Communication

Total Synthesis of (–)-Xishacorene B from (R)-Carvone using a C–C Activation Strategy

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Total Synthesis of (–)-Xishacorene B from (*R*)-Carvone using a C–C Activation Strategy

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Supporting Information Placeholder

ABSTRACT: The activation of C–C bonds that are traditionally viewed as unreactive, when coupled with other bond-forming processes, can offer new approaches to the synthesis of complex molecular scaffolds. In this manuscript, we demonstrate the conversion of carvone to unusual bicyclo[3.3.1] and [3.2.1] frameworks by exploiting a Pd(0)-catalyzed C–C bond activation reaction and a radical cyclization process. This sequence is applied to a 10-step synthesis of the diterpene xishacorene B.

The formation of carbon-carbon (C–C) bonds is paramount to the synthesis of complex organic molecules such as terpenoid natural products,[1] which consist primarily of a carbon skeleton. Therefore, in developing strategies for the total synthesis of terpenoids, significant emphasis is often placed on methods that form new C–C bonds.[2] As part of a program to exploit readily-available, 'chiral pool' reagents for terpene syntheses,[3] we recognized that C–C activation of carvone, when coupled with new C–C bond forming processes, would yield novel structural frameworks that significantly expand the scope of complex molecules conventionally accessible from carvone (see **1**→**3**, Figure 1A). We have shown previously that this type of transformation can be realized by converting epoxy carvone (**4**) to bis-hydroxylated pinene derivatives (see **5**, Figure 1B) using a method by Bermejo,[4] followed by Pd(0)-catalyzed cross coupling with vinyl or aryl halides to provide access to structures such as **6**, which form the core of myriad natural products.

In this communication, we demonstrate that vinylated adducts related to **6** are easily advanced to unusual bicyclo[3.3.1]nonane frameworks in one or two steps. We showcase the utility of this bicyclization sequence in a short synthesis of the natural product xishacorene B (**7**).

Xishacorene B is a member of a new family of diterpenes recently isolated from the soft coral *Sinularia polydactyla* (0.0008% yield of dry coral material) off the coast of the Xisha Islands in China.[5] Preliminary biological screening of these secondary metabolites revealed that they have activity as promoters of concanavalin A-induced T-lymphocyte proliferation. Thus, these molecules may prove useful as a starting point for the development of new small molecule immunopotentiators.

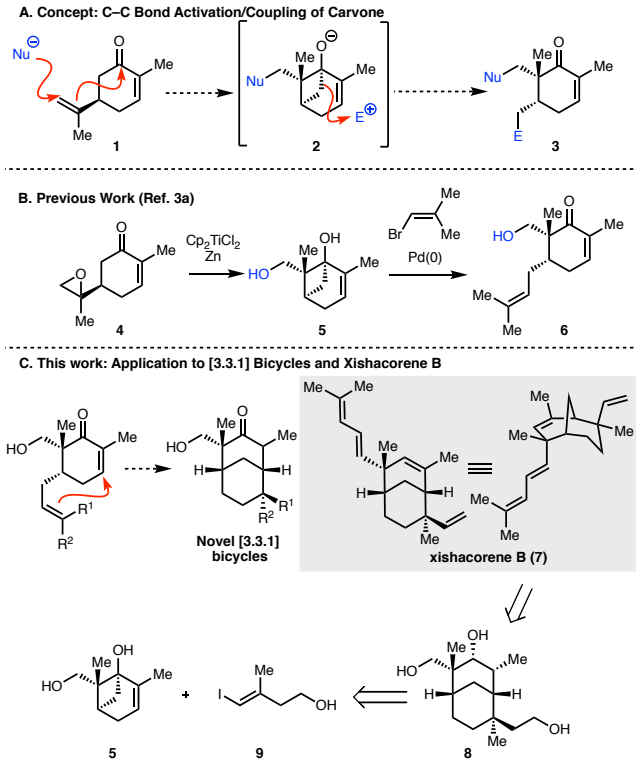
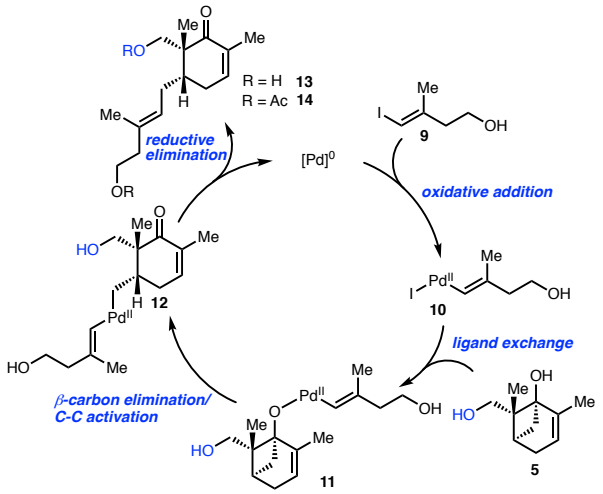


Figure 1. Use of C–C activation starting from carvone for natural product synthesis

Retrosynthetically, we envisioned xishacorene B (**7**, Figure 1C) arising from bicyclo[3.3.1]nonane **8**. In turn, **8** could be brought back to cyclobutanol **5**[4] and vinyl iodide **9**.[6] We commenced our synthetic studies by optimizing the cross coupling of cyclobutanol **5** and vinyl iodide **9** (Table 1). On the basis of the precedent of Uemura,[7] this coupling likely involves insertion of a Pd(0)-complex into **9** to provide a Pd(II)-species that undergoes ligand exchange to form alkenyl Pd-alkoxide **11**. At this stage, *β*-carbon elimination/C–C bond activation would result in cleavage of the cyclobutanol to yield alkyl palladium intermediate **12**. Reductive elimination to **13** would then complete the catalytic cycle. Key to the success of this coupling sequence would be to achieve reductive elimination from **12** over a competing β-hydride elimination.[8] We hypothesized that this would be possible by the judicious

Table 1. Optimization of the Pd-catalyzed C-C-activation/coupling sequence.

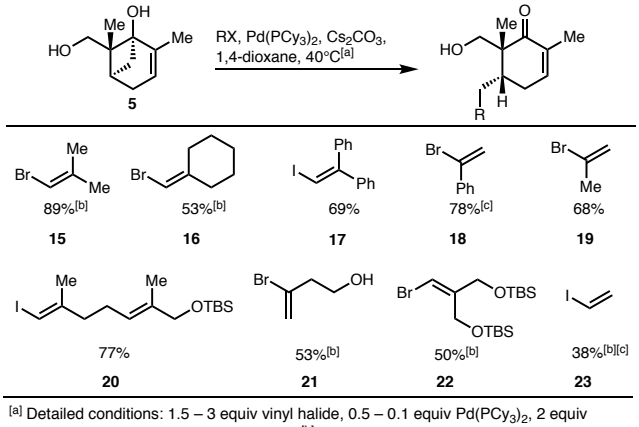


entry	*Pd-complex*	*solvent*	*conversion*[a]	*yield* **13**[a]	*yield* **14**[a]
1	$Pd(PCy_3)_2$	1,4-dioxane	> 98%	85%[b]	-
2	$Pd(PCy_3)_2$	1,4-dioxane	> 98%	74%[c]	-
3	$Pd(PCy_3)_2$	1,4-dioxane	67%	49%[d]	-
4	$Pd(PPh_3)_4$	1,4-dioxane	81%	63%	-
5	$Pd[P(tBu)_2Ph]_2$	1,4-dioxane	73%	56%	-
6	$Pd(PCy_3)_2$	benzene	92%	63%	-
7	$Pd(PCy_3)_2$	EtOAc	> 98%	17%	70%

[a] Determined by ^{1}H-NMR analysis using benzyl benzoate as an internal standard. [b] Reagents and conditions: 5 mol% of Pd-complex, 1.5 equiv of vinyl iodide, 2.0 equiv Cs_2CO_3, 30°C, 18 h. [c] 1.1 equiv vinyl iodide instead of 1.5 equiv [d] 18°C instead of 30°C.

choice of ligands on the Pd complex. We identified $Pd(PCy_3)_2$ as the optimal palladium complex, and temperatures of 30–40 °C as well as the use of cyclobutanol **5** bearing free hydroxy groups to be ideal (Table 1, entry 1). The highest yields for the coupling were obtained using 1.5 equivalents of vinyl iodide **9**. Lowering the amount of **9** to 1.1 equivalents and the reaction temperature to 18 °C resulted in lower yields (entries 2 and 3). Using benzene as a solvent (entry 6) gave the product in lower yield relative to 1,4-dioxane. Interestingly, with EtOAc as the solvent, the cross-coupling proceeded with attendant acylation of the

Figure 2. Scope of the Pd-catalyzed C–C-activation/coupling sequence



[a] Detailed conditions: 1.5 – 3 equiv vinyl halide, 0.5 – 0.1 equiv $Pd(PCy_3)_2$, 2 equiv Cs_2CO_3, 1,4-dioxane (0.2 M), 40°C, 18 h. [b] Elevated temperature required, see the SI for details. [c] Isolated as inseparable mixture of alkene isomers, see the SI for details.

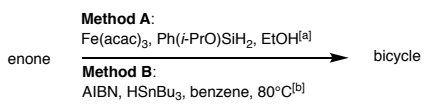
free hydroxy groups, providing an opportunity for *in-situ* acyl-protection simply by choice of solvent (**14,** entry 7).

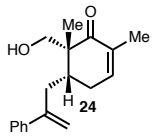
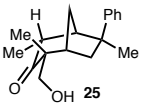
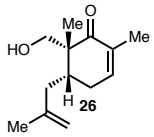
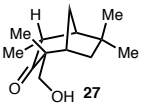
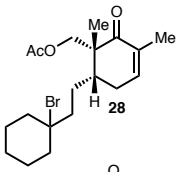
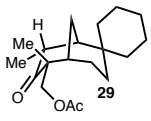
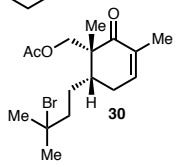
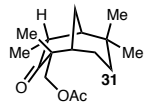
As shown in Figure 2, the optimized conditions are readily extended to the coupling of **5** with a range of vinyl halides, providing the corresponding adducts in good to excellent yields. In general, vinyl iodides required lower reaction temperatures to proceed, whereas vinyl bromides required higher temperatures. In the coupling with **22**, it is interesting to note that the product of the cross-coupling provides the skeleton of an isomer of the natural product cassiol.[9]

For the construction of bicyclic scaffolds including the [3.3.1]-framework of the xishacorene family, we sought to utilize the coupling products illustrated in Figure 2 in Mukaiyama-type hydrogen atom transfer (HAT) reactions. Inspired by the work of Baran,[10] Shenvi[11] and others,[12] a variety of HAT conditions that would lead to cyclization were explored.

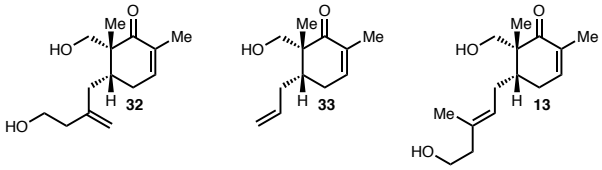
The desired cyclization occurred with varying degrees of efficiency for several substrates (e.g., for **24** and **26**, a 28% yield and 32% yield, respectively, of the [3.2.1] bicycles

Table 2. Cyclization to bicyclo[3.3.1] and [3.2.1] bicycles.



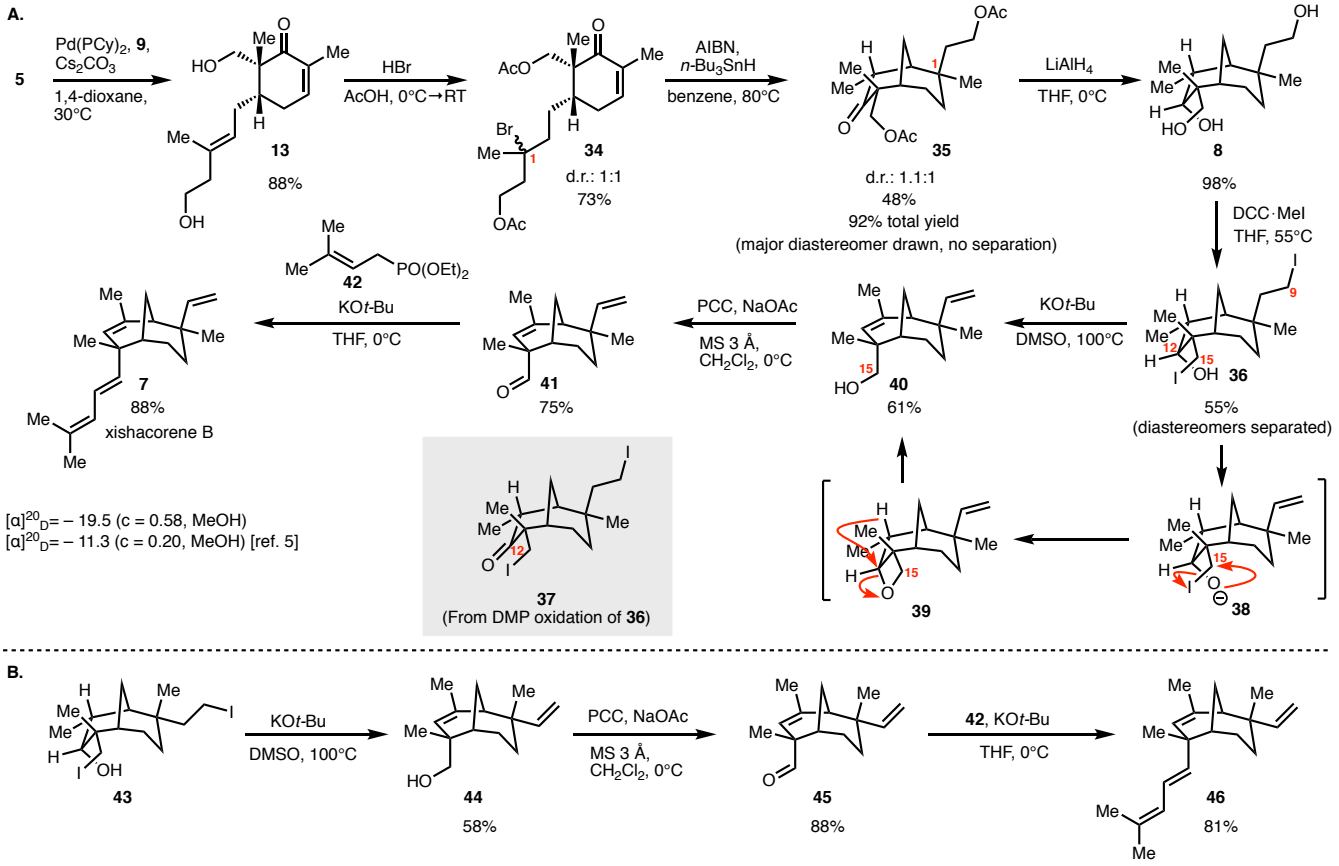
entry	enone	method	product	yield
1		**A**		28%[c]
2		**A**		32%
3		**B**		75%
4		**B**		89%

Unsuccessful HAT-substrates:



[a] Detailed conditions: 1 equiv $Fe(acac)_3$, 2–2.5 equiv $Ph(i\text{-}PrO)SiH_2$, EtOH (0.1 M – 0.2 M), 0°C – rt, 2 h. [b] Detailed conditions: 0.2 equiv AIBN, 4 equiv $HSnBu_3$, benzene (0.1 M), 80°C, 50 min. [c] Isolated as an inseparable mixture containing minor side products.

Scheme 1. Synthesis of xishacorene B and 1-epi-xishacorene B (**46**).



were obtained, see entries 1 and 2 in Table 2). More challenging substrates such as **32** and **33** could not be cleanly transformed to the corresponding bicycles. In particular, enone **13**, an intermediate in the xishacorene synthesis (Scheme 1), only gave small amounts of the Mukaiyama-type cyclization product along with numerous side products. Various HAT conditions using Fe, Co, or Mn-complexes,[13] a range of silanes, and various solvents also resulted in competing side reactions including reduction of the enone double bond or both double bonds in the substrate to give inseparable mixtures of reduction products.

Ultimately, a more effective two-step sequence was identified for bicyclization that began with installation of a tertiary bromide through hydrobromination of the more electron-rich double bond using HBr in AcOH.[14] Cyclization to provide **29** or **31** proceeded smoothly under radical conditions (AIBN, *n*-Bu_3SnH, 80 °C) in good yields (see Table 2, Method B).

In the context of the synthesis of xishacorene B, bromination of **13** (Scheme 1, A) proceeded with concomitant acylation of both hydroxy groups to give **34** in 73% yield as a 1:1-diastereomeric ratio of epimers about the Br-bearing carbon. The radical cyclization proceeded smoothly in 92% yield to give **35** as a 1.1:1 diastereomeric mixture at C1 slightly favoring the desired diastereomer. Attempts to improve the diastereomeric ratio using other initiation conditions (e.g., lauroyl peroxide as an initiator) have not been successful, whereas some other methods including photoredox conditions[15] did not result in any conversion of starting material.

With [3.3.1] bicycle **35** in hand, treatment with $LiAlH_4$ effected global reduction of the two ester groups and the ketone carbonyl to give triol **8** in 98% yield.[16] Subjecting triol **8** to 5 equivalents of DCC·MeI[17] at 55 °C in THF selectively converted the two primary alcohols to the corresponding iodides in the presence of the secondary alcohol at C12.[18] The secondary alcohol group was confirmed by DMP oxidation of the resulting diiodide (**36**) to afford ketone **37**. At this stage, the two C1-epimers that had been carried along following the radical cyclization step (see **34**→**35**) could be separated. Upon treatment of the desired isomer (**36**) with KO*t*-Bu at elevated temperature, elimination of the C9 primary iodide occurred to form a vinyl group. It is presumed that Williamson-etherification by displacement of the C15 iodide by the C12 hydroxyl yields oxetane intermediate **39**,[19,20] which gives alcohol **40** following elimination in an overall transposition of the C12 hydroxyl.[21] Xishacorene B was accessed from **40** using a two-step sequence involving oxidation of the primary hydroxyl to aldehyde **41** (using pyridinium chlorochromate) followed by Horner-Wadsworth-Emmons olefination with phosphonate **42**. The optical rotation of synthetic **7** was found to differ from the reported value of the isolated material (synthetic: –19.5; natural: –11.3). We theorize this might arise from the poor solubility of the very lipophilic **7** in MeOH.

Synthesis of the C1 epimer of xishacorene B (**7**) was also realized using the same sequence but starting with bicycle **43**, the epimer of **36** (Scheme 1B).

In conclusion, we have demonstrated the utility of a C–C activation/cross-coupling sequence for the construction of complex molecular frameworks. Specifically, carvone can be converted in two steps to a hydroxylated pinene derivative that sets the stage for a key cross-coupling. A Pd-catalyzed cyclobutanol C–C cleavage/coupling with vinyl halides followed by radical-mediated C–C bond construction provided rapid access to a variety of [3.3.1] bicycles. Using this approach, the first total synthesis of the marine diterpene xishacorene B has been achieved in 10 steps from carvone without using any protecting groups. Future studies will focus on applying this strategy to the synthesis of xishacorene congeners and their derivatives as well as the investigation of their bioactivity.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Experimental detail and spectroscopic data.

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Notes

The authors declare no competing financial interest.

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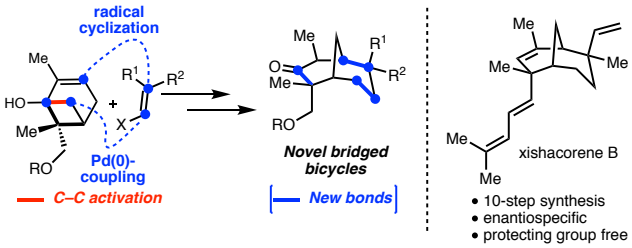
[21] We are grateful to an insightful reviewer for suggesting this pathway for the formation of **40**.


radical cyclization
Me
HO
Me
RO
R1
R2
X
Pd(0)-coupling
C–C activation
Me
O
Me
RO
R1
R2
Novel bridged bicycles
New bonds
Me
Me
Me
Me
xishacorene B
• 10-step synthesis
• enantiospecific
• protecting group free