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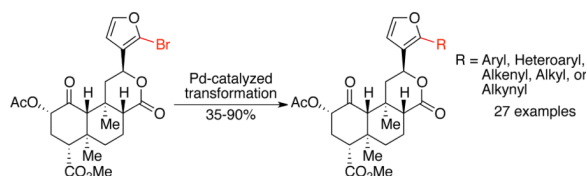
## Palladium-catalyzed Transformations of Salvinorin A, a Neoclerodane Diterpene from *Salvia divinorum*

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### Abstract



Transformations that selectively modify the furan ring present in a variety of natural products would be useful in the synthesis of biological probes but remain largely underexplored. The neoclerodane diterpene salvinorin A, isolated from *Salvia divinorum*, is an example of a furan-containing natural product. Following selective bromination of salvinorin A, Suzuki-Miyaura and Sonogashira couplings were accomplished in moderate to good yields without hydrolyzing the labile C-2 acetate or altering the stereochemistry of the epimerizable centers.

Natural products (NPs) play an important role in drug discovery, serving as either a source or inspiration for approximately half of all approved small-molecule drugs.<sup>1</sup> Although a large number of these drugs are naturally occurring substances, derivatives of NPs are often necessary to improve pharmacokinetic properties. These derivatives have traditionally been accessed through total synthesis<sup>2</sup> and mutasynthesis.<sup>3</sup> In cases where the NP is readily available from the natural source, semisynthesis is an attractive approach. Due to the large and often complex scaffolds nature develops, semisynthesis requires highly selective transformations.

Perhaps the best examples of NP derivatives that have been developed into drugs are the many opioids prescribed for the treatment of pain.<sup>4</sup> While these treatments have proved successful, their action at the  $\mu$  opioid receptor makes them prone to addiction. The  $\kappa$  opioid receptor (KOR) has been proposed as an alternative target for the treatment of pain. However, agents that exert their effects on this receptor are prone to central side-effects including sedation and dysphoria. New KOR probes are needed to better understand the mechanism associated with these side-effects.

Correspondence to: Thomas E. Prisinzano, [prisinza@ku.edu](mailto:prisinza@ku.edu).**Supporting Information Available** Experimental and spectroscopic details are available for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The perennial sage *Salvia divinorum*, a plant traditionally used in divination rituals by the indigenous people of Oaxaca, Mexico has recently gained attention amongst recreational drug users due to the intense hallucinations produced upon inhalation of the pyrolyzed leaves. The major psychoactive component, salvinorin A (**1**), produces these effects by selectively activating the KOR,<sup>5a</sup> making it the first non-nitrogenous opioid receptor agonist. As a result, several binding models have been suggested to explain how **1** interacts with the KOR while lacking a basic nitrogen.<sup>5</sup>

To complement these models, several studies have produced a number of analogues of **1**.<sup>6</sup> These semisynthetic derivatives were synthesized by selectively altering the many functional groups present in **1**. Thus the structure-activity relationships (SAR) regarding the C-2 acetate and C-4 carbomethoxy positions have been thoroughly investigated. In contrast, the lack of chemical handle on the furan ring has limited derivatives with the furan ring intact to only a few examples. Since all proposed binding models have implicated the furan ring, such derivatives would be useful in elucidating additional SAR.

The modification of NPs containing aromatic functionalities has been accomplished by first introducing a halide using enzymatic<sup>3</sup> or chemical methods.<sup>7</sup> The resulting halides were further diversified using various palladium-catalyzed transformations. Despite the large number of examples,<sup>8</sup> this approach has not been applied to furan-containing NPs. Such a method would be useful as this may lead to analogues with improved drug-like properties not just improved potency. The furan ring of **1** was previously brominated selectively at the C-16 position using NBS,<sup>9</sup> however these reaction conditions required long reaction times and produced either low or highly variable yields. The addition of a catalytic amount of Br<sub>2</sub> reduced the reaction time to 30 minutes and consistently provided yields of 49% (Scheme 1). The resulting product **2** was spectroscopically identical to previous reports and the site of bromination was confirmed by single crystal X-ray diffraction.<sup>10</sup> It is not clear at this time why the addition of catalytic Br<sub>2</sub> improves the reactivity for the selective bromination. One possibility is that the Br<sub>2</sub> and NBS form a reactive complex but this suggestion will require additional investigation.

With rapid access to **2**, investigations into further modifications were initiated using Suzuki-Miyara couplings due to their relatively mild reaction conditions. Utilizing the reaction conditions developed by Buchwald<sup>11</sup> produced a complex mixture with two major isomeric products, surprisingly with the base labile C-2 acetate group intact (Scheme 2). <sup>1</sup>H-NMR revealed the products to be the C-8 epimers **3a** and **4a**. Epimerization at the C-8 position is well-documented in both semisynthetic<sup>12</sup> and total synthesis<sup>13</sup> efforts, occurring under both acidic and basic conditions. Furthermore, 8-*epi*-**1** is also found in the smoke of pyrolyzed *S. divinorum*.<sup>14</sup> This epimerization has profound biological impact as 8-*epi*-**1** and its derivatives generally exhibit decreased affinity and efficacy at the KOR.<sup>12</sup> Thus reaction conditions that reduce C-8 epimerization were desired to obtain the necessary quantities of biologically useful probes.

Noting that the formation of **4a** is likely controlled by either base or heat, the amount of K<sub>3</sub>PO<sub>4</sub> added and reaction temperature were varied to minimize epimerization (Table 1). Although reducing the amount of base in the reaction did improve the ratio of **3a/4a**, the accompanying decrease in conversion required extensive chromatography to separate **2** and **3a**. Fortunately, reducing the reaction temperature to 60°C resulted in full conversion and >99:1 selectivity for **3a** over **4a**.

Having optimized the conditions to prevent epimerization, our attention turned to exploring the scope of the reaction (Table 2). In addition to simple phenyl and naphthyl groups, phenyl rings bearing substitutions in the ortho, meta, and para position were possible. As expected,

electron-rich boronic acids typically produced higher yields than electron-deficient ones. Furans substituted at either the 2- or 3-position and a 3-thiophene could be appended to C-16 in moderate yields, however 2-thienyl and 2-pyridinyl boronic acids produced no reaction. In the case of the thiophene, this could be overcome using a MIDA boronate developed by Burke,<sup>15</sup> however the reaction was incomplete even after 24 hours. Despite several attempts using 2-pyridinyl MIDA boronate, **3v** was never successfully formed. It is possible that indoles and otherazole coupling partners may be more successful. Finally, alkenyl and alkylboronic acids produced moderate to good yields of the corresponding products. In the case of phenethyl boronic acid, the expected product was also accompanied by 13% of **1**, presumably from protodebromination.

In addition to monobromination of the furan ring, dibromination can be accomplished by using a stoichiometric amount of bromine. In order to test whether there was any inherent selectivity for the coupling reactions, the dibrominated product (**5**) was submitted to same reaction conditions using only 1 equivalent of PhB(OH)<sub>2</sub>. Interestingly the diarylated product was the only product observed, producing nearly a 1:1 mixture of recovered starting material and **6** (Scheme 3). The lack of either monosubstituted product suggests that the second coupling reaction is faster than the first.

To extend the method from sp<sup>2</sup>- and sp<sup>3</sup>-hybridized substitutions to alkyne substituents, Sonogashira couplings were also investigated. Employing conditions previously used for Sonogashira couplings on bromofurans,<sup>16</sup> several alkynyl substitutions were synthesized (Table 3). Despite an increase in the reaction temperature and large excess of base, no epimerization was observed. Terminal alkynes bearing aromatic rings, both electron-rich and electron-poor, and alkyl chains were appended to furan ring of **1**. To access a terminal alkyne, ethynyltrimethylsilane was used however this reaction produced an inseparable mixture of TMS-protected **7f** and **2**. Treating this mixture with TBAF in CH<sub>2</sub>Cl<sub>2</sub> allowed for facile isolation of **7f** by column chromatography.

A representative portion of the derivatives were screened for activity at the KOR using a calcium mobilization assay (Table 4).<sup>17</sup> Based on these preliminary results, it appears as though some substitutions at the C-16 position are tolerated. Particularly interesting is **3s** which is equipotent with **1**. However the compound with the inverted stereochemistry at C-8 (**4a**) possessed a significant decrease in potency, thus verifying the importance of preventing C-8 epimerization.<sup>12b</sup>

In conclusion, using Suzuki-Miyaura and Sonogashira couplings, a variety of alkyl, alkenyl, aryl, heteroaryl, and alkynyl substituents were appended to the C-16 position of **1**. Due to the many functional groups present in **1**, these transformations required a high degree of chemoselectivity. The resulting derivatives provide access to furan ring-containing probes that have, until now, remained underexplored. The corresponding pharmacological data, which will be presented in due course, should offer valuable insight into how **1** interacts with the KOR. Furthermore, this highly amenable process will be applied to the synthesis of biological probes using other furan-containing NPs.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

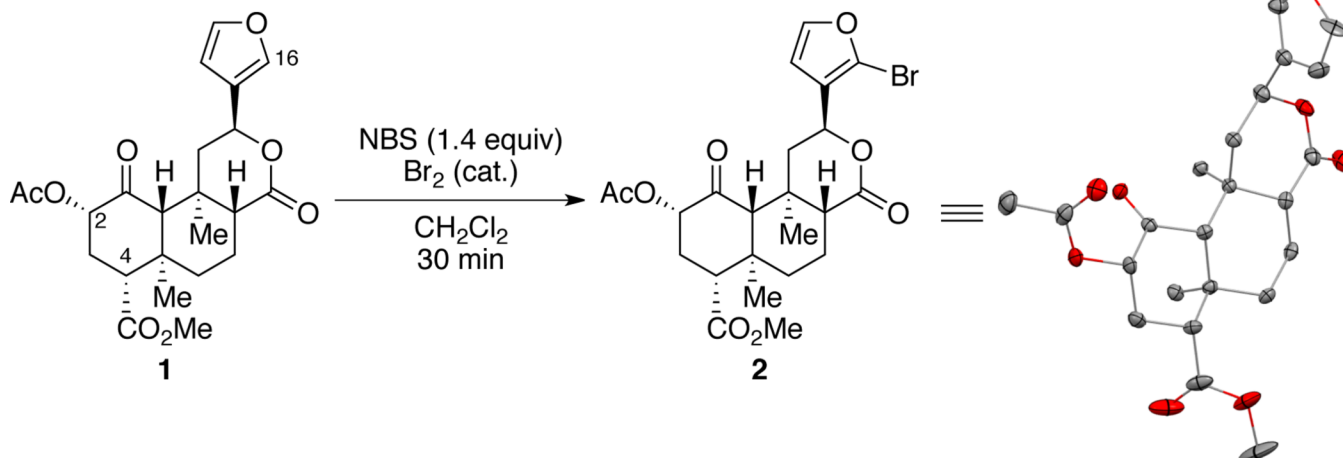
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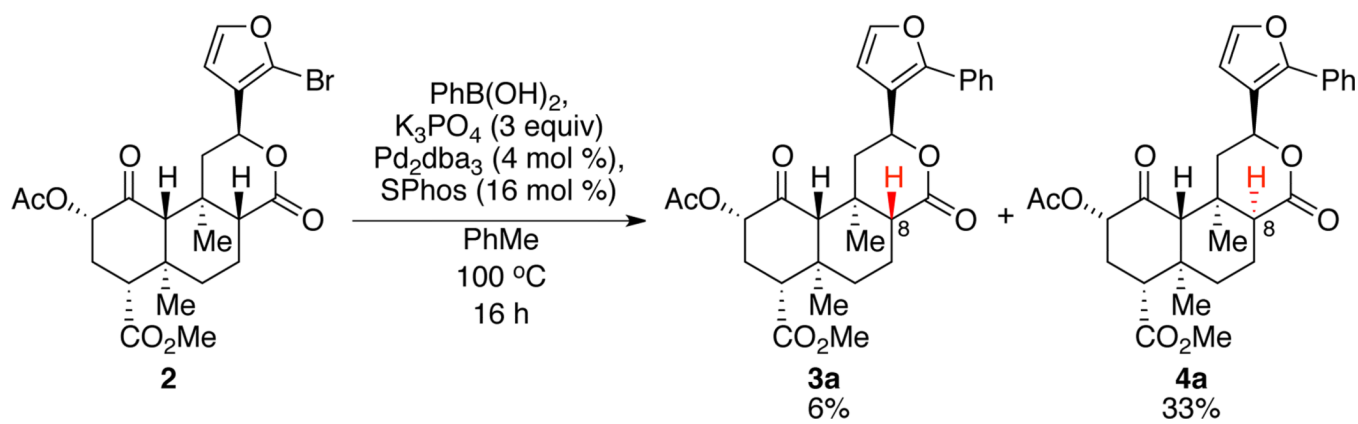
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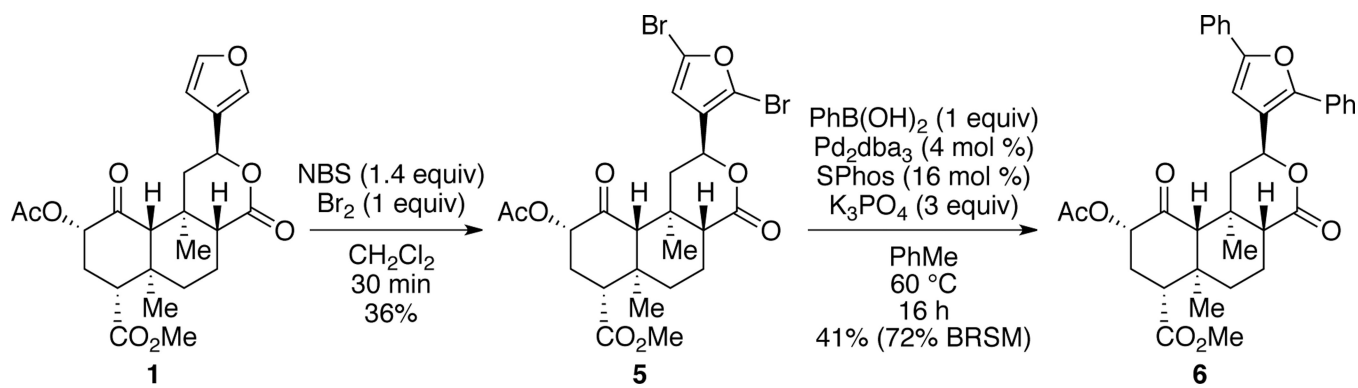
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**Scheme 1.**  
Improved Selective Bromination of **1**



**Scheme 2.**  
Initial Suzuki-Miyaura Reaction Using **2**

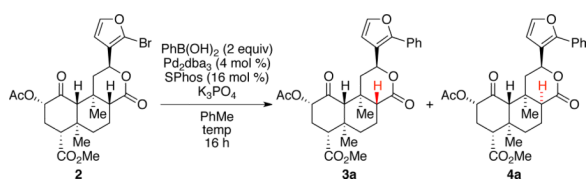


**Scheme 3.**  
Dibromination and Arylation of **1**



Table 1

Optimization of Suzuki-Miyaura Reaction to Minimize Epimerization








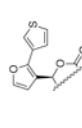



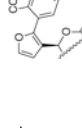
entry	equiv of base	temp (°C)	conv <sup>a</sup> (%)	ratio 3a/4a <sup>b</sup>
1	3.0	100	100	12:1
2	2.5	100	91	80:1
3	2.0	100	17	>99:1
4	3.0	60	100	>99:1

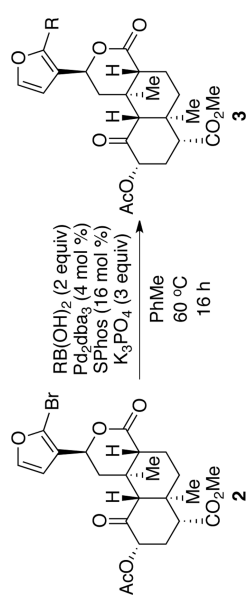
<sup>a</sup> Conversion measured by GC-MS

<sup>b</sup> Ratio of **3a/4a** measured by HPLC.

Table 2

Modifications Made to the C-16 Position Using the Optimized Suzuki-Miyaura Conditions

entry	product	yield (%) <sup>a</sup>	entry	product	yield (%) <sup>a</sup>
1		77	12		61
2		82	13		60
3		77	14		58
4		90	15		67
5		74	16		68



entry	product	yield (%) <sup>a</sup>	entry	product	yield (%) <sup>a</sup>
6		66	17		47 <sup>b,c</sup>
7		83	18		53
8		72	19		76
9		41	20		87
10		35	21		39 <sup>d</sup>
11		62	22		0

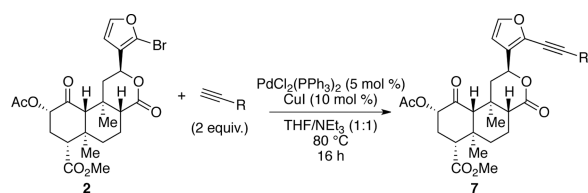
<sup>a</sup> Isolated yield.

*b* Reaction conditions: **2** (1 equiv), 2-thiophenboronic acid MIDA ester (1.2 equiv), Pd(OAc)<sub>2</sub> (5 mol %), SPhos (10 mol %), K<sub>3</sub>PO<sub>4</sub> (7.5 equiv), 5:1 dioxane/H<sub>2</sub>O, 60 °C, 24 h.

*c* 69% BRSM.

*d* 13% of **1** recovered.

Table 3

Sonogashira Couplings of **2**

entry	alkyne	product	yield (%) <sup>a</sup>
1			56
2			83
3			78
4			59
5			59
6			55 (16) <sup>b</sup>

<sup>a</sup> Isolated yield<sup>b</sup> Isolated yield after treatment with TBAF

**Table 4**

## Selected KOR Activity Data

entry	compound	EC <sub>50</sub> ± SE <sup>a</sup> (nM)	E <sub>max</sub> <sup>b</sup> (% (-)-U69,593)
1	<b>1</b>	29 ± 6	95 ± 5
2	<b>3a</b>	72 ± 11	101 ± 4
3	<b>4a</b>	3451 <sup>c</sup>	91
4	<b>3g</b>	971 ± 45	111 ± 3
5	<b>3p</b>	145 ± 40	72 ± 2
6	<b>3s</b>	29.8 ± 3.4	115 ± 7

<sup>a</sup>EC<sub>50</sub> = Effective concentration for 50% maximal response. Data are from at least 3 independent experiments.

<sup>b</sup>E<sub>max</sub> = % which compound stimulates compared to (-)-U69,593.

<sup>c</sup>n = 1.