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An intramolecular *para*-phenolic allylation free radical cyclization strategy for the synthesis of alkaloids and terpenes with spiro[4.5] decane architectures

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ABSTRACT

A Tsuji-Trost variant of the Winstein-Masamune reaction has been investigated for the synthesis of the AC spirocyclic ring system **9** bearing a quaternary carbon found in the fawcettimine type *Lycopodium* alkaloids magellanine **1** and lycojaponicumin B **2** and cyclopiane diterpenes such as conidiogenone **3**. Annulation of the B ring for the synthesis of tricyclic ABC cores was demonstrated utilizing a 5-*exo*-trig free radical cyclization of a primary carbon radical onto a cyclohexadienone generated with tri-*n*-butylgermanium hydride (**9** → **11**).

The control of stereochemistry in the installation of quaternary carbons remains an enduring challenge in complex total synthesis of natural products.[1] The *Lycopodium* alkaloids magellanine **1**[2] and lycojaponicumin B **2**,[3] *Cyclopiane* diterpene conidiogenone **3**,[4] and *Acorane* terpene colletoic acid **4**[5] shown in Fig. 1 are prime examples of such molecules. Each contains a stereogenic spirocyclic quaternary carbon embedded within a spiro[4.5]decane core. The complexity of these polycyclic architectures is further increased by the presence of contiguous chirality centers.

To synthesize the spiro[4.5]decane substructures found in **1**–**4**, we envisioned utilizing a phenolic dearomatization strategy.[6] Specifically, the classic Winstein-Masamune[7] anionic phenolic dearomatization that proceeds via an $Ar_{1,5}$ mechanism generates a spiro[4.5]decane substructure of **1**–**4**. To wit, potassium *tert*-butoxide (an exogenous base) in refluxing *tert*-butanol deprotonates the phenol **5** which subsequently reacts via vinylogous enolate reactivity to displace an electrophile at an sp^3-hybridized carbon terminus to afford spiro[4.5]deca-1,4-diene-3-one **6** (Fig. 2). This strategy[8] has been demonstrated in contemporary complex molecule syntheses such as galanthamine,[9a] resiniferatoxin,[9b] and platensimycin.[9c]

A limitation of the traditional Winstein-Masamune reaction is the carbon bearing the leaving group is sp^3 hybridized. Further functionalization of that carbon is therefore particularly difficult. Recently, two independent publications by the Hamada[10] and You[11] groups utilizing palladium (**7** → **9**) and iridium catalysis (**8** → **10**) have effected a Tsuji-Trost[12] 5-*exo*-trig allylation variant

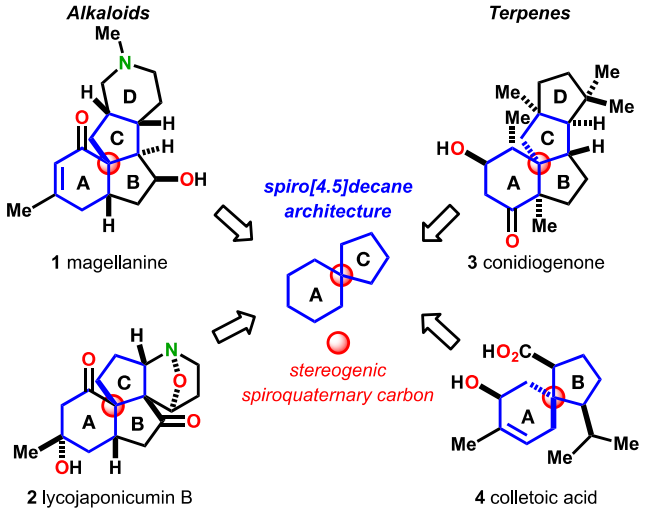

Fig. 1. Alkaloid and Terpene Natural Products Bearing the Spiro[4.5]decane Core Architecture.

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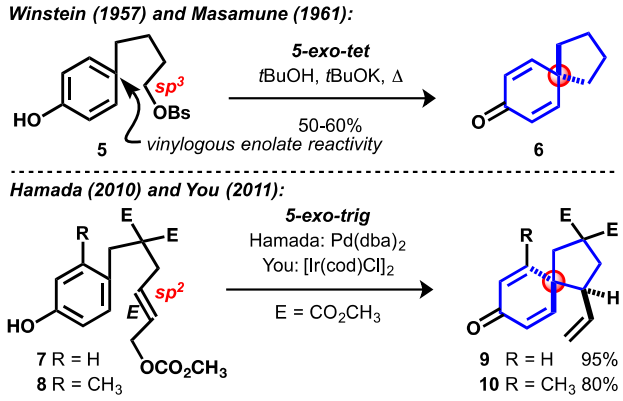
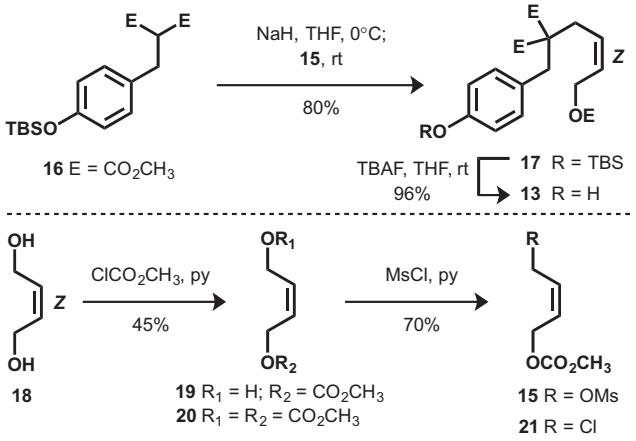


Fig. 2. Classical Winstein-Masamune Spirocyclization (**5** → **6**) and the Contemporary Tsuji-Trost Transition Metal Variants (**7/8** → **9/10**).



Scheme 2. Synthesis of TTWM Spirocyclization Precursor **13** Utilizing *bis*-Electrophile **15**.

of the classic Winstein-Masamune reaction. The use of phenol nucleophiles as vinylogous enolates in the intramolecular Tsuji-Trost allylation had been relatively unexplored over the past half century. Therefore a Tsuji-Trost Winstein-Masamune phenolic allylation would be an ideal solution for the syntheses of molecules such as **1**–**4** as a vinyl group is deposited at the electrophilic carbon for post-cyclization modifications.

Our general retrosynthetic strategy for the construction of the ABC tricyclic cores found in **1**–**3** is depicted in Scheme 1. To expeditiously validate this strategy, we chose a generic model system **11** that lacks a D ring. The B ring of the angular tricyclic carbon backbone in **11** would arise via a 5-*exo*-trig radical cyclization of a primary carbon radical onto the β-carbon of a cyclohexadienone. The radical would be generated from halohydrin **12** that would arise from chemo- and regioselective difunctionalization of the more electron rich alkene in **9**. The spiro[4.5]decane **9** and quaternary carbon would be synthesized by deploying the Tsuji-Trost Winstein-Masamune intramolecular phenolic allylation of **13**. This ultimately leads back to a *para*-substituted phenol **14** and a *bis*-electrophile **15**. The phenol **14** is an ideal platform to commence synthetic efforts given the high degree of unsaturation that is conserved through the TTWM reaction to the cyclohexadienone **9**.

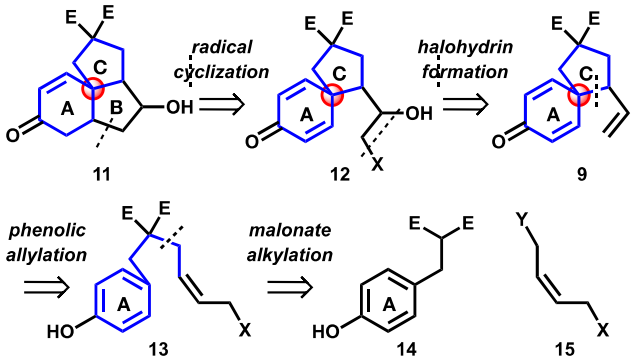
Our efforts toward **11** commenced with the synthesis of benzylidene malonate **16** shown in Scheme 2 prepared in 3-steps from 4-hydroxybenzaldehyde according to the Hamada protocol.[10] Briefly, Knoevenagel condensation of 4-hydroxybenzaldehyde with dimethylmalonate was carried out in toluene in the presence of piperidine and catalytic acetic acid at reflux to afford benzylidene malonate in 99% yield. Subsequent hydrogenation of the olefin with hydrogen gas in the presence of 10% palladium on carbon in methanol smoothly afforded reduced malonate in 97% yield. The phenol was protected as the *tert*-butyldimethylsilyl ether with TBSCl, imidazole and catalytic DMAP in DMF giving in 95% yield. At this stage the allylic carbonate was installed via alkylation of the sodium enolate with the *bis*-electrophile **15**. The silyl protecting group of **17** was quantitatively cleaved with TBAF in THF at ambient temperature giving the desired precursor **13** in 96% yield.

Installation of the allylic carbonate utilized a new *bis*-electrophile synthesis that is amenable to regioselective alkylation (Scheme 2). To that end, *cis*-1,4-butanediol **18** was treated with one equivalent of methyl chloroformate in tetrahydrofuran to afford a 1:1 mixture of the mono-**19** and di-**20** that were readily separable by normal phase silica gel column chromatography. The allylic alcohol **19** was rapidly sulfonylated with methanesulfonyl chloride at 0 °C in less than one hour to afford **15** in 70% yield.[13] It should be noted that extended reaction times lead to chloride displacement of the mesylate **15** to the allylic chloride **21**. The methylene groups of **20** are readily differentiated by ^{1}H NMR with the allylic CH_2 near the sulfonate at 4.74 ppm and that of the carbonate at 4.87 ppm. This differentially protected allylic 1,4-diol is an ideal annulating agent for the intramolecular phenolic *para*-allylation.

With gram quantities of the spirocyclization precursor **13** in hand, we examined the palladium-catalyzed conditions shown in Table 1. Entries 1–4 at ambient temperature showed clean conversion of **13** to **9** after 6 h by TLC, however the isolated yields after workup and purification were poor to moderate (13–42%). We sought to reduce the reaction time by utilizing microwave heating in a closed system to minimize catalyst inactivation.

We discovered that with strict degassing of the reaction mixture at ambient temperature by sparging nitrogen gas for at least 15 min was crucial to the successful conversion of **13** to **9**. The optimal temperature and time with microwave heating was 40 °C for a total of 40 min. After the first 20 min, ^{1}H NMR showed 51% conversion and the remaining material was fully converted after an additional 20 min heating cycle. While the microwave heating showed full conversion to product by ^{1}H NMR, the isolated yields of **9** were typically between 50 and 60%.

With usable quantities of alkene **9** in hand, we set out to chemoselectively functionalize the more electron rich pendant alkene in a regioselective fashion as either the selenohydrin **22a** or halohydrins **22b**/**22c**. As the cyclohexadienone alkenes in **9** are electron-deficient we anticipated that reagents such as NBS, NIS and PhSeCl in aqueous acetonitrile would install a secondary hydroxyl group along with a primary halide or selenide. Table 2



Scheme 1. Retrosynthetic strategy for the synthesis of tricyclic architecture **11**.