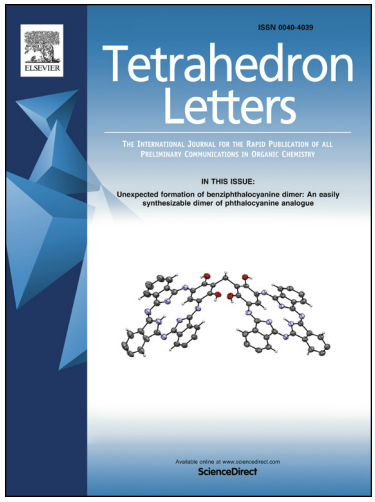

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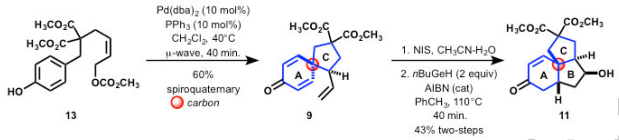

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An Intramolecular *para*-Phenolic Allylation Free Radical Cyclization Strategy for the Synthesis of Alkaloids and Terpenes with Spiro[4.5]decane Architectures

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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 Figure 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 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.

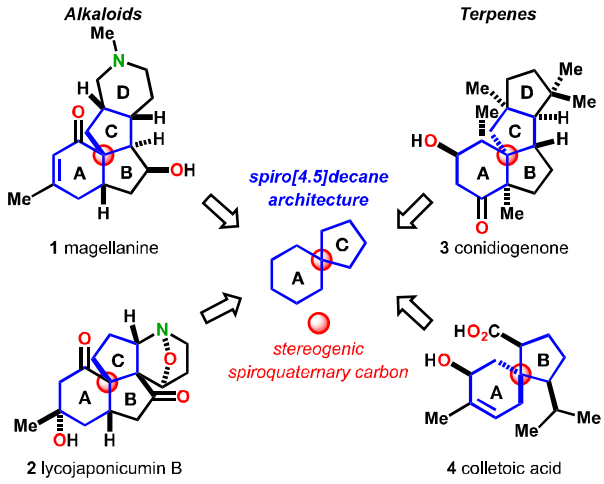

Figure 1. Alkaloid and Terpene Natural Products Bearing the Spiro[4.5]decane Core Architecture.

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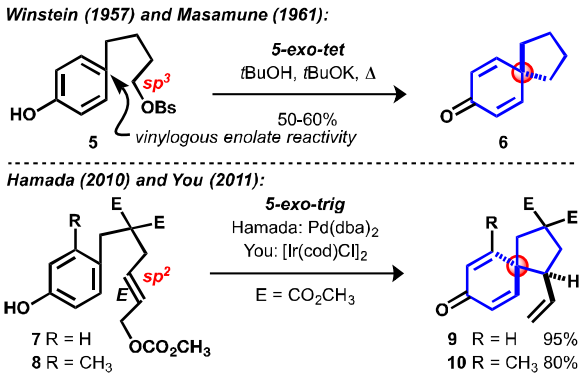
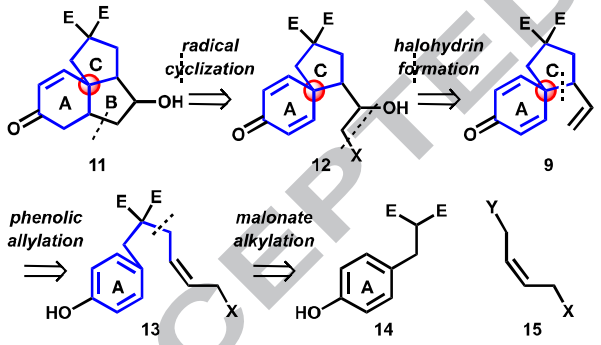


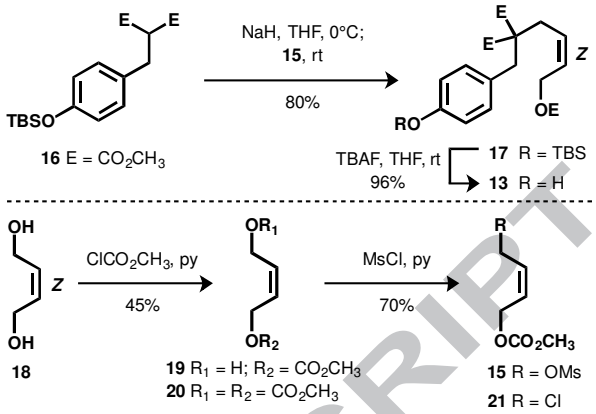
Figure 2. Classical Winstein-Masamune Spirocyclization (**5**→**6**) and the Contemporary Tsuji-Trost Transition Metal Variants (**7/8**→**9/10**).

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**.



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

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.

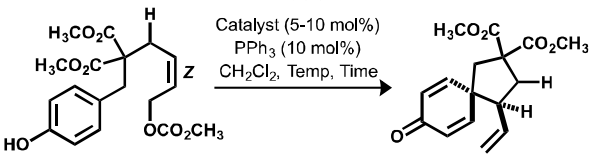


Scheme 2. Synthesis of TTWM Spirocyclization Precursor **13** Utilizing *bis*-Electrophile **15**.

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 hours 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.

Table 1



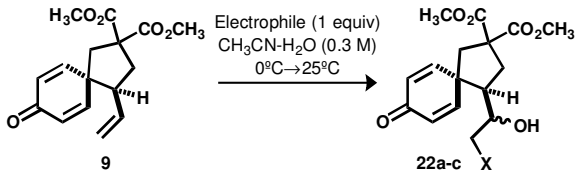
Entry	Catalyst	Time	Temp (°C)	% Yield 9[b]
1	$Pd[PPh_3]_4$	6 hr	25	13
2	$Pd(dba)_2$	24 hr	25	27
3	$Pd_2(dba)_3$•$CHCl_3$	6 hr	25	29
4	$Pd_2(dba)_3$	6 hr	25	42
5	$Pd_2(dba)_3$•$CHCl_3$	40 min	[a]40	29
6	$Pd[PPh_3]_4$	40 min	[a]40	50
7	$Pd_2(dba)_3$	40 min	[a]40	60

[a]μ-wave heating in a Biotage Initiator+ Synthesizer; [b]Isolated yield after silica gel chromatography.

Table 1. Palladium Catalyzed Intramolecular Phenolic Allylation of **13** under Thermal and Microwave Heating.

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

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 summarizes the best results of these electrophile initiated oxidation experiments. The selenohydrin **22a** was isolated in 87% yield while the bromohydrin **22b** and iodohydrin **22c** were typically lower isolated yields hovering around 55%.



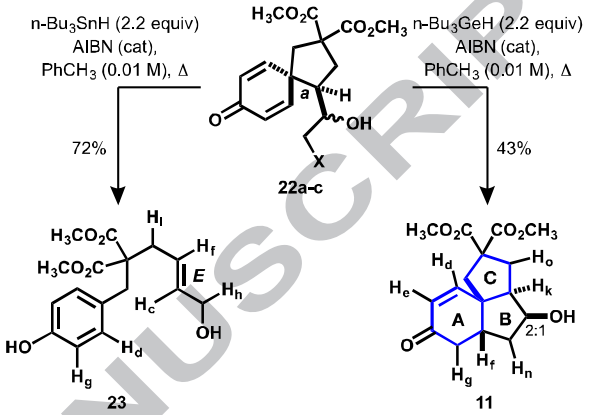
Entry	22	Electrophile	X	Time	% Yield 22
1	**22a**	PhSeCl	PhSe	4 hr	87[a]
2	**22b**	NBS	Br	22 hr	55[a]
3	**22c**	NIS	I	22 hr	56[a]
4	**22c**	NIS	I	1.5 hr	not isolated[b]

[a]Isolated yield after silica gel chromatography.; [b]Crude material carried on without purification.

Table 2. Chemo- and regio-selective alkene halo(seleno)hydrin formation.

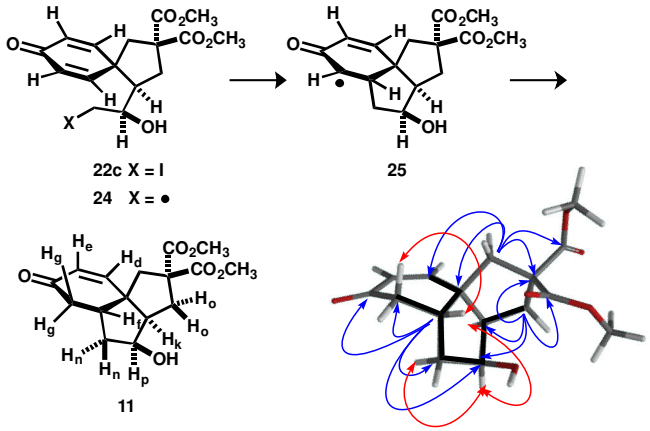
With substrates **22a-c** now synthesized, our focus now shifted toward investigating carbon radical initiation to induce a 5-*exo*-trig radical cyclization thereby constructing the angular tricylic ABC cores found in **1-3**. During our investigation employing tin hydride reagents, we observed smooth conversion of **22a or 22b** to a more polar spot by TLC (R_f = 0.30 (1:1 hexanes-acetone). Examination of the ^{1}H NMR revealed a structure other than the desired tricyclic compound that contained both aromatic protons and an internal alkene functionality (signals at 5.74 and 5.62 ppm). This material was fully characterized with 2D NMR and determined to be the rearomatized phenol **23** containing a primary allylic alcohol. The *trans* conformation of the alkene was established based on the coupling constant ($^3J_{c,f}$ = 15.7 Hz). COSY NMR was used to identify the spin systems in the structure located at the alkene ($H_l \rightarrow H_f \rightarrow H_c \rightarrow H_h$) and the phenol ($H_g \rightarrow H_d$). HSQC and HMBC confirmed the connectivity of the phenol. Additionally, ^{13}C chemical shifts supported the presence of the phenol (155 ppm) and primary alcohol (63 ppm). We speculate that addition of nBu$_3$Sn• to the cyclohexadienone carbonyl of **22** is more favorable than generation of the primary carbon radical. The formation of a stabilized ring divinyl radical then leads to subsequent fissure of bond ***a*** and ensuing radical rearrangement processes.

Independent reports from the Beckwith and Clive groups have demonstrated the utility of tri-*n*-butylgermanium hydride to selectively generate carbon radicals from alkyl iodides in the presence of cyclohexadienones.[14] We were pleased to observe that upon treatment of iodide **22c** with nBu$_3$GeH and AIBN in refluxing toluene, the desired tricyclic compound was indeed produced in 43% yield. The structure of **11** was fully elucidated using extensive 1D and 2D NMR experiments.



Scheme 3. Rearomatization (**22b/c→23**) with tin hydride versus cyclization with germanium hydride (**22c→11**).

Given the geometrical constraints of this system, the primary carbon radical **24** is forced to add to the electron deficient β-carbon of the proximal alkene of the spiro[4.5]cyclohexadienone from the bottom face. This addition gives *cis* ring fusion in the bicyclo[4.3.0]nonane, whereas addition from the top face would give a strained *trans* ring junction. The ensuing stabilized radical **25** is then quenched by nBu$_3$GeH and concomittantly sets the correct desired *trans* relationship between H_f and H_k. Based on the stereochemistry of the spirocycle **9**, the stereochemistry of H_k (pointing down) is conserved. It should be noted that the radical addition to the distal olefin would result in an energetically disfavored *trans* ring junction about the bicycle[3.3.0]octane



substructure.

Scheme 4. Plausible radical cyclization pathway and structure elucidation of tricycle **11**.

Initial examination of the alkene region of the ^{1}H NMR revealed loss of the cyclohexadienone symmetry and showed new peaks at 5.87 (H_e) and 5.44 (H_d) ppm both integrating for one proton. COSY correlations, as indicated by the bold black lines, was used to identify and connect the spin systems in the structure showing connectivity of the ABC rings ($H_g \rightarrow H_f \rightarrow H_n \rightarrow H_p \rightarrow H_k \rightarrow H_o$) and the alkene region ($H_e \rightarrow H_d \rightarrow H_f$). The correlation of $H_d \rightarrow H_f$ is a result of "W" coupling which was realized through observation of the 3-dimensional structure. ^{13}C NMR, DEPT135 and HSQC experiments showed two new CH_2 groups at 68.2 ppm and 39.6 ppm belonging to CH_g and CH_n, respectively. HMBC, as indicated by the blue arrows, further supported the connectivity of the tricycle as shown in Scheme 4. NOESY correlations, as indicated by the red arrows, were utilized to confirm the major secondary alcohol diastereomer. It was seen that H_p only showed correlation with H_k and not H_f implying the alcohol for the major diastereomer pointed up.

In conclusion we have carried out an 8-step synthesis of the ABC tricyclic core **11** found in numerous alkaloid and terpene natural products from 4-hydroxybenzaldehyde in 18% yield. Salient features of this route include the development of a new orthogonally activated *bis*-electrophile **15** in the malonate alkylation of **16**, demonstration of the Tsuji-Trost-Winstein-Masamune spirocyclic allylation **13→9**, and nBu$_3$Ge• initiated 5-exo-trig radical cyclization of **9→11**. We are currently investigating the application of this strategy to complex alkaloids and terpenes such as those identified in Figure 1.

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13. **Spectral Data of 18:** R_f = 0.41 (1:1 hexanes-EtOAc; uv then PMA); ^{1}H NMR ($CDCl_3$, 400 MHz) □ 3.05 (s, 3H), 3.80 (s, 3H), 4.74 (d, J = 6.0 Hz, 2H), 4.87 (d, J = 6.0 Hz, 2H), 5.88 (m, 1H), 5.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) □ 38.1 (q), 55.0 (q), 62.8 (t), 64.7 (t), 126.8 (d), 129.5 (d), 155.5 (s); HRMS (ESI): Exact mass calcd for $C_7H_{12}O_6S$ $[M+Na]^+$ 247.0252. Found 247.02450.
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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

- Spiro[4.5]cyclohexadienone is an ideal scaffold to synthesize complex alkaloids and terpenes
- 1,4-bis-electrophile composed of an allylic carbonate and allylic mesylate has been synthesized
- Intramolecular phenolic allylation utilized in the synthesis of spiro[4.5]decane substructure
- Germanium hydride initiated free radical cyclization achieved angular tricycle formation