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Total Synthesis of (–)-Xylogranatopyridine B via a Palladium-Catalyzed Oxidative Stannylation of Enones

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Abstract

We report a total synthesis of the pyridine-containing limonoid alkaloid (–)-xylogranatopyridine B in 11 steps from commercially available dihydrocarvone. The central pyridine ring was assembled by a late-stage fragment coupling approach employing a modified Liebeskind pyridine synthesis. One fragment was prepared by an allyl-palladium catalyzed oxidative enone β-stannylation, in which the key bimetallic β-stannyl palladium enolate intermediate undergoes a β-hydride elimination. This methodology also allowed introduction of alkyl and silyl groups to the β-position of enones.

Limonoid natural products are characterized by structural diversity generated through oxidative ring fragmentations and skeletal rearrangements.[1–3] These structural reorganizations lead to unique scaffolds such as the mexicanolide 8α-hydroxycarapin (**1**)[4] and the limonoid alkaloid xylogranatopyridine B (**2**).[5] The range of limonoid architectures is responsible for the diverse biological activities of this family,[6] including kinase inhibitors and compounds that reduce reactive oxygen species involved in neurodegenerative[7] and other effects.[8]

Xylogranatopyridine B (**2**), a trace isolate from the leaves of a Chinese mangrove (*Xylocarpus granatum*), is a member of a recently discovered group of limonoid alkaloids typified by phosphatase-inhibitory activity and a pyridine ring embedded in the core structure.[5,9] The putative biosynthesis of the pyridine-containing limonoid involves cleavage of the C9–C10 bond of a mexicanolide-type limonoid, such as **1**, followed by condensation with an ammonia equivalent to form the pyridine in **2** (Figure 1A).[9,10] Although a biomimetic approach could be pursued to generate the highly substituted pyridine, topological analysis suggested that a concise route would be possible by deconstruction of the pyridine substructure into two fragments that could be joined at a late stage.

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectroscopic data for all new compounds including ^{1}H- and ^{13}C NMR spectra (PDF)

The authors declare no competing financial interest.

Our retrosynthetic analysis begins with structural simplification of the A-ring to intermediate **3**. In a forward sense, a selective benzylic oxidation and vicinal difunctionalization would allow for the conversion of **3** to **2**. The tetrasubstituted pyridine **3** could be fashioned by the Liebeskind pyridine synthesis,[11] which entails a convergent Chan-Lam-type cross-coupling of achiral oxime **4** and a stannane fragment, such as **5a**, followed by oxidative 6π-electrocyclization.

Existing methods for the synthesis of β-stannyl enones similar to **5a** require the activation and cross-coupling of 1,3-diketones starting materials like **6**,[12,13] which themselves are often challenging substrates to prepare (Figure 1B). Alternatively, based on our previously reported Pd-catalyzed dehydrogenation,[14] we anticipated that stannane **5a** could be accessed by the direct conversion of an abundantly available enone precursor (**8a**) via bimetallic intermediate 7. This would require a selective transmetalation of Pd with the metal enolate, rather than with the allyl stannane, to form a Pd enolate that could regenerate the enone functionality via a β-hydride elimination. If feasible, this approach would allow for the introduction of a diverse array of nucleophiles directly to the β-position of enones, obviating the activation of 1,3-diketones.

Various stannane nucleophiles were employed to perturb the identity of the transient metal enolate **7** (Scheme 1). In contrast to our previous reports of zinc enolate-mediated carbonyl α,β-dehydrogenation, we found that a lithium enolate performed well in this context: conjugate addition of tributylstannyllithium to enone **8a** provided **5a** in 50% isolated yield using the Pd and allyl oxidant system developed for ketone dehydrogenation (entry l).[14d] In contrast, when a distannylzinc nucleophile[15] was employed, **5a** was formed with decreased efficiency (25%, entry 2). The use of a Et_2Zn-derived stannylzincate[16] provided a somewhat lower yield (42%) due to incomplete dehydrogenation (entry 3).

Interestingly, the zincate nucleophile derived from Me_2Zn was completely ineffective for dehydrogenation and instead yielded a complex mixture of byproducts (entry 4). The Pd-catalyzed dehydrogenation of the enolate accessed from a stannylcuprate nucleophile[17] led to complete decomposition of 7 (entry 5). Due to the increased equivalents of nucleophilic species in entries 2–5, a proportionate increase in the amount of oxidant was necessary to observe any conversion of **7**. Large quantities of stannyl enone **5a** necessary for the synthesis of xylogranatopyridine B could be prepared in 43–50% isolated yield by employing this methodology on up to 35-g scale. Though efficient dehydrogenation occurred at room temperature, obtaining **5a** reproducibly and preventing product decomposition required heating to 60 °C, which led to precipitation of Pd.

We examined the scope of the oxidative stannylation (Scheme 2A). α-Santonin was oxidatively stannylated to provide **5b** in 44% yield. The oxidative stannylation of (–)-carvone required a zincate nucleophile for modest product formation (30%) as the use of the stannyllithium nucleophile was less effective. Silyllithium[18] nucleophiles were also used to provide the oxidatively silylated products **5d–5f**. The higher yield of the silylation to form **5d** (79%) as compared to the stannylation to form **5a** reflects the more efficient dehydrogenation in the presence of a silane. The synthesis of **5f** demonstrates that the

reaction system is amenable to a vinylogous dehydrogenation of lactones. Synthetic modification of the C–Si bond may allow for further elaboration of these products.

Under a set of modified conditions, alkyl groups were also incorporated to the β-position of enones (Scheme 2B).[19] Mixed trialkylzincate[20] nucleophiles derived from commercial dialkylzinc (**5g–5i, 5k**), organolithium (**5j**), and Grignard reagents (**5l, 5m**) readily underwent conjugate addition to cycloalkenones to give zincate enolates that could be dehydrogenated. The functional group tolerance of organozincate conjugate additions partially restricts the substrate scope of this oxidative alkylation.

With a scalable protocol to form **5a** we undertook the synthesis of xylogranatopyridine B (Scheme 3). The preparation of oxime **4** involved methylcuprate addition to 3-methyl-2-cyclohexenone (**9**) and trapping with TMSCl to provide enoxysilane **10**. Using Yamamoto's conditions for oxime formation with in situ generated TIPS-NO_2,[21] **10** was oxidized to the α-keto oxime (**11**) in 63% yield over the two-step vicinal difunctionalization of enone **9**. Methylenation and benzoylation of the α-keto oxime provided fragment **4**.

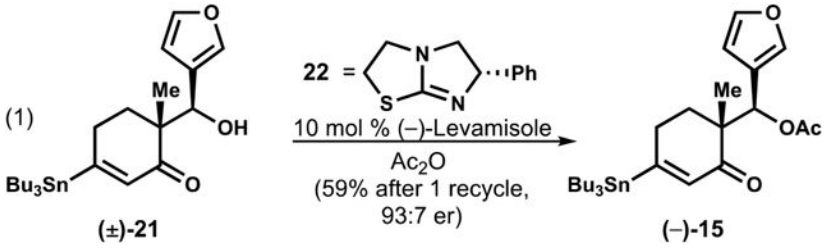
The synthesis of stannane fragment **16** began with inexpensive dihydrocarvone (**13**), which was converted to 6-methylcyclohexenone (**8a**) in 55% yield via ozonolytic fragmentation[22] followed by the aforementioned Pd-catalyzed oxidative stannylation. A diastereoselective aldol between the lithium enolate of **5a** and 3-furaldehyde (**14**) provided **15** after acylation. Treatment of acetate **15** with LiTMP initiated an intramolecular acetate aldol, in which the intermediate adduct was trapped with Burgess reagent to provide fragment **16**.

With access to both fragments in 4–5 steps on decagram-scale, we forged the central pyridine.[11] The ring synthesis employed oxime benzoate **4** and stannane **16** rather than the previously reported boronic acid due to the stannane's relative ease of preparation and tolerance to subsequent reactions. Typical Chan-Lam coupling conditions[11,23] predominantly resulted in decomposition of oxime **4** and destannylation of **16**. We determined that the use of quinuclidine was more optimal than previously reported amine additives.[24] The tetracyclic core of xylogranatopyridine B (**3**) was obtained in 43% yield by heating the same reaction vessel to initiate a 6π-electrocyclization and aromatization. In practice, an isomeric mixture of **4** was employed, but independent subjection of each of the oxime isomers demonstrated both are competent substrates for the Chan-Lam coupling, suggesting that either **4** or **17** may be undergoing thermal isomerization. This mechanistic pathway is supported by the control experiment wherein substitution of des-stannyl-**16** for **16** in the reaction conditions does not lead to the product **3**.

With the completed carbon framework in hand, we turned our attention to the selective oxidation of the benzylic position adjacent to the more electron-rich pyridine meta-position (Cl) over the more electron-deficient ortho-position (C11).[25] A broad examination of oxidants identified the Cr(V) complex[26] as the optimal reagent to provide ketone **18** in 56% yield along with 27% recovered **3**. It is remarkable that selective oxidation occurred in the presence of numerous oxidizable functionalities (e.g. furan, pyridine nitrogen, etc.).

Ketone **18** underwent smooth α,β-dehydrogenation with the conditions previously developed in our laboratory[14d] to provide enone intermediate **19** in 67% yield on 1-g scale. It is interesting to note that additional optimization of the reported conditions was not required even in the presence of the basic pyridine functionality in **19**. A Mukaiyama–Michael reaction with **19** and the enoxysilane derived from methyl acetate, in the presence of catalytic TBSOTf, provided an intermediate enoxysilane as a 1:1 mixture of diastereomers at C5. Although direct methylation of the corresponding enolate was feasible, the alkylations were inefficient owing to the base sensitivity of **2**. To circumvent the unselective alkylation, Simmons–Smith cyclopropanation proceeded with high diastereoselectivity (>20:1 dr) and deprotection of the siloxycyclopropane with TBAT occurred smoothly to give a combined yield of 75% for the mixture of C5 epimers and a 31% isolated yield of the single diastereomer **20**. The use of Zeise's dimer, $[PtCl_2(C_2H_4)]_2$,[27] was optimal for opening cyclopropanol **20** to form xylogranatopyridine B (**2**) in 69% yield.

The racemic synthesis of **2** was rendered asymmetric through Birman's acylative kinetic resolution of alcohol (±)-**21** using (–)-Levamisole (**22**),[28] providing acetate (–)-**15** in 93:7 er and 43% yield on decagram scale (eq 1). The unreacted alcohol could be converted back to **5a** by a retro-aldol elicited by K_2CO_3/MeOH in 89% yield, and a total yield of 59% of (–)-**15** could be obtained after one round of recycling. The enantioenriched material provided (–)-xylogranatopyridine B.



The total synthesis of the limonoid alkaloid, (–)-xylogranatopyridine B, required a longest linear sequence of 11 steps from commercially available materials. This synthesis was enabled by the development of an oxidative enone β-functionalization, which provided rapid access to stannane **16** and demonstrated the use of allyl-Pd catalysis for enabling C–C and C–X bond constructions. Furthermore, the strategic combination of a modified Liebeskind pyridine ring synthesis and a late-stage benzylic oxidation allowed for a convergent assembly of the limonoid alkaloid skeleton. With a scalable route established to the core scaffold, current efforts are underway to further explore the biological activities of the limonoid alkaloids and their synthetic derivatives.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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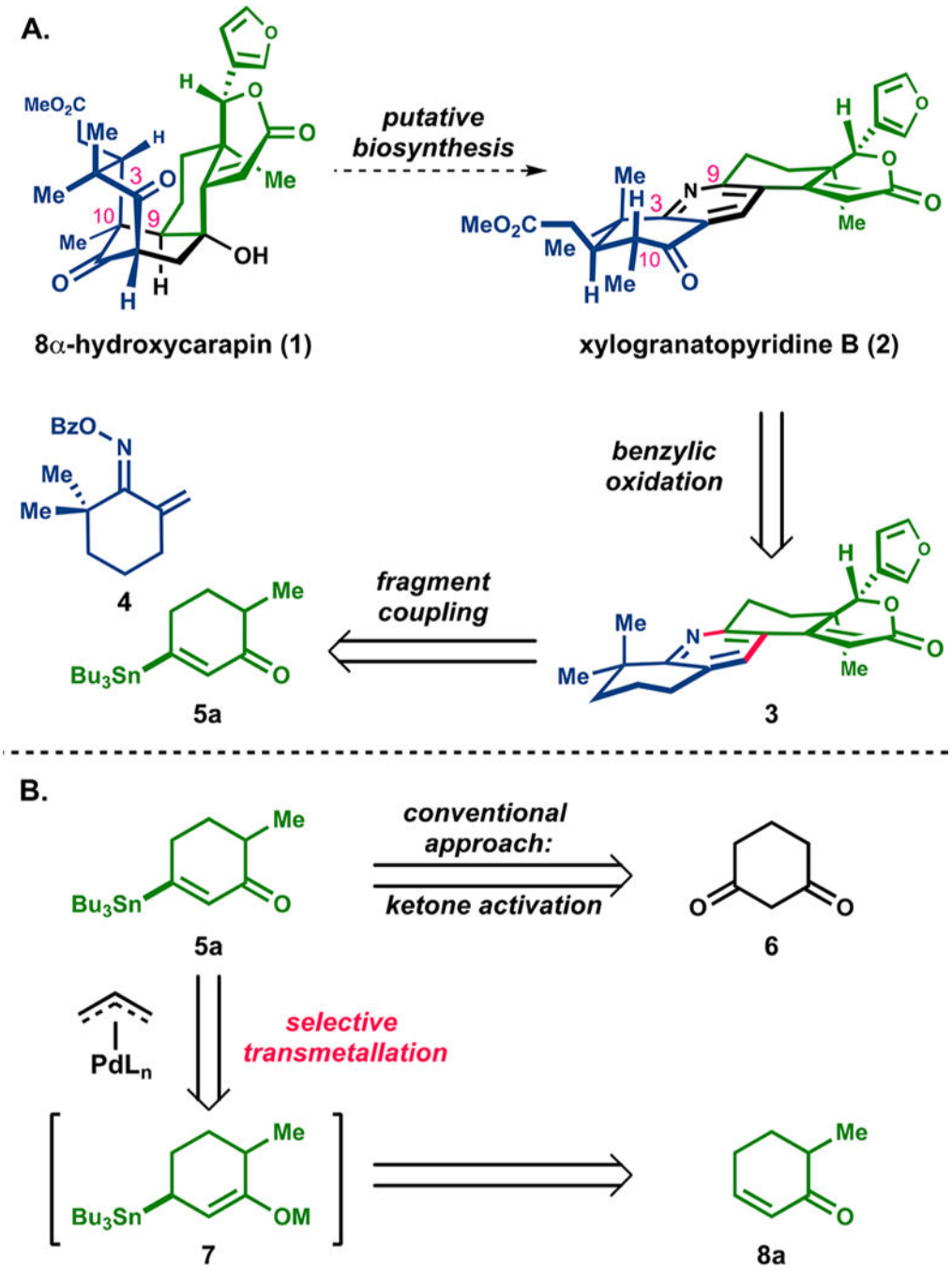
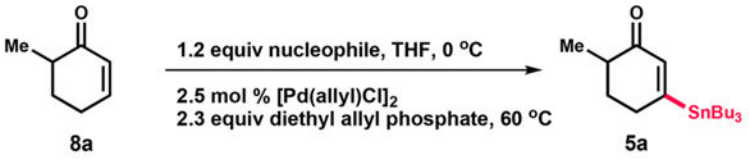


Figure 1.

(A) Putative biosynthesis and abiotic retrosynthetic analysis. (B) Pd-mediated oxidative *β*-stannylation of enones to form **5a**.

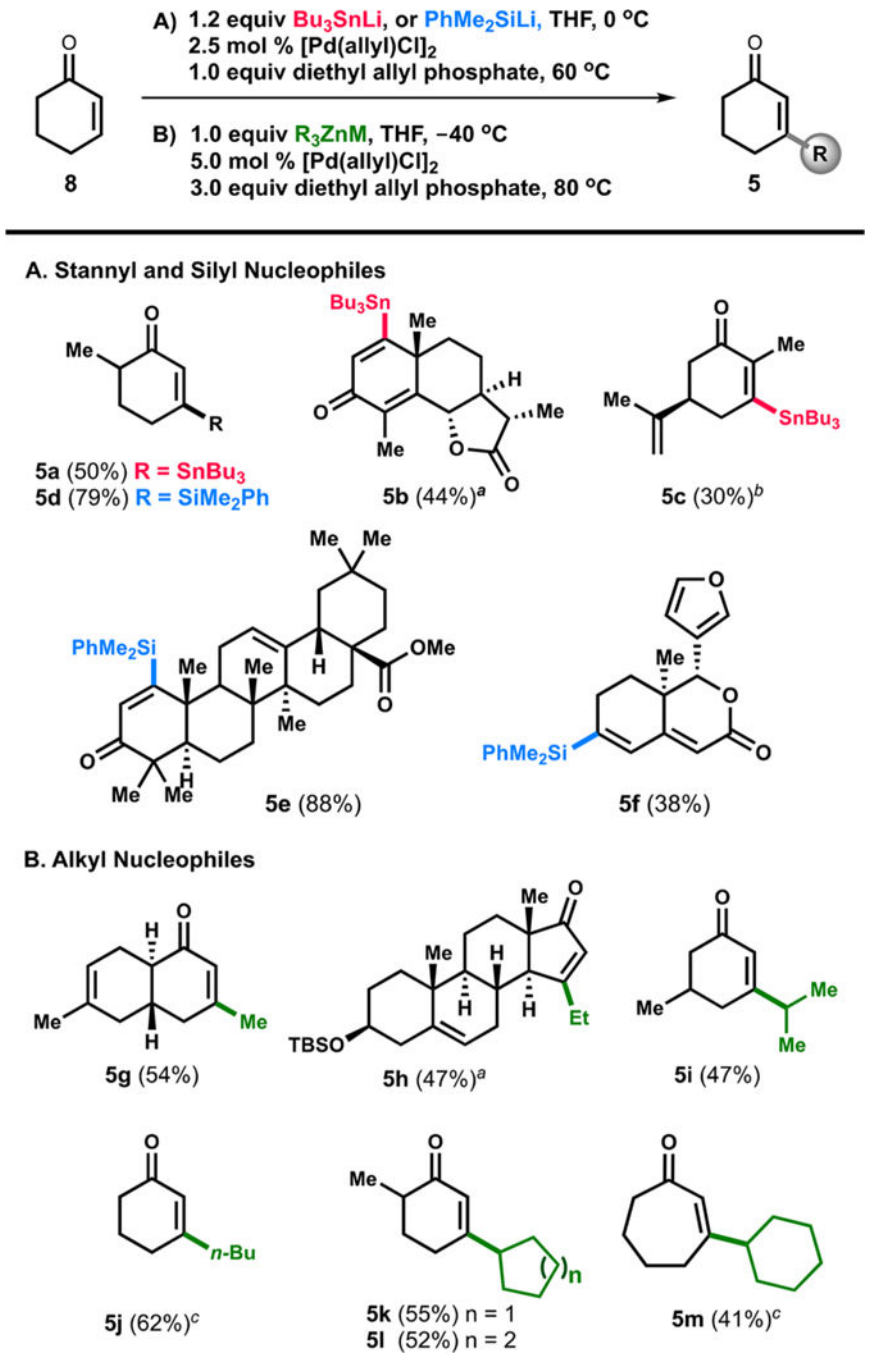


8a 5a

Entry	Nucleophile	^{1}H-NMR Yield (%)[a]
1	Bu_3SnLi	50 (85)[b]
2	$(Bu_3Sn)_2Zn$	25 (79)
3	$Bu_3SnZnEt_2Li$	42 (82)
4	$Bu_3SnZnMe_2Li$	0 (87)
5	$(Bu_3Sn)_2CuLi$	0 (91)

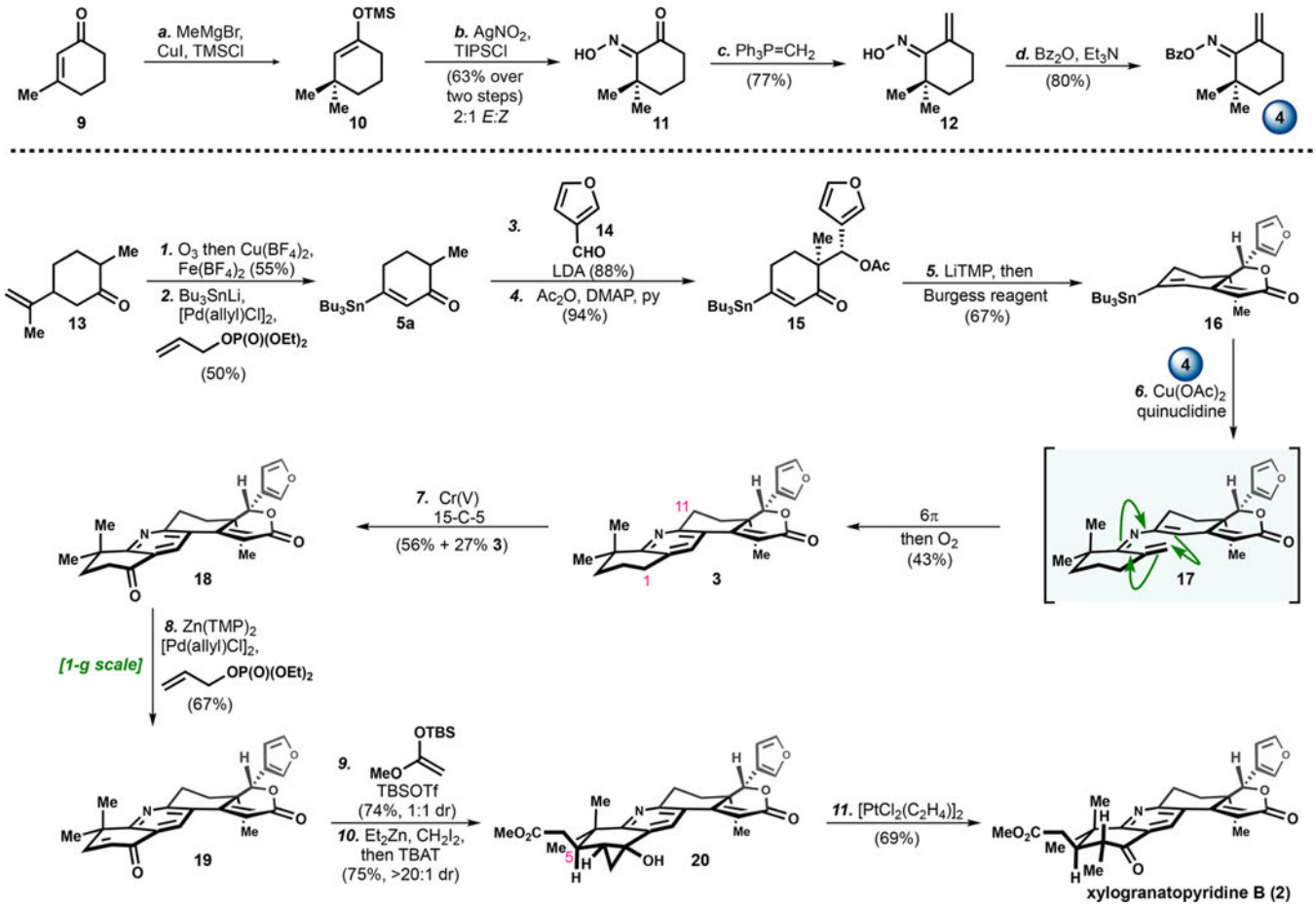
Scheme 1. Optimization of the Synthesis of Stannane 5a

[a]^{1}H-NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. The conversion of starting material is indicated in parentheses. [b]Isolated yield using 1.0 equiv of diethyl allyl phosphate.



Scheme 2. Scope of Oxidative Enone Functionalization

[a]Conjugate addition was conducted at 23 °C. [b]1.0 equiv of $Bu_3SnZnEt_2Li$ and 2.3 equiv of diethyl allyl phosphate was used. [c]Conjugate addition was conducted at −78 °C.



Scheme 3. Total Synthesis of Xylogranatopyridine B (2)

[a]Reagents and conditions: (a) LiCl (0.1 equiv), CuI (5 mol %), TMSCl (1.1 equiv), MeMgBr (1.2 equiv), −40 °C, THF, 10 min; (b) $AgNO_2$ (1.2 equiv), TIPSCl (1.4 equiv), −40 °C, MeCN, 2 h; **10** (1.0 equiv), −40 to −20 °C, 2 h, 63% over 2 steps; (c) $Ph_3P{=}CH_2$ (3.0 equiv), PhMe, 23 to 60 °C, 1.5 h, 77%; (d) Bz_2O (1.1 equiv), Et_3N (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2 0 to 23 °C, 1 h, 80%; (1) O_3, MeOH, −40 °C, 4 h; $Cu(BF_4)_2$ (1.5 equiv), $Fe(BF_4)_2$ (1.2 equiv), −40 to 23 °C, 1 h, 55%; (2) Bu_3SnLi (1.2 equiv), $[Pd(allyl)Cl]_2$ (2.5 mol %), diethyl allyl phosphate (1.0 equiv), THF, 60 °C, 1 min, 50%; (3) LDA (1.1 equiv), **14** (1.2 equiv), −78 °C, THF, 0.5 h, 88%; (4) Ac_2O (2.0 equiv), py (3.0 equiv), DMAP (0.1 equiv), 0 °C, CH_2Cl_2, 0.5 h, 94%; (5) LiTMP (2.5 equiv), −78 to 23 °C, THF; Burgess reagent (3.0 equiv), 60 °C, 2 h, 67%; (6) $Cu(OAc)_2$ (1.0 equiv), quinuclidine (2.0 equiv), **4** (1.5 equiv), 60 °C, DMF, 12 h; O_2, 100 °C, 1 h, 43%; (7) $Na[OCr(O_2COC(CH_3)C_2H_5)_2]$ (10.0 equiv), 15-C-5 (0.5 equiv), 75 °C, MeCN, 14 h, 56% + 27% **3**; (8) $Zn(TMP)_2$ (1.4 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), diethyl allyl phosphate (1.2 equiv), 85 °C, 1 h, 67%; (9) TBSOTf (5 mol %), 1-(TBS)-1-methoxyethene (1.5 equiv), CH_2Cl_2, 0 to 23 °C, 0.5 h, 75%, 1:1 dr at C5; (10) Et_2Zn (2.0 equiv), CH_2I_2 (4.0 equiv), 0 to 23 °C, PhMe, 6 h; TBAT (10.0 equiv) in THF, 12 h, 75%; (11) $[PtCl_2(C_2H_4)]_2$ (10 mol %), CH_2Cl_2, 23 °C, 5 h, 69%.