Title
C–C Bond Cleavage of α-Pinene Derivatives Prepared from Carvone as a General Strategy for Complex Molecule Synthesis

Journal
Accounts of Chemical Research, 55(5)

ISSN
0001-4842

Authors
Lusi, Robert F
Perea, Melecio A
Sarpong, Richmond

Publication Date
2022-03-01

DOI
10.1021/acs.accounts.1c00783

Peer reviewed

ACCOUNTS of chemical research

pubs.acs.org/accounts Article

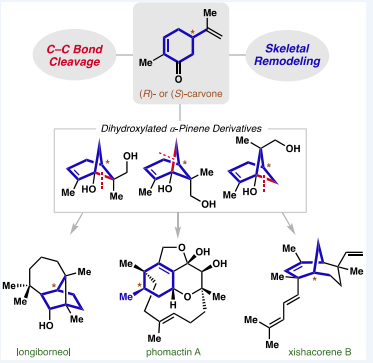
C−C Bond Cleavage of α-Pinene Derivatives Prepared from Carvone as a General Strategy for Complex Molecule Synthesis

Robert F. Lusi,[§] Melecio A. Perea,[§] and Richmond Sarpong*

Cite This: *Acc. Chem. Res.* 2022, 55, 746−758 Read Online

ACCESS | Metrics & More | Article Recommendations

CONSPECTUS: The preparation of complex molecules (e.g., biologically active secondary metabolites) remains an important pursuit in chemical synthesis. By virtue of their sophisticated architectures, complex natural products inspire total synthesis campaigns that can lead to completely new ways of building molecules. In the twentieth century, one such paradigm which emerged was the use of naturally occurring "chiral pool terpenes" as starting materials for total synthesis. These inexpensive and naturally abundant molecules provide an easily accessed source of enantioenriched material for the enantiospecific preparation of natural products. The most common applications of chiral pool terpenes are in syntheses where their structure can, entirely or largely, be superimposed directly onto a portion of the target structure. Less straightforward uses, where the structure of the starting chiral pool terpene is not immediately evident in the structure of the target, can be more challenging to implement. Nevertheless, these "nonintuitive" approaches illustrate the ultimate promise of chiral pool-based strategies: that any single chiral pool terpene could be applied to syntheses of an indefinite number of structurally diverse complex synthetic targets.



By definition, such strategies require carefully orchestrated sequences of C−C bond forming and C−C cleaving reactions which result in remodeling of the terpene architecture. The combination of traditional rearrangement chemistry and transition-metal-catalyzed C−C cleavage methods, the latter of which were primarily developed in the early twenty-first century, provide a rich and powerful toolbox for implementing this remodeling approach. In this Account, we detail our efforts to use a variety of C−C cleavage tactics in the skeletal remodeling of carvone, a chiral pool terpene. This skeletal remodeling strategy enabled the reorganization of the carvone scaffold into synthetic intermediates with a variety of carboskeletons, which we, then, leveraged for the total syntheses of structurally disparate terpene natural products.

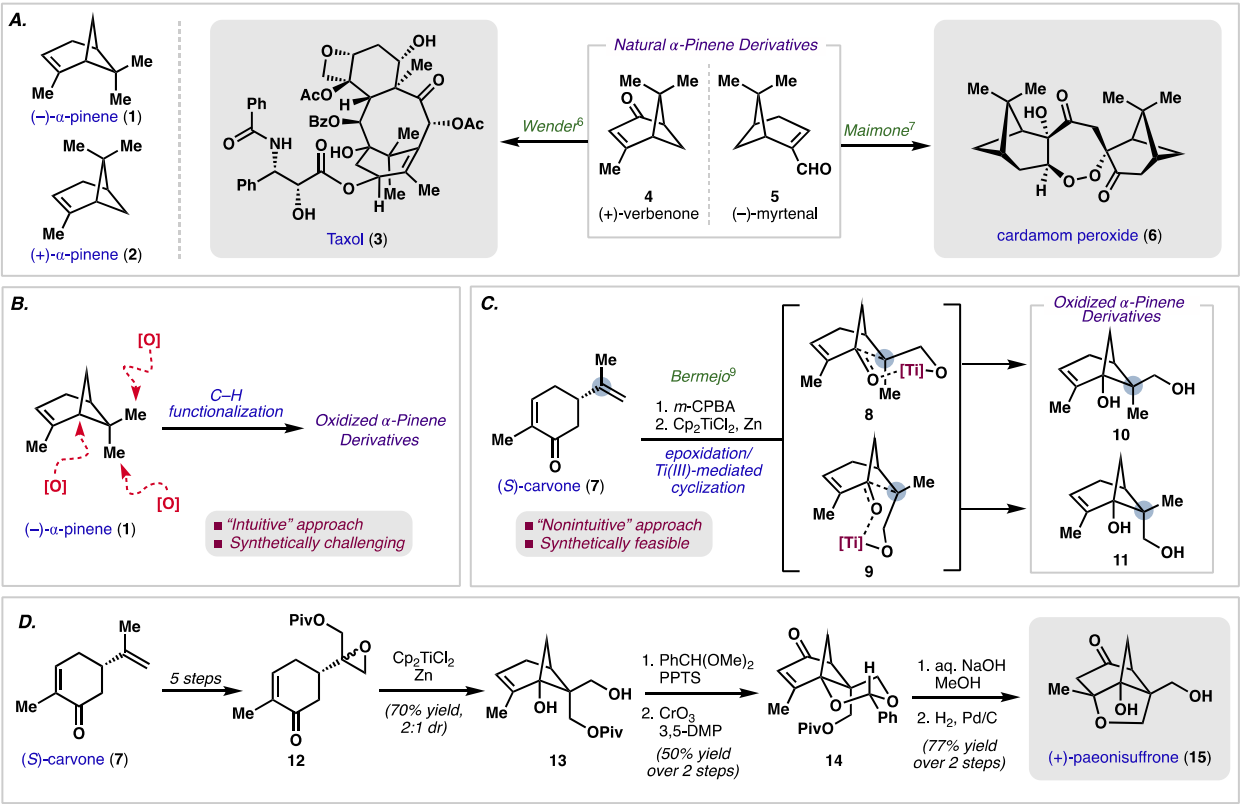
We begin by describing our initial investigations into various, mechanistically distinct C−C cleavage processes involving cyclobutanols synthesized from carvone. These initial studies showcased how electrophile-mediated semipinacol rearrangements of these cyclobutanols can lead to [2.2.1]bicyclic intermediates, and how Rh- and Pd-catalyzed C−C cleavage can lead to a variety of densely functionalized cyclohexenes pertinent to natural product synthesis. We, then, present several total syntheses using these synthetic intermediates, beginning with the bridged, polycyclic sesquiterpenoid longiborneol, which was synthesized from a carvone-derived [2.2.1]bicycle following a key semipinacol rearrangement. Next, we discuss how several members of the macrocyclic phomactin family were synthesized from a cyclohexene derivative prepared through a Rh-catalyzed C−C cleavage reaction. Finally, we describe our synthesis of the marine diterpene xishacorene B, which was prepared using a key Pd-catalyzed C−C cleavage/cross-coupling that facilitated the assembly of the core [3.3.1]bicycle that is resident in the natural product structure.

KEY REFERENCES

- Masarwa, A.; Weber, M.; Sarpong, R. Selective C−C and C−H Bond Activation/Cleavage of Pinene Derivatives: Synthesis of Enantiopure Cyclohexenone Scaffolds and Mechanistic Insights. *J. Am. Chem. Soc.* **2015**, *137*, 6327−6334.[1] *This work demonstrates that Rh-catalyzed C−C bond cleavage and electrophile induced semipinacol rearrangements of carvone derived cyclobutanols can be used to access densely functionalized cyclohexyl and [2.2.1]-bicyclic intermediates.*
- Lusi, R. F.; Sennari, G.; Sarpong, R. Total Synthesis of Nine Longiborneol Sesquiterpenoids Using a Function-alized Camphor Strategy. *Nat. Chem.*, 2022. 10.1038/s41557-021-00870-4.[2] *This work demonstrates that the [2.2.1]bicycle intermediates accessed by scaffold remodeling of carvone can be used to prepare bridged polycyclic*

Received: December 17, 2021
Published: February 16, 2022

Scheme 1. Pinene Derivatives in Chemical Synthesis: (A) Synthesis of Taxol and Cardamom Peroxide from Verbenone and Myrtenal, (B) "Intuitive" C−H Functionalization Approach to Pinene Derivatives, (C) "Nonintuitive" Carvone-Remodeling Approach to Pinene Derivatives, and (D) Bermejo's Synthesis of (+)-Paeonisuffrone



terpenes, enabling a synthetic strategy that is orthogonal to traditional approaches.

- Kuroda, Y.; Nicacio, K. J.; da Silva, I. A., Jr.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R. Isolation, Synthesis, and Bioactivity Studies of Phomactin Terpenoids. *Nat. Chem.* **2018**, *10*, 938−945.[3] *This work demonstrates that our scaffold remodeling strategy can enable efficient preparation of the cyclohexyl fragment of the phomactin diterpenoids. This addresses a long-standing challenge in the synthesis of these molecules and enables a uniquely divergent synthesis.*
- Kerschgens, I.; Rovira, A. R.; Sarpong, R. Total Synthesis of (−)-Xishacorene B from (R)-Carvone Using a C−C Activation Strategy. *J. Am. Chem. Soc.* **2018**, *140*, 9810−9813.[4] *This work demonstrates the Pd-catalyzed C−C bond cleavage/cross-coupling as a strategy to access the diterpene xishacorene B.*

1. INTRODUCTION

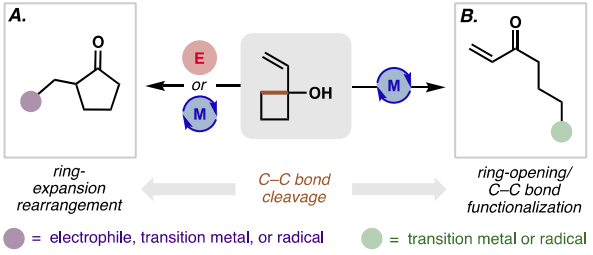
Chiral pool terpenes (e.g., **1** and **2**, Scheme 1A) are a collection of naturally occurring, stereochemically rich feedstock chemicals that have been employed for decades as building blocks in the synthesis of topologically complex natural products.[5] One prominent example of this paradigm is Wender's 1997 total synthesis of Taxol (**3**), in which the naturally occurring α-pinene (**1** and **2**) derivative verbenone (**4**) was utilized in a creative photorearrangement (Scheme 1A).[6] In a complementary example, Maimone and co-workers illustrated how leveraging myrtenal (**5**), another naturally occurring α-pinene derivative, in a novel "oxygen-stitching" strategy could facilitate rapid access to the antimalarial natural product cardamom peroxide (**6**; Scheme 1A).[7] Notably, in Wender's synthesis, the carbonyl group in verbenone, which is derived from an oxidation of the allylic methylene of α-pinene, enabled the key photorearrangement. In Maimone's synthesis, the aldehyde of myrtenal, resulting from oxidation of the allylic methyl group of α-pinene, set the stage for accessing the cardamom peroxide skeleton using a McMurry coupling. Therefore, it stands to reason that oxidation at other sites of α-pinene, such as at the bridgehead position or either methyl of the *gem*-dimethyl grouping, could pave the way to other natural product scaffolds. However, accessing the requisite oxygenated derivatives directly from pinene (i.e., the intuitive approach) is challenging as it would require site-selective functionalizations of unreactive C(sp^3)−H bonds (Scheme 1B).[8] To circumvent this obstacle, Bermejo and co-workers developed a non-intuitive strategy for accessing unnatural hydroxylated pinene derivatives such as **10** and **11** (Scheme 1C). Epoxidation of the isopropenyl moiety of (*S*)-carvone (**7**), followed by a Ti(III)-mediated epoxide radical ring-opening/cyclization, likely proceeding through chairlike transition states **8** and **9**, furnished pinene cyclobutanols **10** (as the major diastereomer) and **11** (as the minor disatereomer).[9] This carvone-remodeling tactic subsumed the carvone isopropenyl unit into the characteristic [3.1.1]bicycle of pinene and ultimately provided an opportunity to achieve both oxygenation of the bridgehead position and the *gem*-dimethyl groups. Following this initial report, Bermejo and co-workers showcased the power of this strategy in a concise synthesis of (+)-paeonisuffrone (**15**;

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 1D).[10] Beginning from (*S*)-carvone, the authors synthesized epoxy pivalate **12**, which was then subjected to the key Ti(III)-mediated cyclization to afford cyclobutanol **13** as the major diastereomer. Protection of the resulting diol followed by allylic oxidation provided enone **14**, which was converted to (+)-paeonisuffrone by cleavage of the pivalate group and 1,4-addition of the unveiled primary hydroxy group into the enone. Overall, this work set the stage for our own recognition that these cyclobutanols could provide a platform for further development of novel synthetic strategies.

Motivated by our group's longstanding interest in developing new strategies for chemical synthesis, we sought to employ the Bermejo dihydroxylated pinenes as versatile intermediates in the preparation of diverse families of natural products. The versatility of these pinene derivatives can be attributed to two key characteristics: (1) both enantiomers of **10** and **11** are readily prepared from carvone, a feedstock chemical available in both enantiomeric forms, and (2) the bicycles feature an embedded cyclobutanol motif, which could be manipulated in myriad ways to achieve structural diversification. Cyclobutanols, by virtue of their ring strain,[11] are privileged scaffolds for C−C bond cleavage methodologies.[12] Specifically, they are known to undergo both ring-expansion rearrangements[13] (Scheme 2A) and ring-opening/

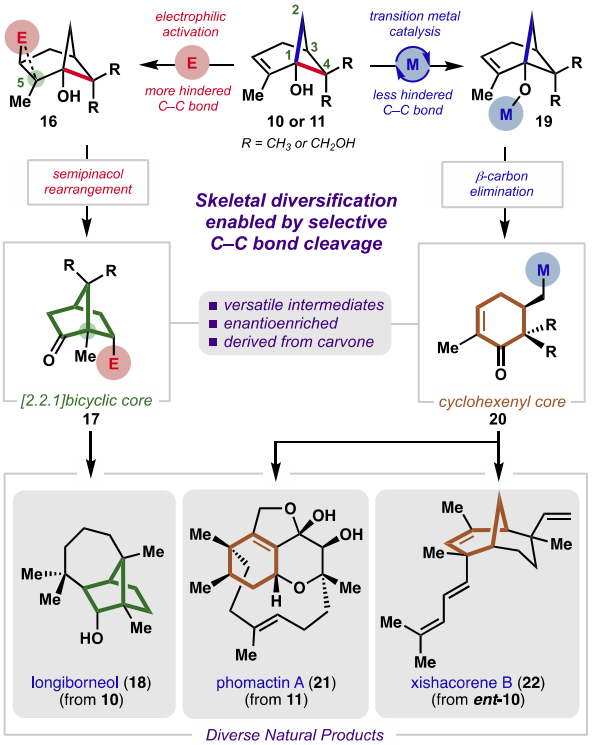
Scheme 2. C−C Bond Cleavage Paradigm of Cyclobutanols: (A) Ring-Expansion Rearrangements and (B) Ring-Opening/C−C Bond Functionalization



C−C bond functionalizations (Scheme 2B) via either two-electron[14] or one-electron[15] pathways. At the outset of our studies, C−C bond cleavage tactics involving chiral pool derived cyclobutanols were relatively underexplored in complex molecule synthesis,[16] which, to us, prompted the fundamental question of the research described herein: can C−C bond cleavage serve as a strategy to effect deep-seated skeletal changes in **10** and **11** to remodel them into a variety of natural product precursors? Execution of this strategy would not only set the stage for the synthesis of structurally disparate natural products but would also showcase the nonintuitive utility of carvone and C−C bond cleavage tactics in complex molecule synthesis.

In designing our strategy, we envisioned that either of the two C−C bonds proximal to the tertiary hydroxy group of the cyclobutanol in **10** or **11** could be selectively cleaved by leveraging their distinct steric environments (Scheme 3). We hypothesized that selectivity for these orthogonal C−C bond cleavage events could be achieved depending on the specific reaction conditions employed. For instance, activation of the olefin group in **10** or **11** with an appropriate electrophile would render the C5 position electrophilic (see intermediate **16**), promoting selective cleavage/migration of the more substituted C1−C4 bond[17] (highlighted red in Scheme 3) via

Scheme 3. Our General C−C Bond Cleavage Strategies Employed in the Total Synthesis of Complex Terpene Natural Products



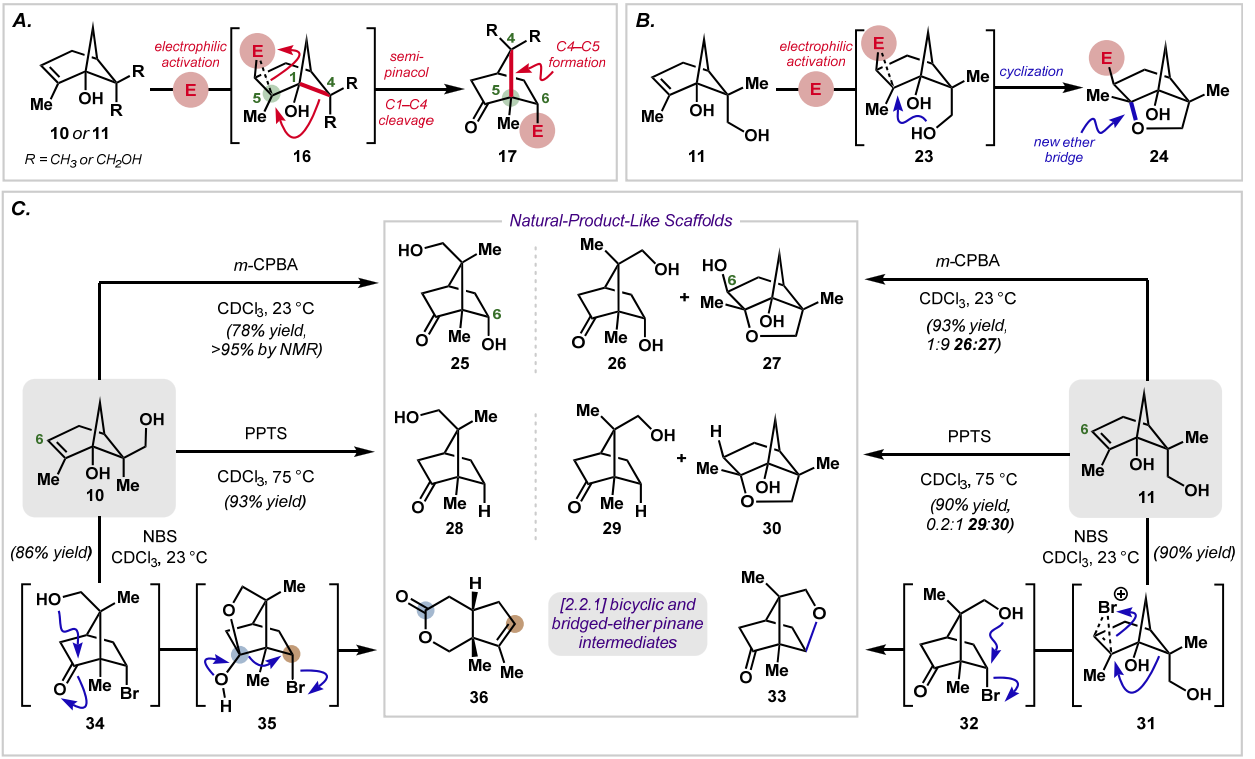
semipinacol rearrangement.[18] Such a reaction would furnish [2.2.1]bicyclic intermediates (such as **17**), which we envisioned could be used to access natural products such as longiborneol[2] (**18**). Conversely, generation of a transition metal alkoxide (**19**) from **10** or **11** would lead to selective cleavage of the less substituted C1−C2 bond[19] (highlighted blue in Scheme 3) through a *β*-carbon elimination, leading to versatile organometallic-cyclohexenyl intermediates (e.g., **20**) that are poised to undergo further complexity-building reactivity. Reaction products derived from these intermediates would set the stage for syntheses of natural products such as phomactin A[3] (**21**) and xishacorene B[4] (**22**). Traditionally, accessing highly substituted, stereochemically rich cyclohexenyl cores, such as **20**, in an efficient manner has been challenging.[3] Notably, our strategy would serve as a solution to this long-standing problem. Overall, in concert with the work of Bermejo and co-workers, these strategies enable rapid access to enantioenriched, highly functionalized pinene, camphor, and cyclohexenone derivatives from carvone, thus providing a general platform for diverse terpene natural product synthesis.

2. ELECTROPHILE-MEDIATED SKELETAL REMODELING OF CARVONE-DERIVED PINENE-DERIVATIVES

We, first, investigated rearrangements of **10** and **11** induced by electrophilic activation of the alkene group and found that two modes of reactivity could be achieved.[1] In the first mode (Scheme 4A), which is observed with both **10** and **11**, electrophilic activation of the more sterically accessible face of the C−C double bond (opposite the C4 quaternary center) creates an electrophilic site at C5, leading to a strain-accelerated semipinacol rearrangement. This sequence results

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 4. Electrophile-Mediated Skeletal Remodeling of Carvone-Derived Cyclobutanols: (A) Synthesis of Bicyclo[2.2.1] Scaffolds (25, 26, 28, 29, 33), (B) Synthesis of Ether-Bridged Tricyclic Scaffolds (27, 30, 33), and (C) Overview of Reaction Conditions Leading to Natural-Product-like Scaffolds



in selective C1−C4 bond cleavage, furnishing bicyclo[2.2.1] carboskeletons (e.g., **17**). In cases where C5 remains coordinatively saturated (e.g., when **10** or **11** is epoxidized), this selectivity likely results from the stereoelectronically more favored antiperiplanar relationship between the C1−C4σ and the C5−Eσ* orbitals.[17] Furthermore, upon protonation of **10** or **11** to generate a C5 carbocation, selectivity for C1−C4 bond cleavage is also observed due to the greater migratory aptitude of C4, compared to C2. In the second mode, additional products were observed, due to the stereochemical configuration of C4 in **11**. In this case, electrophilic activation resulted in cyclization of the primary hydroxy group to C5 (see intermediate **23**), which furnished ether-bridged tricycles (e.g., **24**). This mode of reactivity was not unexpected, as it resembles the final conjugate addition employed in Bermejo's synthesis of (+)-paeonisuffrone (see **14** → **15**, Scheme 1). Thus, the reactivity paradigms of **10** and **11** with electrophilic reagents are as follows: **10** leads to bicyclo[2.2.1] products, through semipinacol rearrangement, while **11** leads to similar [2.2.1]bicycles as well as tricyclic ethers resulting from nucleophilic etherification (Scheme 4A, B).

We examined the scope of the reactions outlined above with respect to the electrophile (Scheme 4C). We found that **10** reacted with *m*-CPBA to give dihydroxycamphor **25** (Scheme 4C, top left). Notably, epoxide ring-opening, through the desired semipinacol rearrangement, resulted in hydroxylation of the C6 position. Similarly, treatment of **11** with *m*-CPBA gave **26** and **27** in a 1:9 ratio (Scheme 4C, top right). Reactions of **10** and **11** with pyridinium *p*-toluenesulfonate (PPTS) led to similar products (**28**−**30**), where C6 was converted to a methylene group (Scheme 4C, middle). Presumably, these products are generated via a C5 carbocation intermediate. Unexpectedly, we found that subjecting **11** to *N*-bromosuccinimide (NBS) gave tricyclic ether **33** (Scheme 4C, bottom right). This product likely resulted from conversion of **11** to the corresponding bromonium ion (**31**), which then underwent a semipinacol rearrangement to brominated camphor derivative **32**. Nucleophilic attack of the hydroxy group onto the alkyl bromide then gave tricyclic ether **33**. When **10** was treated with NBS, a similar semipinacol rearrangement gave alkyl bromide **34** (Scheme 4C, bottom left). In this case, nucleophilic addition of the hydroxy group into the proximal ketone produced acetal **35**, which underwent a Grob fragmentation to yield bicyclic lactone **36**.

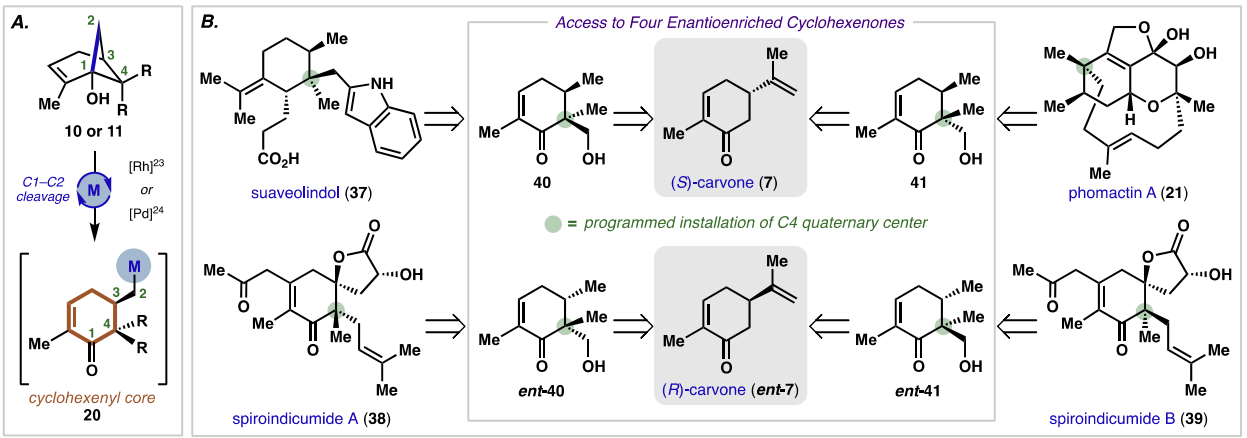
In summary, reaction of **10** or **11** with *m*-CPBA, PPTS, and NBS yields a variety of highly diverse natural product-like scaffolds. These include: bridged-ether pinane (**27** and **30**), hydroxylated camphor analogues (**25**, **26**, **28**, and **29**), and 5/6-fused bicyclic ring systems (**36**). In the past, substituted camphor analogues have been valuable intermediates in total synthesis; however, there are few strategies for the preparation of C6 functionalized derivatives.[20] Notably, our preparation of these analogues from carvone serves as a nonintuitive solution to this long-standing challenge. By leveraging **28** as a starting material in our synthesis of longiborneol (vide infra), we have showcased how camphor derivatives may serve as valuable intermediates in the preparation of complex molecules.

3. TRANSITION METAL-CATALYZED SKELETAL REMODELING OF CARVONE-DERIVED PINENE DERIVATIVES

Concurrent with our investigations into the skeletal restructuring of cyclobutanols **10** and **11** using electrophilic activation, we envisioned an orthogonal strategy for skeletal remodeling

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

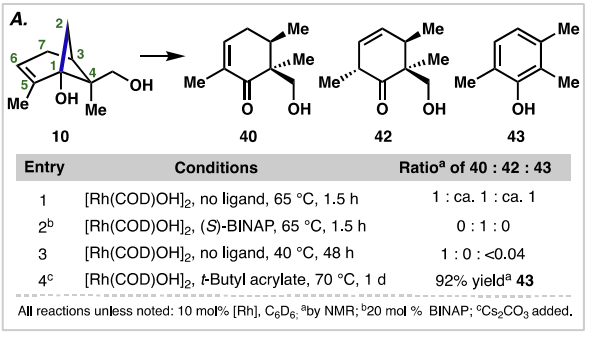
Scheme 5. Transition Metal-Catalyzed Skeletal Remodeling of Carvone-Derived Cyclobutanols: (A) General Cyclohexenone Synthesis and (B) Unified Synthesis of Natural-Product-like Scaffolds from Carvone



through transition metal catalysis.[1] Specifically, we hypothesized that transition metal-catalyzed β-carbon elimination could effect cleavage of the sterically less-hindered C1−C2 bond of **10** or **11** and lead to the synthetically versatile cyclohexenyl core (**20**). This metalated intermediate could be leveraged to access a variety of products, all of which contain a preinstalled quaternary center and several functional groups poised for subsequent derivatization (Scheme 5A). In general, while C−C bond cleavage processes face several thermodynamic and kinetic obstacles,[21] it is well-established that strained systems, such as cyclobutanols, are primed for both Rh(I)-catalyzed[22] and Pd(II)-catalyzed[23] C−C bond cleavage. Additionally, the ability to tune transition metal complexes both sterically and electronically, combined with their well-documented propensity to promote β-carbon elimination at the least sterically hindered C−C bond, added to our confidence that we could achieve the desired selectivity. Ultimately, we envisioned that this approach would have the potential to establish a unified synthetic approach to several enantioenriched natural products (e.g., **21**, **37**−**39**), each containing a densely functionalized cyclohexenyl core with an all-carbon quaternary center (Scheme 5B). These natural products would, thus, be prepared in enantioenriched form from the corresponding cyclohexenone derivatives (e.g., **40** and **41**, or enantiomers thereof), starting from the appropriate enantiomer of carvone (**7** or *ent*-**7**). Because complete control over the absolute and relative configurations of the C3−C4 stereodiad is achieved, this strategy, in principle, could extend beyond the representative natural products shown in Scheme 5 and ultimately enable access to myriad natural products containing this key cyclohexenyl motif.

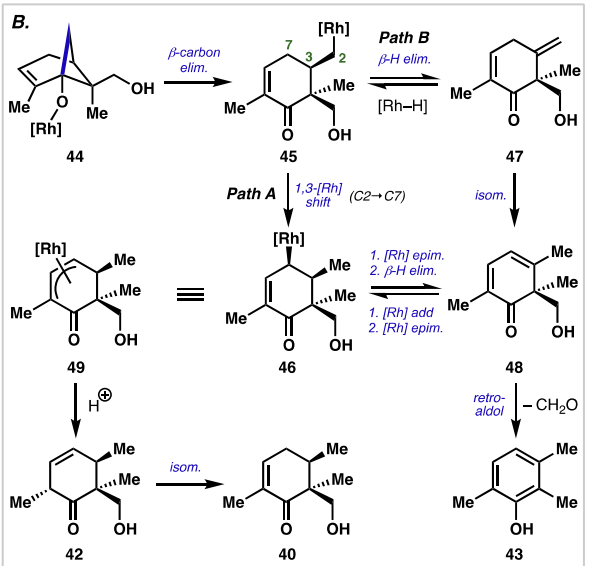
Our studies commenced by first examining the Rh-catalyzed C−C bond cleavage of cyclobutanol **10** using conditions similar to those employed by Murakami[24] and Cramer[25] (Scheme 6). Using **10**, we found that treatment with $[Rh(COD)OH]_2$ at 65 °C for 1.5 h (entry 1, Scheme 6A) afforded a mixture of products, including desired cyclohexenone **40** and side-products **42** and **43**. The addition of (*S*)-BINAP (entry 2) precluded the formation of cyclohexenone **40** and phenol **43** and instead provided cyclohexene **42**, exclusively. Notably, use of *R*-BINAP led to no observed products from the ring-opening reaction, and only delivered a complex reaction mixture. Gratifyingly, it was found with further optimization that the desired cyclohexenone (**40**)

Scheme 6. Rh-Catalyzed C−C Bond Cleavage of Major Cyclobutanol 10: (A) Optimization of C−C Bond Cleavage of 10 and (B) Proposed Mechanism of C−C Bond Cleavage of 10



Entry	Conditions	Ratio[a] of 40 : 42 : 43
1	$[Rh(COD)OH]_2$, no ligand, 65 °C, 1.5 h	1 : ca. 1 : ca. 1
2[b]	$[Rh(COD)OH]_2$, (*S*)-BINAP, 65 °C, 1.5 h	0 : 1 : 0
3	$[Rh(COD)OH]_2$, no ligand, 40 °C, 48 h	1 : 0 : <0.04
4[c]	$[Rh(COD)OH]_2$, *t*-Butyl acrylate, 70 °C, 1 d	92% yield[a] **43**

All reactions unless noted: 10 mol% [Rh], C_6D_6; [a]by NMR; [b]20 mol % BINAP; [c]Cs_2CO_3 added.



could be obtained as the major product over a prolonged reaction time and at a lower temperature without need for a ligand (entry 3).

The proposed mechanism for the formation of **40**, **42**, and **43** from cyclobutanol **10** is outlined in Scheme 6B. The pathway to all three products begins with in situ generated Rh-alkoxide **44** undergoing selective C1−C2 β-carbon elimination to furnish C2 alkyl-Rh intermediate **45**. At this divergence

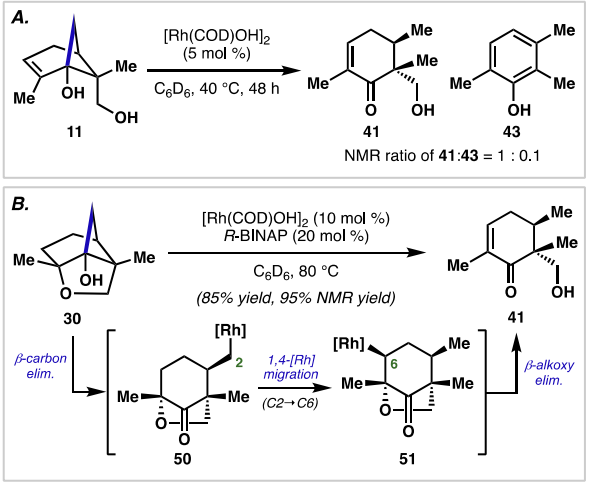
https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

point, **45** can lead either to products **40** and **42**, or product **43** via two possible pathways (path A and B). Beginning with formation of **40** and **42**, C2 alkyl-Rh **45** can either undergo a 1,3-Rh shift[26] through C−H activation[27,28] (Path A) or a series of isomerization events (path B) to give C7 alkyl-Rh intermediate **46**. More specifically, the synthesis of **46** via path B entails the C2 alkyl-Rh complex (**45**) first undergoing β-hydride elimination to give cyclohexenone intermediate **47**, followed by isomerization of the newly formed C2−C3 exomethylene to the internal C3−C7 olefin to provide diene **48**. Reinsertion of Rh−H[29] (formed from the preceding β-hydride elimination) to the C3−C7 olefin of **48** furnishes C7 alkyl-Rh intermediate **46**, which can be represented by its π-allyl form (**49**). Protonation of the presumed Rh-enolate[30] delivers cyclohexene **42**, and further isomerization of this product to establish conjugation delivers desired cyclohexenone **40**. On the other hand, phenol **43** is formed following formation of diene **48** through path A by epimerization of the C7 alkyl-Rh intermediate **46**, followed by β-hydride elimination, or through path B (vide supra). Upon formation of diene **48**, a retro-aldol/aromatization process extrudes formaldehyde, thus giving phenol **43**. Of note, the addition of *t*-butyl acrylate to the reaction mixture (entry 4, Scheme 6A) provided phenol **43** as the major product in 92% yield, presumably by trapping the Rh−H formed during **45** → **47**, and thereby impeding the previously competitive formation of **40**. Additionally, when the derivative of **10** bearing an acetylated primary hydroxy group was subjected to these reaction conditions (not shown), acetylated **48** was obtained as the major product (70% yield), thus providing further support for our mechanistic rationale.

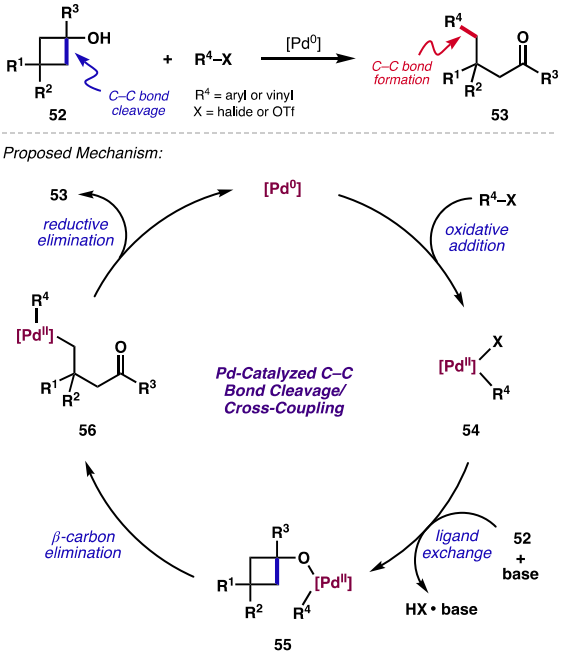
In addition to major cyclobutanol **10**, minor cyclobutanol **11** also proved competent in the Rh-catalyzed C−C bond cleavage reaction (Scheme 7A). Treatment of **11** with the optimized conditions developed for **10** (see Scheme 6A, entry 3) provided desired cyclohexenone **41** as the major product with minimal competing formation of phenol **43** (Scheme 7A). Alternatively, cyclohexenone **41** could be obtained from ether-bridged tricycle **30** upon treatment with $[Rh(COD)OH]_2$ and *R*-BINAP at 80 °C (Scheme 7B). This process is believed to proceed through β-carbon elimination to form C2 alkyl-Rh intermediate **50**, followed by a 1,4-Rh migration[31] to provide C6 alkyl-Rh intermediate **51**. This intermediate then undergoes a β-alkoxy elimination to forge cyclohexenone **41** in overall good yield (85% yield, 95% by ^{1}H NMR).

Following our studies into the Rh-catalyzed C−C bond cleavage of cyclobutanols **10** and **11**, we expanded upon this work by developing a complementary Pd-catalyzed tandem C−C bond cleavage/cross-coupling approach.[32] Previously, Uemura and co-workers demonstrated a Pd-catalyzed C−C bond cleavage/cross-coupling of simple *tert*-cyclobutanols (e.g., **52**) with aryl or vinyl halides (Scheme 8).[33]

Scheme 7. (A) Rh-Catalyzed C−C Bond Cleavage of Minor Cyclobutanol 11 and (B) Rh-Catalyzed C−C Bond Cleavage of Tricycle 30



Scheme 8. Pd-Catalyzed C−C Bond Cleavage/Cross-Coupling by Uemura and Coworkers

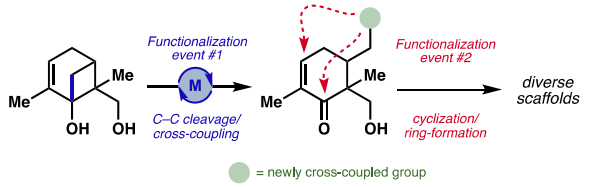


Mechanistically, this sequence begins with a Pd(0) oxidative addition into the C−X bond of the cross-coupling electrophile to give **54**, followed by ligand exchange with cyclobutanol **52** to form Pd-alkoxide **55**. Next, β-carbon elimination leads to alkyl-Pd intermediate **56**, which undergoes reductive elimination to furnish cross-coupled product **53** with concomitant regeneration of the Pd(0) catalyst. We recognized that this chemistry could enable restructuring and further functionalization of the carvone-derived cyclobutanols (**10** and **11**) via (1) ring-opening/cross-coupling and (2) reaction between the cross-coupled group and the newly unveiled ketone/enone, thus setting the stage for rapid construction of diverse natural product-like scaffolds (Scheme 9).

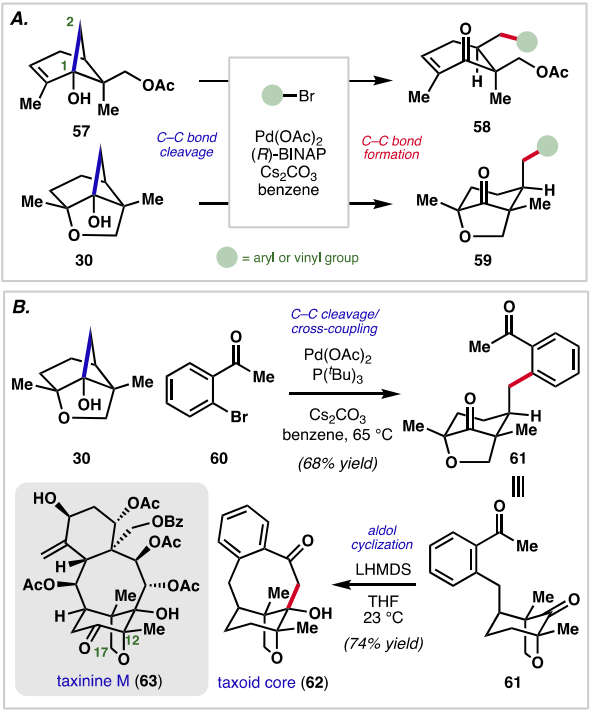
After some investigation, we discovered that acetate-protected **57** (derived from the major diastereomer) and ether-bridged tricycle **30** (derived from the minor cyclobutanol) were also amenable to this type of reactivity (Scheme 10A). Specifically, a $Pd(OAc)_2$/(*R*)-BINAP precatalyst system afforded a range of ring-opened/cross-coupled products (generalized as **58** and **59**) from the reaction of the two bridged cyclobutanols with a variety of aryl (or vinyl) bromides. Furthermore, we demonstrated that the strategy outlined in Scheme 9 could be applied to access the core (**62**) of a unique class of C17−C12 oxo-bridged taxoids (Scheme

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 9. Sequential Functionalizations of Pinene Cyclobutanols Enabled by Pd-Catalyzed C−C Bond Cleavage



Scheme 10. (A) Pd-Catalyzed Tandem C−C Bond Cleavage/Cross-Coupling of Cyclobutanols 30 and 57 and (B) Synthesis of Taxoid Core 62 from Cyclobutanol 30



10B), such as taxinine M (**63**).[34] The synthesis of **62** began with coupling **30** and aryl bromide **60** to afford cross-coupled adduct **61**. Enolization of the northern ketone with LHMDS followed by intramolecular aldol addition of the resulting enolate to the southern ketone forged the central eight-membered ring, furnishing the tetracyclic framework of these taxoids (i.e., **62**). Notably, this sequence constitutes the first synthesis of the core of this class of taxoid natural products.

In summary, our lab was able to effectively develop two transition-metal-catalyzed C−C bond cleavage paradigms based on rhodium and palladium catalysis. With rhodium catalysis, both the major and minor cyclobutanols could be remodeled to synthetically versatile, stereochemically rich cyclohexyl motifs. In a complementary fashion, palladium catalysis enabled further functionalization of these cyclohexyl motifs by leveraging the cross-coupling ability of the in situ generated alkyl-Pd intermediate. In the following sections, we describe how our aforementioned electrophile-mediated rearrangement strategy (Section 2), along with these transition metal-catalyzed cyclobutanol opening reactions have proven to be effective strategies for the syntheses of various terpenoids, including the longinorneol sesquiterpenoids,[2] phomactin diterpenoids,[3] and the diterpene xishacorene B.[4]

4. TOTAL SYNTHESIS OF LONGIBORNEOL SESQUITERPENOIDS

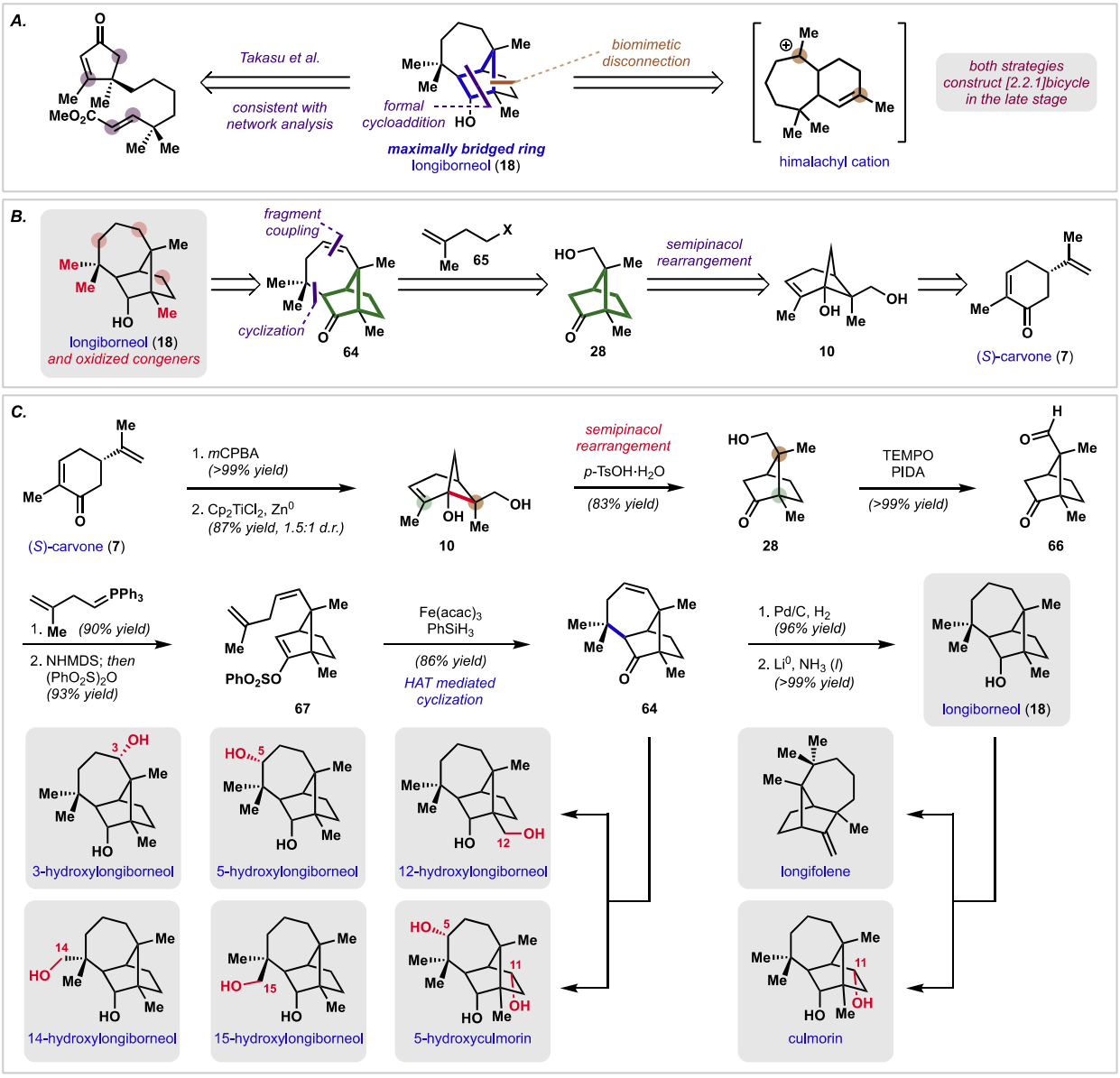
We identified the longiborneol family of natural products (**18** and oxidized congeners)[35] as ideal synthetic targets that could be prepared using our carvone-derived bicyclo[2.2.1] intermediates. Additionally, we envisioned that intermediates en route to these natural products would serve as ideal platforms for exploring late-stage diversification enabled by C−H functionalization.

Traditional strategies for formulating a retrosynthesis for longiborneol would prompt an immediate disconnection of the [2.2.1]bicycle (Scheme 11A). For example, classical bond network analysis[36] favors disconnection of the western ring of the bicycle, as it is the maximally bridged ring.[37] The proposed biosynthesis of the molecule similarly forms the bicycle at the end,[38] and so would be disconnected first in a bioinspired retrosynthesis. While such strategies have proven effective in previous syntheses,[39−41] we hypothesized that a more efficient synthesis could be achieved by first accessing a topologically complex fragment and then constructing the remainder of the natural product around this core fragment. Thus, we proposed that longiborneol (**18**) could arise from late-stage intermediate **64**, which features ketone and alkene functional handles that could strategically enable late stage oxidation (Scheme 11B). In turn, **64** could be accessed from two fragments, **28** and **65**, by a fragment coupling and cyclization sequence, in the forward sense. Finally, functionalized camphor derivative **28** could be elaborated from carvone using our nonintuitive remodeling sequence (**7** → **10** → **28**).[1] We note that Kuo and Money synthesized longiborneol using a similar strategy to the one that we proposed.[42] In their report, the seven-membered ring was constructed with a key Mukaiyama aldol condensation, which formed the C6−C7 bond. While effective for ring formation, this tactic necessitated several concession steps to subsequently install the C6 all-carbon quaternary center. To address this key challenge, we sought to implement a novel cyclization tactic based on hydrogen atom transfer (HAT) chemistry,[43] which we believed could effectively accomplish simultaneous cyclization and installation of the C6 quaternary center. Overall, this approach would ultimately lead to a more efficient and succinct total synthesis.

Our synthesis began with (*S*)-carvone, which was converted to cyclobutanol **10** by epoxidation of the isopropenyl moiety followed by reductive epoxide-opening and cyclization (Scheme 11C). Hydroxy-pinene **10** was then converted to 8-hydroxy camphor (**28**) by our aforementioned acid-catalyzed semipinacol rearrangement.[1] Oxidation of the primary hydroxy group to the aldehyde with TEMPO/PIDA furnished **66**. Aldehyde **66** underwent a selective Wittig olefination, and the remaining carbonyl group was converted to the corresponding vinyl sulfonate by treatment with sodium bis(trimethylsilyl)-amide (NHMDS) followed by trapping of the resulting enolate with benzenesulfonic anhydride, to deliver **67**. Vinyl phenyl-sulfonate **67** proved to be a competent cyclization precursor, as treating it with iron(III) acetylacetonate (acac) and phenyl silane delivered our desired late-stage intermediate (**64**). For this reaction, we propose that an iron hydride facilitates a HAT to the terminal position of the 1,1-disubstituted alkene, generating a tertiary alkyl radical which cyclizes onto the vinyl phenyl sulfinate, a previously unprecedented radical acceptor in HAT cyclizations.[43] Subsequent fragmentation reforms the ketone, and presumably extrudes a sulfinyl radical,

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 11. Total Synthesis of Longiborneol Natural Products: (A) Traditional Retrosynthetic Disconnections of Longiborneol, (B) Our Retrosynthesis, and (C) Our Total Synthesis



to provide **64**.[44,45] Notably, this reaction achieved both the desired cyclization and forged the C6 quaternary center simultaneously, thus addressing long-standing challenges in the synthesis of longiborneol. Finally, tricycle **64** was converted to longiborneol by hydrogenation of the alkene group followed by diastereoselective, dissolving-metal reduction of the carbonyl group. Additionally, we showed that **64** and longiborneol (**18**), collectively, could be converted to a wide variety of oxygenated congeners, thus demonstrating the first ever unified approach to the longiborneol family of molecules, as well as longifolene.

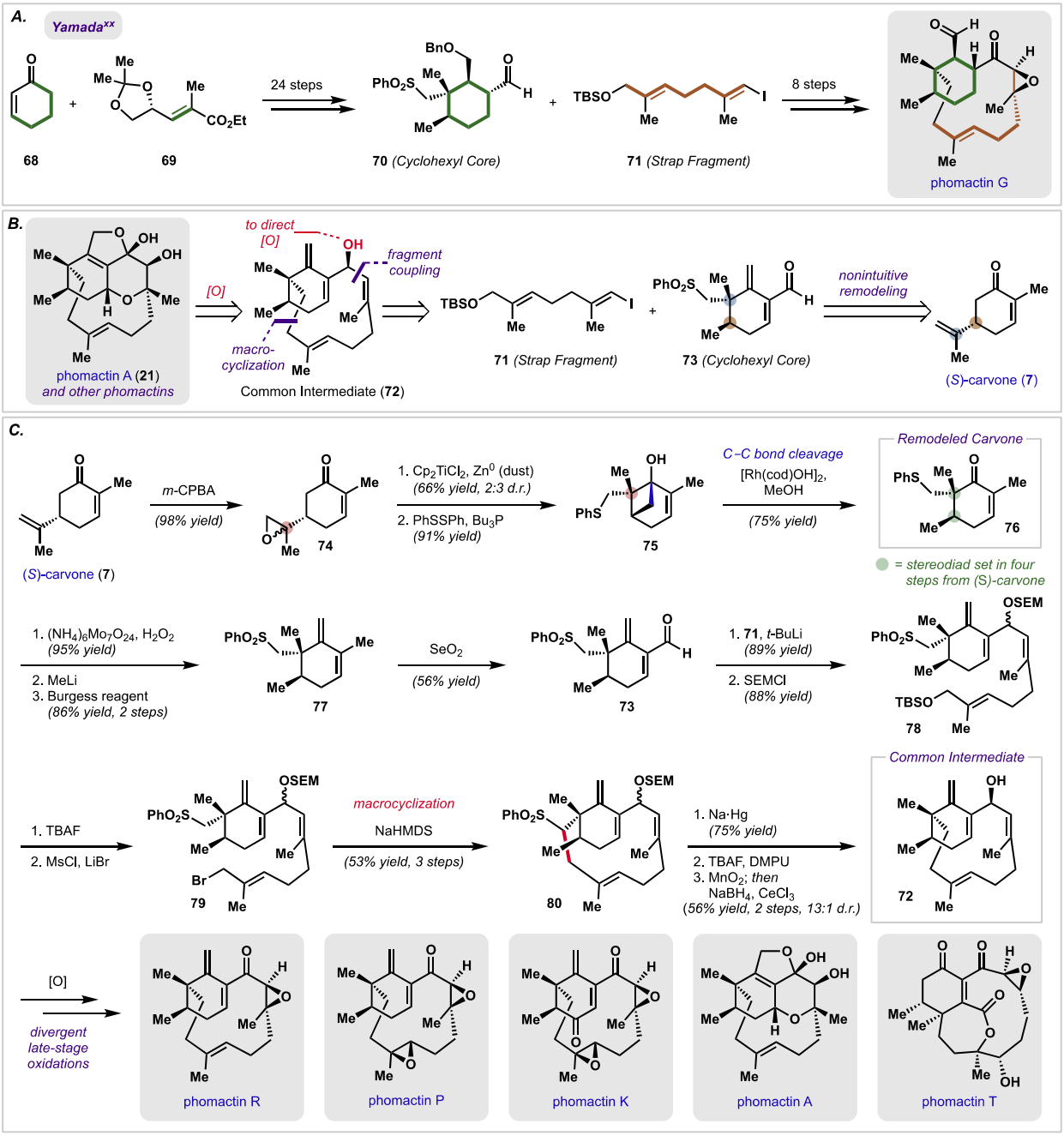
Our synthesis of longiborneol required only nine steps—the shortest published route, to date—and supports our hypothesis that a "bicycle-first" strategy can result in a highly efficient total synthesis. The brevity of our synthesis ultimately hinged on two key tactics: (1) the carvone remodeling sequence we had previously developed, which enabled facile access to key intermediate **28** in only three steps from the chiral pool terpene, and (2) the HAT-mediated cyclization, which allowed concomitant formation of the seven-membered ring and the C6 quaternary center.

5. TOTAL SYNTHESIS OF PHOMACTIN DITERPENOIDS

We initiated our synthetic studies of the phomactin congeners due to outstanding challenges in previous syntheses of these diterpenoid natural products, which we hypothesized could be addressed using our carvone remodeling strategy. Phomactin A (**21**) was isolated in 1991 from the fungus *Phoma* sp.[46] Subsequently, numerous phomactins have been isolated,[3] and collectively, these secondary metabolites have been the subject of intense synthetic investigation.[47−50] In their pioneering synthesis of phomactin G (Scheme 12A), Yamada and co-workers constructed the natural product from a cyclohexyl fragment (**70**) and a "strap" fragment (**71**), which were doubly coupled to forge the macrocylic skeleton of the natural product.[48] This visionary "fragment-based approach" has since

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 12. Total Synthesis of Phomactin Natural Products: (A) Yamada's Synthesis of Phomactin G, (B) Our Retrosynthesis, and (C) Our Total Synthesis

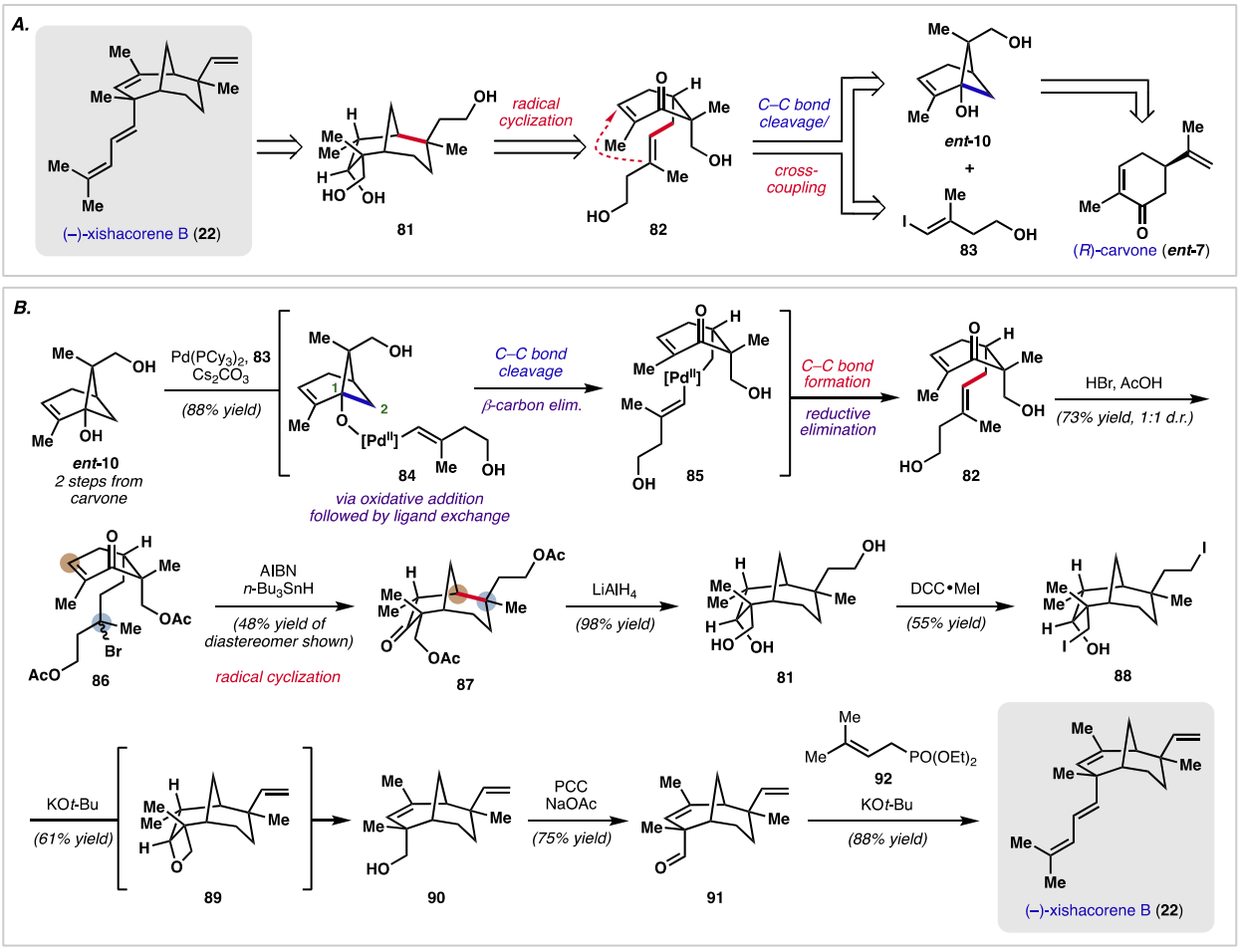


become a staple of phomactin syntheses. This previous study served as an invaluable source of inspiration when we formulated our retrosynthesis of the phomactins. Despite Yamada's conceptual advance, this synthesis does not address two major challenges, which are also endemic to subsequent phomactin synthesis,[49,50] that would become the focal points of our strategy: (1) application of a unified strategy to access a variety of phomactin congeners and (2) concise preparation of the cyclohexyl core in enantioenriched form. With respect to the first challenge, we proposed that several phomactins could be obtained from common intermediate **72**, which features a variety of activated positions and a hydroxy group that could be utilized in subsequent directed oxidations (Scheme 12B). This common intermediate could, in turn, be accessed from Yamada's strap fragment (**71**) and cyclohexyl fragment **73** by a coupling/macrocyclization sequence. Finally, we envisioned that cyclohexyl fragment **73** could arise from (*S*)-carvone via a nonintuitive remodeling process similar to those described above.[1] In this case, our carvone remodeling strategy would uniquely enable an efficient total synthesis, as it would allow succinct, enantiospecific preparation of the cyclohexyl fragment (**73**) from an enantioenriched feedstock chemical.

In accordance with our retrosynthesis, our synthesis (Scheme 12C) began with epoxidation of the isopropenyl moiety of (*S*)-carvone to give **74**, followed by a reductive epoxide opening/cyclization to afford **11**. Hydroxypinene **11** then underwent a Mitsunobu reaction, to replace the primary hydroxy group with a phenyl thioether, and the resulting

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

Scheme 13. Total Synthesis of (−)-Xishacorene B: (A) Our Retrosynthesis and (B) Our Total Synthesis



intermediate (**75**) was treated with a rhodium precatalyst in methanol to effect C−C bond cleavage, furnishing **76**. Remodeled carvone intermediate **76**, which is synthesized in a concise four step sequence, features the key stereodiad of the phomactin cyclohexyl motif, and contains several functional groups, which can be leveraged for peripheral functionalizations. Oxidation of the thioether moiety to a sulfone, addition of methyllithium to the carbonyl, and elimination of the resulting tertiary alcohol yielded diene **77**. Selenium dioxide-mediated oxidation of the allylic methyl group completed cyclohexyl core **73**. Lithiated strap fragment **71** was coupled to **73** by addition to the aldehyde, and the resulting secondary alcohol was protected as a 2-(trimethylsilyl)ethoxymethyl (SEM) ether to give **78**. Selective cleavage of the TBS group followed by a Finkelstein reaction of the unveiled hydroxy group furnished allylic bromide **79**. Treatment of **79** with NaHMDS next effected a sulfone alkylation, which yielded macrocycle **80**. Reductive cleavage of the sulfone followed by cleavage of the SEM ether yielded a mixture of diastereomeric secondary alcohols. This mixture was enriched for the desired isomer by oxidation and Luche reduction of the resulting enone, thus providing access to common intermediate **72**. A variety of oxidation tactics (not shown) were utilized to complete total syntheses of phomactins R, P, K, A, and T from intermediate **72**.

Ultimately, compared to previous syntheses, our approach to the phomactins addressed the major, outstanding challenges of synthetic efficiency and versatility. By employing C−C cleavage tactics on hydroxypinene **11**, we prepared our key cyclohexyl fragment **73** in only eight steps from carvone. We, then, leveraged **73** to synthesize common intermediate **72**, which we successfully diversified to five different phomactin congeners.

6. TOTAL SYNTHESIS OF (−)-XISHACORENE B DITERPENE

When the isolation of xishacorene B (**22**, Scheme 13) was reported in 2017,[51] we saw an opportunity to demonstrate the power of our Pd-catalyzed ring-opening/cross-coupling remodeling sequence to quickly assemble the natural product skeleton. The xishacorene diterpenes contain an architecturally fascinating [3.3.1] bicyclic core and also possess medicinally relevant immunopotentiating bioactivity. Developing an efficient approach to this bicyclic core became the focal point in our synthetic strategy.[4] In a retrosynthetic sense (Scheme 13A), it was envisioned that xishacorene B could arise from hydroxylated [3.3.1]bicycle **81**. This bicycle could be taken back to cyclohexenone **82**, which in the forward sense would undergo a radical cyclization from the appended olefin group to the enone. Cyclohexenone **82** was designed to arise from the (*R*)-carvone-derived major cyclobutanol (*ent*-**10**), which would be primed to undergo the key Pd-catalyzed C−C bond cleavage/cross-coupling sequence with vinyl iodide **83** in the forward sense. In this way, the palladium-catalyzed remodeling tactics we had developed would enable introduc-

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

tion of all the carbon atoms of the bicyclic structural core in a short sequence from (*R*)-carvone—along with functional handles that would quickly enable cyclization.

Our forward synthesis (Scheme 13B) began with treatment of *ent*-**10** and **83** with a Pd(0) catalyst, generating Pd(II)-alkoxide **84** through oxidative addition into **83** followed by ligand exchange with *ent*-**10**. C−C bond cleavage through *β*-carbon elimination next afforded alkyl-Pd(II) intermediate **85**, which, upon reductive elimination, furnished enone **82**. Bromination[52]—with concomitant acetylation of the hydroxy groups—using HBr and AcOH afforded alkyl bromide **86**. Treatment of this cyclization precursor (**86**) with AIBN and *n*-Bu_3SnH formed a tertiary radical that cyclized onto the enone, completing the [3.3.1] bicyclic core (**87**). Reduction of the ketone and global cleavage of the acetate groups with LAH provided triol **81**, which was subjected to iodination conditions using DCC·MeI to give bis-iodinated alcohol **88**. Upon treatment with KO*t*-Bu, elimination of the eastern iodide occurred and S_N2 cyclization of the secondary hydroxy group to the proximal western iodide gave oxetane **89**. Subsequent E_2 elimination by oxetane ring-opening then afforded **90**. Oxidation of the primary hydroxy group to the aldehyde using PCC furnished **91**, which underwent Horner−Wadsworth−Emmons olefination with phosphonate ester **92** to give (−)-xishacorene B in 10 steps from (*R*)-carvone. Notably, this sequential C−C bond cleavage/radical cyclization strategy was also extended to the synthesis of other [3.3.1] and [3.2.1]-bicycles, thus demonstrating the generality of this approach.

Overall, this synthesis of xishacorene B serves as a prime example of how implementing a C−C bond cleavage/cross-coupling strategy can streamline the synthesis of complex diterpene natural products. Similar to the intramolecular aldol cyclization used in our synthesis of taxoid core **62** (Scheme 10B), the radical cyclization step in this synthesis further showcases the effectiveness of C−C bond cleavage in setting the stage for subsequent complexity-building reactions.

7. SUMMARY AND OUTLOOK

In this Account, we have described our efforts to build a general platform for the synthesis of diverse, complex terpenes from synthetically versatile dihydroxylated pinene derivatives (e.g., **10** and **11**). We developed three main strategies to diversify these cyclobutanols into structurally distinct intermediates: (1) electrophilic activation of the alkene functionality, which facilitated access to bicyclo[2.2.1] intermediates, (2) Rh-catalyzed cyclobutanol ring-opening, which furnished densely functionalized cyclohexenone scaffolds, and (3) Pd-catalyzed cyclobutanol ring-opening/cross-coupling, which enabled further complexity-building reactions. Thus, far, we have demonstrated total syntheses implementing each of these strategies. Utilizing an acid-catalyzed semipinacol rearrangement, we accessed hydroxycamphor **28**, from **10**. We employed intermediate **28** in a strategically unique synthesis of longiborneol, in which the natural product was constructed around the [2.2.1] bicyclic skeleton of the camphor derivative. Our analysis of existing total syntheses of the phomactin diterpenoids indicated that efficient syntheses of requisite cyclohexyl fragments was a persistent challenge. Through a rhodium-catalyzed ring-opening of a derivative of **11**, we synthesized a key cyclohexyl fragment in only eight steps, which enabled access to several phomactin congeners. Finally, we employed a Pd-catalyzed, tandem ring-opening/cross-coupling followed by a radical cyclization event to construct the [3.3.1]bicycle motif of xishacorene B from carvone in only five steps. This intermediate was then elaborated to the natural product in an additional five steps. Key to the success of these syntheses was our recognition that the core of each natural product could be obtained, nonintuitively, from carvone through deep-seated skeletal reorganization, enabled by the C−C bond cleavage tactics detailed above. Together, the structurally disparate nature of these terpenoids definitively demonstrates that we have developed a platform that can enable syntheses of a variety of complex molecule targets. Moving forward, our objective is to increase the diversity and complexity of natural products that can be prepared from **10** and **11**, which will further showcase the remarkable flexibility of these unusually hydroxylated pinene derivatives as synthetic intermediates.

AUTHOR INFORMATION

Corresponding Author

Richmond Sarpong − *Department of Chemistry, University of California, Berkeley, Berkeley, California 94720, United States*; orcid.org/0000-0002-0028-6323; Email: rsarpong@berkeley.edu

Authors

Robert F. Lusi − *Department of Chemistry, University of California, Berkeley, Berkeley, California 94720, United States*

Melecio A. Perea − *Department of Chemistry, University of California, Berkeley, Berkeley, California 94720, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.accounts.1c00783

Author Contributions

[§]R.F.L. and M.A.P. contributed equally to this work.

Notes

The authors declare no competing financial interest.

Biographies

Robert F. Lusi received an Sc. B. degree in chemistry from Brown University in 2015, where he worked in the research group of Prof. Amit Basu. He is currently a Ph.D. candidate at the University of California Berkeley, advised by Richmond Sarpong, where his research focuses on the total synthesis and late-stage diversification of complex terpenoids.

Melecio A. Perea graduated with his B.S. in chemistry in 2016 from New Mexico Highlands University. He, then, began his Ph.D. studies at the University of California, Berkeley, conducting research in the laboratory of Professor Richmond Sarpong. At Berkeley, his research focuses on the total synthesis of complex terpene natural products.

Richmond Sarpong is a Professor of Chemistry at the University of California Berkeley, where he and his group specialize in synthetic organic chemistry. Richmond became interested in chemistry after seeing, firsthand, the effectiveness of the drug ivermectin in combating river blindness during his childhood in Ghana, West Africa. Richmond described his influences and inspirations in a TEDxBerkeley talk in 2015 (Face of Disease in Sub-Saharan Africa—https://www.youtube.com/watch?v=nIsY87-zkXA). Richmond completed his undergraduate studies at Macalester College in St. Paul, MN, and his graduate work was carried out with Prof. Martin Semmelhack at Princeton. He conducted postdoctoral studies at Caltech with Prof. Brian Stoltz.

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758

■ ACKNOWLEDGMENTS

R.F.L and M.A.P. are both grateful to the NSF for graduate research fellowships (DGE 1752814). M.A.P. is grateful to the NIGMS for a predoctoral fellowship (F31GM139368). R.S. thanks the National Institutes of General Medical Sciences (R35 GM130345) for providing the primary support for the work reported here.

■ REFERENCES

(1) Masarwa, A.; Weber, M.; Sarpong, R. Selective C−C and C−H Bond Activation/Cleavage of Pinene Derivatives: Synthesis of Enantiopure Cyclohexenone Scaffolds and Mechanistic Insights. *J. Am. Chem. Soc.* **2015**, *137*, 6327−6334.

(2) Lusi, R. F.; Sennari, G.; Sarpong, R. Total Synthesis of Nine Longiborneol Sesquiterpenoids Using a Functionalized Camphor Strategy. *Nat. Chem.*, 2022. DOI: 10.1038/s41557-021-00870-4.

(3) Kuroda, Y.; Nicacio, K. J.; da Silva, I. A., Jr.; Leger, P. R.; Chang, S.; Gubiani, J. R.; Deflon, V. M.; Nagashima, N.; Rode, A.; Blackford, K.; Ferreira, A. G.; Sette, L. D.; Williams, D. E.; Andersen, R. J.; Jancar, S.; Berlinck, R. G. S.; Sarpong, R. Isolation, Synthesis, and Bioactivity Studies of Phomactin Terpenoids. *Nat. Chem.* **2018**, *10*, 938−945.

(4) Kerschgens, I.; Rovira, A. R.; Sarpong, R. Total Synthesis of (−)-Xishacorene B from (*R*)-Carvone Using a C−C Activation Strategy. *J. Am. Chem. Soc.* **2018**, *140*, 9810−9813.

(5) Brill, Z. G.; Condakes, M. L.; Ting, C. P.; Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **2017**, *117*, 11753−11795.

(6) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. The Pinene Path to Taxanes. 5. Stereocontrolled Synthesis of a Versatile Taxane Precursor. *J. Am. Chem. Soc.* **1997**, *119*, 2755−2756.

(7) Hu, X.; Maimone, T. J. Four-Step Synthesis of the Antimalarial Cardamom Peroxide via an Oxygen Stitching Strategy. *J. Am. Chem. Soc.* **2014**, *136*, 5287−5290.

(8) To the best of our knowledge, there have not been methods established for the direct C−H functionalization of the bridgehead and *gem*-dimethyl positions of α-pinene. There have, however, been a number of advancements in enzyme-mediated functionalization of α-pinene at other positions of the carbon scaffold, such as Bell, S. G.; Chen, X.; Sowden, R. J.; Xu, F.; Williams, J. N.; Wong, L.-L.; Rao, Z. Molecular Recognition in (+)-α-Pinene Oxidation by Cytochrome $P450_{cam}$. *J. Am. Chem. Soc.* **2003**, *125*, 705−714.

(9) Bermejo, F. A.; Fernández Mateos, A.; Marcos Escribano, A.; Martín Lago, R.; Mateos Burón, L.; Rodríguez López, M.; Rubio González, R. Ti(III)-Promoted Cyclizations. Application to the Synthesis of (*E*)-*endo*-bergamoten-12-oic-acids. Moth oviposition stimulants isolated from Lycopersicon hirsutum. *Tetrahedron* **2006**, *62*, 8933−8942.

(10) Martín-Rodriguez, M.; Galán-Fernández, R.; Marcos-Escribano, A.; Bermejo, F. A. Ti(III)-Promoted Radical Cyclization of Epoxy Enones. Total Synthesis of (+)-Paeonisuffrone. *J. Org. Chem.* **2009**, *74*, 1798−1801.

(11) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. Cyclobutanes in Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740−7752.

(12) Wu, X.; Zhu, C. Recent Advances in Ring-Opening Functionalization of Cycloalkanols by C−C σ-Bond Cleavage. *Chem. Rec.* **2008**, *18*, 587−598.

(13) For a further discussion of cyclobutanols undergoing ring-expansion reactions, see: Natho, P.; Allen, L. A. T.; Parsons, P. J. Recent Advances in the Ring Expansion of Cyclobutanols, Oxetanols, and Azetidinols. *Tetrahedron Lett.* **2020**, *61*, 151695.

(14) For a further discussion of cyclobutanols undergoing transition metal-mediated C−C bond cleavage via two electron pathways, see: Murakami, M.; Ishida, N. Cleavage of Carbon−Carbon σ-Bonds of Four-Membered Rings. *Chem. Rev.* **2021**, *121*, 264−299.

(15) For a further discussion of cyclobutanols undergoing transition metal-mediated C−C bond cleavage via one electron pathways, see: Morcillo, S. P. Radical-Promoted C−C Bond Cleavage: A Deconstructive Approach for Selective Functionalization. *Angew. Chem., Int. Ed.* **2019**, *58*, 14044−14054.

(16) For recent examples of C−C bond cleavage strategies in total synthesis, see: Wang, B.; Perea, M. A.; Sarpong, R. Transition Metal-Mediated C−C Single Bond Cleavage: Making the Cut in Total Synthesis. *Angew. Chem., Int. Ed.* **2020**, *59*, 18898−18919.

(17) The C1−C4 bond (unlike the C1−C2 bond) has an antiperiplanar relationship to the C5 electrophilic position, thus fulfilling the stereoelectronic requirement for the desired semipinacol rearrangement. For a detailed discussion about stereoelectronics and antiperiplanarity, see: Alabugin, I. V. σ/σ-Interactions. In *Stereoelectronic Effects*; Wiley, 2016; Chapter 6, pp 97−113.

(18) For a discussion of stereoelectronic effects in the context of semipinacol rearrangements, see: Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. Semipinacol Rearrangement in Natural Product Synthesis. *Chem. Rev.* **2011**, *111*, 7523−7556.

(19) We hypothesized that a transition-metal could be tuned sterically and electronically to facilitate the desired cleavage of the less sterically hindered C1−C2 bond.

(20) Money, T. Camphor: A Chiral Starting Material in Natural Product Synthesis. *Nat. Prod. Rep.* **1985**, *2*, 253−289.

(21) For C−C bond cleavage thermodynamic and kinetic considerations, see: Murakami, M.; Ishida, N. Potential of Metal-Catalyzed C−C Single Bond Cleavage for Organic Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13759−13869.

(22) Murakami, M. Rhodium-Catalyzed Restructuring of Carbon Frameworks. *Chem. Rec.* **2010**, *10*, 326−331.

(23) Nishimura, T.; Ohe, K.; Uemura, S. Oxidative Transformation of *tert*-Cyclobutanols by Palladium Catalysis under Oxygen Atmosphere. *J. Org. Chem.* **2001**, *66*, 1455−1465.

(24) Ishida, N.; Sawano, S.; Masuda, Y.; Murakami, M. Rhodium-Catalyzed Ring Opening of Benzocyclobutenols with Site-Selectivity Complementary to Thermal Ring Opening. *J. Am. Chem. Soc.* **2012**, *134*, 17502−17504.

(25) Seiser, T.; Cramer, N. Rhodium-Catalyzed C−C Bond Cleavage: Construction of Acyclic Methyl Substituted Quaternary Stereogenic Centers. *J. Am. Chem. Soc.* **2010**, *132*, 5340−5341.

(26) For precedent of a 1,3-Rh shift pathway followed by proto-demetalation, see ref 25.

(27) Seiser, T.; Roth, O. A.; Cramer, N. Enantioselective Synthesis of Indanols from *tert*-Cyclobutanols Using a Rhodium-Catalyzed C−C/C−H Activation Sequence. *Angew. Chem., Int. Ed.* **2009**, *48*, 6320−6323.

(28) Computational studies were performed to support a 1,3-Rh shift via a C−H activation pathway. See ref 1 for details.

(29) Matsuda, T.; Shigeno, M.; Murakami, M. Asymmetric Synthesis of 3,4-Dihydrocoumarins by Rhodium-Catalyzed Reaction of 3-(2-Hydroxyphenyl)cyclobutanones. *J. Am. Chem. Soc.* **2007**, *129*, 12086−12087.

(30) Navarre, L.; Darses, S.; Genet, J.-P. Tandem 1,4-Additon/Enantioselective Protonation Catalyzed by Rhodium Complexes: Efficient Access to α-Amino Acids. *Angew. Chem., Int. Ed.* **2004**, *43*, 719−723.

(31) See refs 27 and 29, for examples of a 1,4-Rh shift.

(32) Weber, M.; Owens, K.; Masarwa, A.; Sarpong, R. Construction of Enantiopure Taxoid and Natural Product-like Scaffolds Using a C−C Bond Cleavage/Arylation Reaction. *Org. Lett.* **2015**, *17*, 5432−5435.

(33) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. Palladium-Catalyzed Asymmetric Arylation, Vinylation, and Allenylation of *tert*-Cyclobutanols via Enantioselective C−C Bond Cleavage. *J. Am. Chem. Soc.* **2003**, *125*, 8862−8869.

(34) Beutler, J. A.; Chmurny, G. M.; Look, S. A.; Witherup, K. M. Taxinine M, A New Tetracyclic Taxane From *Taxus Brevifolia*. *J. Nat. Prod.* **1991**, *54*, 893−897.
(35) Bahadoor, A.; Schneiderman, D.; Gemmill, L.; Bosnich, W.; Blackwell, B.; Melanson, J. E.; McRae, G.; Harris, L. J. Hydroxylation of Longiborneol by a *Clm2*-Encoded CYP450 Monooxygenase to Produce Culmorin in *Fusarium graminearum*. *J. Nat. Prod.* **2016**, *79*, 81−88.
(36) Corey, E. J.; Howe, W. J.; Orf, H. W.; Pensak, D. A.; Petersson, G. General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures. *J. Am. Chem. Soc.* **1975**, *97*, 6116−6124.
(37) Determined with MaxBridge: Marth, C. J.; Gallego, G. M.; Lee, J. C.; Lebold, T. P.; Kulyk, S.; Kou, K. G. M.; Qin, J.; Lilien, R.; Sarpong, R. Network-Analysis-Guided Synthesis of Weisaconitine D and Liljestrandinine. *Nature* **2015**, *528*, 493−498.
(38) Hanson, J. R.; Nyfeler, R. Studies in Terpenoid Biosynthesis. Part 18. Biosynthesis of Culmorin. *J. Chem. Soc., Perkin Trans.* **1976**, *1*, 2471−2475.
(39) For examples of longiborneol total syntheses where the bicycle is formed at a late stage, see refs 40 and 41.
(40) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. Total Synthesis of (±)-Culmorin and (±)-Longiborneol: An Efficient Construction of Tricyclo[6.3.0.$0^{3,9}$]undecan-10-one by Intramolecular Double Michael Addition. *J. Org. Chem.* **2000**, *65*, 4112−4119.
(41) Welch, S. C.; Walters, R. L. Stereoselective Total Syntheses of (±)-Longicyclene, (±)-Longicamphor, and (±)-Longiborneol. *J. Org. Chem.* **1974**, *39*, 2665−2673.
(42) Kuo, D. L.; Money, T. Enantiospecific Synthesis of Longiborneol and Longifolene. *Can. J. Chem.* **1988**, *66*, 1794−1804.
(43) For a comprehensive review on HAT chemistry, see: Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912−9000.
(44) Shevick, S. L.; Wilson, C. V.; Kotesova, S.; Kim, D.; Holland, P. L.; Shenvi, R. A. Catalytic Hydrogen Atom Transfer to Alkenes: A Roadmap for Metal Hydrides and Radicals. *Chem. Sci.* **2020**, *11*, 12401−12422.
(45) Kim, D.; Rahaman, S. M. W.; Mercado, B. Q.; Poli, R.; Holland, P. L. Roles of Iron Complexes in Catalytic Radical Alkene Cross-Coupling: A Computational and Mechanistic Study. *J. Am. Chem. Soc.* **2019**, *141*, 7473−7485.
(46) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. Phomactin A; A Novel PAF Antagonist from a Marine Fungus Phoma sp. *J. Am. Chem. Soc.* **1991**, *113*, 5463−5464.
(47) For selected examples of previous phomactin syntheses, see ref 48−50.
(48) Miyaoka, H.; Saka, Y.; Miura, S.; Yamada, Y. Total Synthesis of Phomactin D. *Tetrahedron Lett.* **1996**, *37*, 7107−7110.
(49) Huang, J.; Bao, W.; Huang, S.; Yang, W.; Lizhi, Z.; Du, G.; Lee, C.-S. Formal Synthesis of (+)-Phomactin A. *Org. Lett.* **2018**, *20*, 7466−7469.
(50) Mohr, P. J.; Halcomb, R. L. Total Synthesis of (+)-Phomactin A Using a *B*-Alkyl Suzuki Macrocyclization. *J. Am. Chem. Soc.* **2003**, *125*, 1712−1713.
(51) Ye, F.; Zhu, Z.-D.; Chen, J.-S.; Li, J.; Gu, Y.-C.; Zhu, W.-L.; Li, X.-W.; Guo, Y.-W. Xishacorenes A−C, Diterpenes with Bicyclo[3.3.1]nonane Nucleus from the Xisha Soft Coral *Sinularia poldactyla*. *Org. Lett.* **2017**, *19*, 4183−4186.
(52) Johnson, T. C.; Chin, M. R.; Han, T.; Shen, J. P.; Rana, T.; Siegel, D. Synthesis of Eupalinilide E, a Promoter of Human Hematopoietic Stem and Progenitor Cell Expansion. *J. Am. Chem. Soc.* **2016**, *138*, 6068−6073.

https://doi.org/10.1021/acs.accounts.1c00783
Acc. Chem. Res. 2022, 55, 746−758