product **39** in 55% yield along with 25% of the Grob fragmentation product (**40**). This fragmentation could be partially suppressed by converting the tertiary hydroxy group of **35** to a TMS ether, thus forming desired adduct **41** in 61% yield. To complete the macrocycle, primary alcohol **41** was converted to allylic bromide **42** which upon treatment with NaHMDS cleanly afforded macrocyclic product **43** with no trace of competing Grob fragmentation.³¹ The TMS group was readily cleaved under the action of an acidic Amberlyst[®] resin and methanol to give **44**.

<u>Divergent Reactivity in the Rh(I)-Catalyzed C–C Bond Cleav-</u> age

Our access to **44** demonstrated that the rigid [3.1.1]bicycle could be employed in the rapid construction of the carbocyclic framework of the phomactin natural products. With the macrocycle in place, we next investigated the selective scission of the embedded cyclobutanol. It is known that Rh(I) catalysts are efficient at effecting the desired C-C cleavage/protodemetalation on simpler substrates.³² However, the cyclobutanol ring opening of a complex substrate such as **44** was unprecedented. We were uncertain as to how (A) the additional strain resident in the macrocycle would affect the selectivity of the C-C bond cleavage, (B) whether Grob fragmentation would predominate, or (C) whether the presence of several double bonds in the substrate might bind the Rh complex in an unproductive manner or participate in unwanted side reactions.

We were pleased to find that heating cyclobutanol 44 with 10 mol % [Rh(cod)OH]₂ to 40 °C in deuterated benzene resulted in the desired C-C bond cleavage. However, it did not result in formation of desired cyclohexenone 45, but instead yielded the related β , γ -unsaturated ketone **46** (Scheme 3A). β_{γ} -Unsaturated ketone **46** presumably forms via the intermediacy of alkyl rhodium species 47 which undergoes a 1,3-Rh shift to give allylic rhodium species **48**.²² Protodemetalation with protonation occurring at the α position then furnishes the observed product. To probe this mechanistic hypothesis, small amounts of D₂O were added to the reaction mixture. A deuterium incorporation of 90% was observed at the position α to the carbonyl (see *d*-46) whereas no deuterium incorporation was observed on the methyl group (i.e., at C19), supporting an intramolecular rhodium shift that results in a protonation at C19.

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Scheme 2. Synthesis of Macrocycle via π-Allyl Stille Cross-Coupling



Interestingly, unconjugated enone 46 could not be readily purified and isolated. Upon its exposure to air, rapid oxidation occurred to give a 1:1 mixture of hydroxy enone 49 and enedione 50 in a combined yield of 50% (Scheme 3B).33 Although unexpected, we recognized that this facile oxidation could be beneficial since several of the phomactin natural products bear oxygenation at C13 (e.g., phomactins B2) (2) and K (9), see Figure 2). One possible explanation for this facile oxygenation is that the weakened α C–H bond of 46 allows for facile hydrogen atom abstraction to give allylic radical **51**.³⁴ Radical combination with triplet oxygen would form allylic peroxy species 52. This peroxy intermediate could either undergo in situ reduction to yield hydroxy enone 49 or suffer the formal loss of a hydroxyl radical to give enedione **50**. Importantly, hydroxy enone **49** was found to be stable and did not oxidize to enedione 50 over prolonged exposure to air. Furthermore, hydroxy enone 49 could be selectively formed if dimethyl sulfide was added to the reaction mixture immediately upon exposure of unconjugated enone 46 to air (Scheme 3C), supporting the hypothesis that both oxidation products arise from peroxy species 52.

Optimization of the Rh(I)-catalyzed C–C cleavage for conjugated enone **45** required a subsequent olefin isomerization. Although employing various bases was unsuccessful, switching the solvent from benzene to methanol enabled clean conversion to desired enone **45** in 89% yield (Scheme 3C). This ring cleavage/olefin isomerization transformation seems to occur through a pathway analogous to that shown in Scheme 3A by first forming β , γ -enone **46** followed by olefin isomerization. Conducting the reaction in deuterated methanol clearly shows the rapid formation of α -deutero ketone **d**-**46**, which slowly converts to γ -deutero enone **d**-**45**, consistent with this proposed mechanism.³⁵

At this point, we were emboldened by the fact that the Rh(I)-catalyzed C–C bond cleavage was achievable on this late-stage, complex substrate (i.e., **44**). Additionally, by subtly altering the conditions for this C–C cleavage transformation, cyclobutanol **44** could be converted into either cyclohexenone **45** or its hydroxylated variant, **49**. However, to fully elaborate either of these compounds into phomactin natural products, selective oxygenation at the doubly allylic position (C2) was required. Unfortunately, oxygenation at C2 proved to be an extremely challenging task. Due to the constrained macrocycle, the two π systems flanking C2 are not coplanar, resulting in less activation than would be

anticipated for a doubly allylic position. Furthermore, upon the generation of a radical at C2, rapid olefin isomerization occurred to form an undesired 1,3-diene system.³⁶ Given these challenges, which were not resolved even after exhaustive experimentation, we settled on examining synthetic routes where oxygenation at C2 was pre-installed.

Scheme 3. (A) Proposed Pathway for the Formation of Unconjugated Enone 46. (B) Mechanistic Hypothesis for the Formation of Oxidation Products 49 and 50. (C) Divergent Outcomes of the Rh(I)-Catalyzed C-C Cleavage



Scheme 4. Synthesis of Macrocycle via 1,2-Addition to Aldehyde 53

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<u>Revised Strategy: Fragment Coupling Using a 1,2-Addition</u> into an Aldehyde

We recognized that instead of appending the linear "strap" portion to allylic acetate **37**, a coupling partner with a higher oxidation state at C2 would maintain oxygenation after the coupling reaction. To this end, 1,2-addition to aldehyde 53, accessed in 3 steps from cyclobutanol 33, was pursued (Scheme 4).³⁷ Treatment of vinyl iodide 54³⁸ with t-butyl lithium at low temperatures followed by the addition of aldehvde 53 readily gave bis-allylic alcohol 55 in 68% yield as a 5:1 mixture of diastereomers. By advancing the major diastereomer, formation of the macrocycle occurred in a similar fashion as described for the previous route (see Scheme 2). The newly formed hydroxy group at C2 in 55 was first protected as the TBS ether, then sulfide oxidation was performed to give sulfone 56. Oxidative cleavage of the PMB group followed by bromination yielded allylic bromide 57, which upon treatment with NaHMDS cleanly afforded macrocycle 58 in 91% yield. Buffered conditions were then employed for silyl group removal (TASF and acetic acid) because the previously employed acidic conditions resulted in ionization of the bis-allylic TBS ether group whereas basepromoted cleavage conditions resulted in Grob fragmentation of **58**. Depending on the reaction temperature, cleavage of primarily one or both silyl ethers could be achieved to give cyclobutanol **59** or diol **60**, respectively.

39 Regarding the Rh(I)-catalyzed C-C bond cleavage step for 40 cyclobutanol **59**, the presence of a silvloxy group at C2 41 brought about a different reactivity profile as compared to 42 the previously employed cyclobutanol 44. Subjecting si-43 lyloxy cyclobutanol 59 to 10 mol % [Rh(cod)OH]2 in ben-44 zene resulted in the formation of triene **61**, presumably 45 arising from β -silvloxy elimination of an intermediate allyl 46 rhodium species (62, Scheme 5). As in our previous studies on cyclobutanol openings, switching the solvent from ben-47 zene to methanol resulted in the formation of desired cyclo-48 hexenone 63. Interestingly, and in direct contrast to the 49 conversion of 44 to 45, when the reaction was conducted in 50 deuterated methanol, deuterium incorporation was ob-51 served at C19 (the newly unveiled methyl group) and not at 52 the y position of enone **63**.³⁹ This observation strongly sup-53 ports protodemetalation at C19 outcompeting the 1,3-Rh 54 shift on alkyl rhodium species 64 in the presence of metha-55 nol. This outcome could be due to the additional steric bulk 56 of the TBS ether suppressing the 1,3-Rh shift and reducing 57 the formation of the competing β -silyloxy elimination 58

product. Of note, diol **60** also participated in the Rh(I)-catalyzed C–C bond cleavage process, producing the desired cyclohexanone (**65**) in 49% yield.





Next, we investigated the reductive removal of the sulfone moiety in macrocycle 65, fully aware that doing so in the presence of an enone moiety could be problematic due to its susceptibility to reduction (Scheme 6). Indeed, several conditions (such as samarium iodide) only served to reduce the enone, whereas milder reductants did not provide any reactivity. Interestingly, Birch-type dissolving metal conditions yielded fully reduced diol 66 as the minor product and cyclopropanol 67 as the major product. Presumably, cyclopropanol 67 formed from the addition of an incipient carbanion into the carbonyl group.⁴⁰ While cyclopropanol 67 was somewhat unstable, it was amenable to selective C-C cleavage by heating the mixture with sodium methoxide to give enone 68.41 In a way, the fortuitously formed cyclopropanol likely served as an in situ "protecting group" for the enone moiety, preventing further reduction under the harsh dissolving metal conditions.

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Scheme 6. Reductive Sulfone Cleavage and Rearrangement of the Resulting Cyclopropanol



At this stage, a single carbon atom remained to be installed through methylenation of enone 68 to complete the phomactin framework. Although seemingly trivial, this one carbon addition proved to be another major challenge. The majority of carbon-based nucleophiles that we investigated did not react with enone 68 (e.g., phosphonium salts or alkyl zinc reagents⁴²) whereas a few added in a 1,4-fashion (e.g., methyl lithium). From an examination of the conformation of **68**, it is clear that the Bürgi-Dunitz approach to the carbonyl group is extremely hindered. The macrocyclic "strap" sits directly underneath the cyclohexenone ring system, completely blocking this face. Moreover, the macrocycle locks the cyclehexenone into a conformation that places the C19 methyl group in a pseudo-axial position, severely obstructing a Bürgi-Dunitz approach to the carbonyl group from the top face.¹⁹ Given the challenges associated with a direct 1,2-addition to encumbered enone 68, we took a few steps back to again revise our synthetic strategy and incorporate the C20 group earlier in the sequence.

<u>Successful Strategy to the Phomactins: Early-Stage Cyclobu-</u> tanol Fragmentation

In order to efficiently install the carbon unit at C20, we recognized that cyclobutanol fragmentation and subsequent methylenation would be required prior to macrocyclization (Scheme 7). In our revised and ultimately successful synthetic approach, unified access to the phomactin terpenoids would be accomplished through selective oxygenation of common synthetic intermediate **25**, which could be formed through macrocyclization of sulfone **69**. As shown previously, addition of the "strap" portion (**70**) can be accomplished by 1,2-addition into aldehyde **71**. We posited that carbonyl methylenation would be viable on a less encumbered substrate such as enone **72**, which in turn can arise from C–C bond cleavage of cyclobutanol **33**.

Scheme 7. Revised Retrosynthetic Analysis with Early-Stage Cyclobutanol Fragmentation



The synthesis sequence commenced with cyclobutanol **33**, which upon exposure to 7.5 mol % of [Rh(cod)OH]₂ resulted in the desired C–C bond fragmentation (Scheme 8). Again, the use of methanol as solvent was required to achieve optimal yields. Sulfide to sulfone oxidation provided enone **72**. Although direct methylenation of enone **72** was still troublesome, we were pleased to find that unlike the more sterically congested **68**, treatment with methyl lithium added a methyl group in a 1,2-fashion to enone **72**. Subjecting the resulting 1,2-adduct to the Burgess reagent provided a two-step methylenation. Allylic oxidation at that stage with excess selenium dioxide provided aldehyde **71**.

Following a similar aldehyde 1,2-addition protocol as before (i.e., $53 \rightarrow 55$), vinyl iodide 70^{43} was treated with *t*-butyl lithium and added to aldehyde 71 at low temperatures to afford bis-allylic alcohol 73 as a 1:1 mixture of diastereomers. Protection of the resulting hydroxy group with a SEM group followed by cleavage of the TBS group and bromination of the primary alcohol group yielded allylic bromide 74. Macrocyclization proceeded smoothly to give macrocycle 75, even without the conformational bias imparted by the rigid [3.1.1] bicyclic scaffold that had been previously employed (i.e., $42 \rightarrow 43$ and $57 \rightarrow 58$). At this stage, reductive de-sulfonylation under Birch conditions afforded a modest amount of desired product 76. However, by switching to sodium-mercury amalgam, 76 was formed in a satisfactory 75% yield. Finally, cleavage of the SEM group with TBAF in DMPU gave alcohol **25** as a 1:1 mixture of diastereomers.⁴⁴ Although the stereochemistry at C2 is ultimately inconsequential, we found that only one of the two alcohol diastereomers was competent in subsequent chemistry. Therefore, a one-pot oxidation/reduction sequence was employed to give **25** as a single diastereomer. In this way, the desired common intermediate to the phomactins (25) is accessible in 16 steps from (+)-carvone, achieved through the strategic application of C-C bond cleavage of carvonederived cyclobutanol 33. This system is readied for diversification into numerous phomactin congeners.

Scheme 8. Final Route to Common Intermediate 25



Synthesis of Phomactins R, P, and K

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With the ultimate goal of synthesizing structurally complex phomactins such as phomactins A and T, we initially set our sights on advancing common intermediate 25 to the relatively less functionalized phomactin R (4, Scheme 9). Initial directed epoxidation studies with VO(acac)₂ and TBHP resulted in a complex mixture of epoxides arising from constitutional isomers as well as diastereomers. At low temperatures, switching the catalyst from VO(acac)₂ to VO(OEt)₃ resulted in improved selectivity, forming the desired epoxide (77) in 72% yield.⁴⁵ Nuclear Overhauser effect (nOe) correlations between the epoxide α -proton and the allylic methyl group aided in confirming the relative configuration of epoxide 77. Further confirmation was achieved upon alcohol oxidation with DMP to yield phomactin R (4), which provided data fully consistent with those reported in the literature, completing the total synthesis in 18 steps from (+)carvone.

Scheme 9. Total Synthesis of Phomactins R, P, and K



In line with the presumed biosynthetic pathway⁴⁶ to these natural products, sequential oxygenation of phomactin R (4) should lead to the formation of phomactins P (6) and K (9), respectively. Indeed, epoxidation of phomactin R (4) with DMDO furnished phomactin P (6); however, the major product was the diastereomeric compound resulting from epoxidation of the other alkene face. Switching the oxidant from DMDO to mCPBA reversed the diastereoselectivity and produced phomactin P (6) in 66% yield. Phomactin P (6) was further oxidized at C13 under Doyle oxidation conditions⁴⁷ using TBHP in the presence of Rh₂(cap)₄ to furnish phomactin K (9) following DBU promoted loss of *t*-butanol.

<u>Structural Revision of Sch 49027 and Synthesis of Phomactins</u> <u>A and T</u>

During the course of our epoxidation studies on common intermediate 25, we discovered that a second epoxidation can occur to give bis-epoxide 78 if the reaction was allowed to warm to 0 °C (Scheme 10). Again, the use of VO(OEt)₃ was critical for the successful formation of the bis-epoxide. We recognized that further oxidation to bis-epoxyketone 79 afforded a compound at the appropriate oxidation state to form phomactin A (1) following an epoxide-opening cascade. In theory, a water molecule could serve to open both epoxides and form tetrahydropyranone derivative 80. Furthermore, water-mediated allylic transposition could give phomactin A (1) following hemiketalization. Unfortunately, this cascade cyclization reaction was not realized in our hands. In fact, no reactivity was observed upon heating bisepoxyketone **79** with water, and the addition of Lewis acids either failed to facilitate reactivity or led to a complex mixture of non-specific decomposition products.

A more controlled and step-wise epoxide opening was next explored from bis-epoxyalcohol **78**. After considerable experimentation, we found that utilizing Me₄NBH(OAc)₃ as a Lewis acid resulted in a mixture of compounds (**81**, **82**, and **83**), all seemingly arising from the same allylic cation (**81** from a Meinwald rearrangement; **82** and **83** from acetate trapping).⁴⁸ The addition of CsOAc to the reaction mixture resulted in a slight increase in the relative amount of acetate **83** that was formed, whereas adding 18-crown-6 to this mixture resulted in complete selectivity for this C20 acetate (**83**). The free diol (**84**) was liberated from **83** by filtration over a pad of silica gel.

Selective mono-oxidation of diol **84** with DMP was accomplished at 0 °C to yield ketone **85**. Surprisingly, quenching the reaction mixture with NaOMe (intended to cleave the acetyl group) resulted in a compound that matched the spectral data for Sch 49027. Although double bond isomerization could not be ruled out, the more likely product of the reaction is allylic alcohol **86**, which led us to speculate that **86** is the true structure of Sch 49027 and not the originally proposed enol-containing **7**. The revised structure for Sch 49027 (**86**) was corroborated by careful analysis of several 2D NMR experiments – key HMBC correlations are indicated in Scheme 10 and COSY correlations were observed between all the protons in the cyclohexyl ring system.⁴⁹

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Scheme 10. Total Synthesis of Phomactin A and Sch 49027 (Revised Structure)



Epimerization of the secondary allylic hydroxy group of Sch 49027 (86) was expected to lead to spontaneous cyclization (see allylic alcohol 88) and formation of phomactin A (1). In practice, oxidation of diol 84 with DMP at room temperature led to the formation of ketone 87 after quenching with NaOMe to cleave the acetyl group and achieve spontaneous hemiketalization. Treatment of ketone 87 with NaBH₄/CeCl₃ or LiAlH₄ did not lead to formation of phomactin A (1) but instead led to the exclusive formation of Sch 49027 (86). This alternative synthesis of 86 further corroborates the revised structure of this natural product. Switching to a sterically larger reductant such as DIBAL-H resulted in a 1:2 mixture of phomactin A (1) and Sch 49027 (86), and utilizing Red-Al® gave a 2.2:1 mixture of the natural products, ultimately yielding phomactin A (1) in 51% and completing its total synthesis in 20 steps from (+)-carvone.

The synthesis of the structurally unique phomactin T (5) required additional oxidation at C20. To achieve this, allylic epoxide 78 was subjected to Me₄NBH(OAc)₃ as before and then quenched with NaOMe to give triol 89 (Scheme 11). Global oxidation of triol 89 with DMP at 60 °C successfully delivered aldehyde 90.50 Pinnick oxidation of aldehyde 90 was unsuccessful. However, we were excited to find that oxidation of 90 with mCPBA in wet DCM directly furnished lactol 92. This process likely occurs first through diastereoselective epoxidation to give epoxy-aldehyde 91, then aldehyde hydration followed by a transannular epoxide opening. Lactol 92 proved unstable to isolation, so a one-step protocol was developed wherein manganese dioxide was added along with mCPBA to directly furnish phomactin T (5) from aldehyde 90, completing the total synthesis of this topologically unique congener in 20 steps from (+)-carvone.

Scheme 11. Total Synthesis of Phomactin T



CONCLUSION

The phomactin terpenoids continue to provide fertile ground for pushing the limits of modern synthetic chemistry. By leveraging a Rh(I)-catalyzed C-C bond cleavage reaction, we were able to access "rearranged" carvone skeletons and address a key challenge in phomactin synthesis the enantiospecific construction of the congested cyclohexyl core. This key recognition of the relationship between carvone and the cyclohexyl core of the phomactins enabled the development of efficient syntheses of diverse phomactin congeners in enantioenriched form, culminating in the syntheses of phomactins A, K, P, R, T and Sch 49027, with the latter structure reassigned as a result of this total synthesis effort. Each of these terpenoids was synthesized in 18-20 steps from (+)-carvone. Additionally, each natural product was produced in just 2-4 steps from a common late-stage intermediate (25) through a series of carefully choreographed oxidation or rearrangement steps, underscoring the unified approach that was developed.

As a result of this total synthesis endeavor, many intricacies of transition metal-mediated C-C bond cleavage have become apparent. Rh(I)-catalyzed fragmentation of cyclobutanols 44 and 59 revealed alternative processes that can occur on complex substrates, for example, rhodium shift, deconjugation, oxygenation, or silvloxy elimination. Additionally, slight differences in substrates or reaction conditions were found to influence the protodemetalation step, a phenomenon uniquely brought to light through the application of C-C cleavage in a complex molecule setting.

More fundamentally, this work has demonstrated the power of strategic C-C bond cleavage reactions in total synthesis. While our strategy of cyclobutanol formation followed by C-C cleavage might be non-intuitive, the overall goal of remodeling carbocyclic skeletons warrants further investigation and applications by the chemical community. Furthermore, transition metal-mediated C-C cleavage processes that concurrently forge one or more new bonds (via cyclization or coupling) uniquely hold the power to deconstruct and reconstruct carbocyclic frameworks in rapid fashion. Future advancements in simultaneous C-C cleavage and reforming processes, as well as methodologies to selectively cleave C-C bonds in unstrained rings, will further advance the field of complex natural product synthesis.51

ASSOCIATED CONTENT

The following is available as Supporting Information: Experimental details and spectroscopic data.

This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) As seen in a related X-ray structure, the C4–C5 bond is the stronger, shorter bond (1.551 Å) compared to the weaker and longer C2–C5 bond (1.567 Å), see ref. 22.

(24) Previous synthetic work to construct the phomactin skeleton indicated that the macrocyclization step can be challenging and low yielding, particularly if the carbon at C1 is sp² hybridized. Macrocyclization with substrates where C1 is sp³ hybridized are often more facile, most likely due to better preorganization of the pendant functional group. For example, see ref. 13f vs 15a. The sulfone alkylation strategy employed in this work was previously shown to be effective, but only if C1 was sp³ hybridized, see ref. 13I and 13s. We initially hypothesized that the rigid [3.1.1]bicycle would help facilitate cyclization while still maintaining sp² hybridization at C1. However, as shown in the final synthetic route (Scheme 8), this rigid bicycle was ultimately not required for successful macrocyclization.

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(35) See Supporting Figures 1 and 2 for details.

(36) See Supporting Table 1 for details.

(37) Other groups have utilized a similar aldehyde addition strategy, see ref. 13z and 14.

(38) Synthesized in 5 steps from 4-pentyn-1-ol. See Supporting Information for details.

(39) See Supporting Figure 3 for details.

(40) Formation of the cyclopropane ring of **67** is likely facilitated by close proximity of the transient carbanion to the carbonyl moiety. A related cyclopropane was observed in the reductive desulfonylation of a phomactin intermediate, see ref. 13cc.

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