

## Asymmetric Synthesis of Salvinorin A, A Potent $\kappa$ Opioid Receptor Agonist

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The neoclerodane diterpene salvinorin A (**1**) was isolated in 1982 from the rare mint *Salvia divinorum*, indigenous to Oaxaca, Mexico.<sup>1</sup> Recent efforts established salvinorin A as a potent and selective  $\kappa$  opioid receptor agonist, the only non-alkaloid psychoactive substance, and the most potent naturally occurring hallucinogen.<sup>2</sup> As a result of its therapeutic potential, renewed isolation efforts have discovered a number of related salvinorin congeners,<sup>3</sup> and a number of analogues of **1** have been prepared by semi-synthesis to probe the pharmacophore and mode of binding.<sup>4</sup> This communication describes the first synthesis of this natural product.

Construction of the tricyclic salvinorin core is predicated on the proposed transannular<sup>5</sup> Michael reaction cascade<sup>6</sup> of bisenone macrocycle **3** (Scheme 1). Conformational analysis<sup>7</sup> of **3** leads to a prediction wherein the resident stereocenters at C<sub>2</sub>, C<sub>4</sub>, and C<sub>12</sub> should mutually reinforce the desired stereochemical course of the reaction. This plan permits the convergent assembly of vinyl iodide **4** and aldehyde **5**, which can be prepared through established methods.

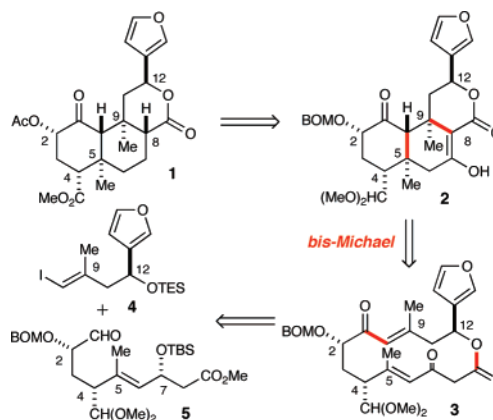
The synthesis of aldehyde **5** began with the Ni(II)–(*R*)-BINAP-catalyzed orthoester alkylation<sup>8</sup> of thiazolidinethione **6**, followed by a subsequent Claisen condensation with ethyl hydrogen malonate<sup>9</sup> to give  $\beta$ -ketoester **7** (Scheme 2). Selective formation of the (*Z*)-enol phosphate permitted an Fe-catalyzed cross-coupling with methylmagnesium chloride<sup>10</sup> to furnish trisubstituted olefin **8**. Reduction to the unsaturated aldehyde then allowed a selective aldol addition of acetate-derived chiral auxiliary **9**.<sup>11,12</sup> The derived allylic alcohol was protected as the *tert*-butyldimethylsilyl (TBS) ether **10**. After revealing the terminal aldehyde, an (–)-*N*-methyl-ephedrine-mediated zinc acetylide addition<sup>13</sup> provided propargylic alcohol **11** in good diastereoselectivity. Alcohol protection as the BOM ether was uniquely effected using NaHMDS and BOMCl at low temperature under Barbier conditions.<sup>14</sup> Semi-hydrogenation, dihydroxylation,<sup>15</sup> and oxidative cleavage furnished fragment **5**.

The synthesis of vinyl iodide **4** employed an asymmetric reduction of ketone **12** using (*R*)-*B*-Me-oxazaborolidene as catalyst<sup>16</sup> to afford alcohol **13** (Scheme 3). Alkyne isomerization<sup>17</sup> of **13** to **14** preceded carboalumination<sup>18</sup> and TES-silyl ether protection.

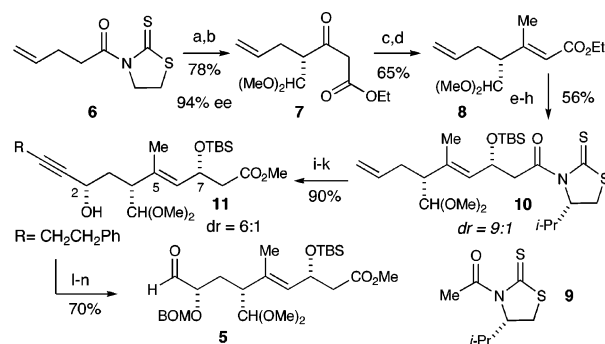
In the coupling event, chelate-controlled addition of the Grignard reagent derived from **4** to aldehyde **5** afforded allylic alcohol **15** (Scheme 4). A series of protecting group manipulations provided seco-acid **16**; subsequent macrolactonization using the Shiina procedure,<sup>19</sup> desilylation, and oxidation afforded macrocycle **3**. Treatment of  $\beta$ -ketolactone **3** with TBAF at –78 °C and warming to 5 °C induced the selective transannular reaction cascade to afford tricycle **2** as a single diastereomer. The reaction delivers two quaternary methyl stereocenters at C<sub>5</sub> and C<sub>9</sub> in a 1,3-diaxial alignment from the corresponding  $\beta,\beta$ -disubstituted enones, moieties known to possess poor reactivity toward conjugate addition.

To complete the synthesis, we employed a deoxygenation sequence involving enol triflate formation,<sup>20</sup> palladium-catalyzed triflate reduction,<sup>21</sup> and subsequent conjugate reduction<sup>22</sup> to yield **17**, epimeric at C<sub>8</sub>. Protonation from the  $\alpha$ -face by *t*-BuOH in situ

### Scheme 1. Synthesis Plan for Salvinorin A (**1**)

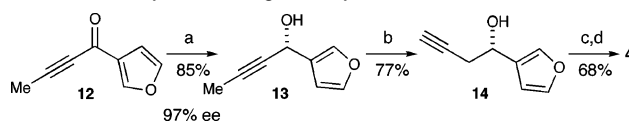


### Scheme 2. Aldehyde Fragment Synthesis<sup>a</sup>



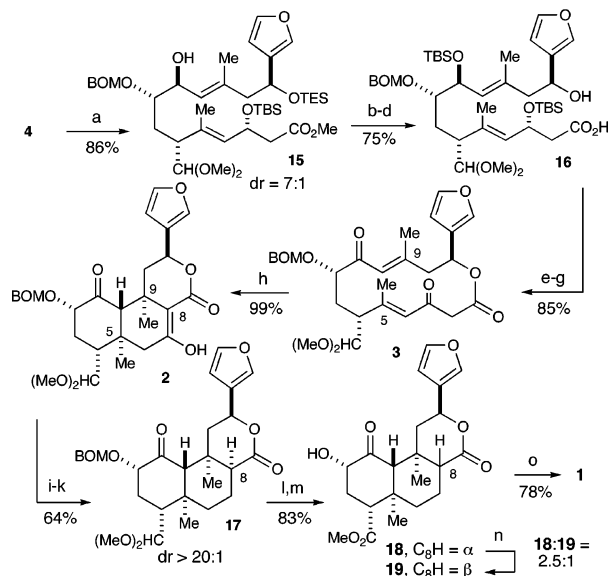
<sup>a</sup> Conditions: (a) Ni–(*R*)-BINAP(OTf)<sub>2</sub>, 2,6-lutidine, BF<sub>3</sub>•OEt<sub>2</sub>, HC(OMe)<sub>3</sub>; (b) HO<sub>2</sub>CCH<sub>2</sub>CO<sub>2</sub>Et, *i*-PrMgCl, 65 °C; (c) LiHMDS; ClPO(OEt)<sub>2</sub>; (d) Fe(acac)<sub>3</sub>, MeMgCl, –20 °C; (e) DIBAL-H, –78 °C; (f) MnO<sub>2</sub>; (g) Sn(OTf)<sub>2</sub>, *N*-ethylpiperidine, **9**, –78 °C; (h) TBSOTf, 2,6-lutidine; (i) K<sub>2</sub>CO<sub>3</sub>, MeOH; (j) OsO<sub>4</sub>, NMO; NaIO<sub>4</sub>; (k) Zn(OTf)<sub>2</sub>, (–)-*N*-Me-ephedrine, Et<sub>3</sub>N, 4-phenyl-1-butene; (l) BOMCl, NaHMDS, –78 °C; (m) Lindlar catalyst, H<sub>2</sub>; (n) K<sub>2</sub>O<sub>8</sub>, NMO, citric acid, 50 °C; Pb(OAc)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>.

### Scheme 3. Vinyl iodide Fragment Synthesis<sup>a</sup>

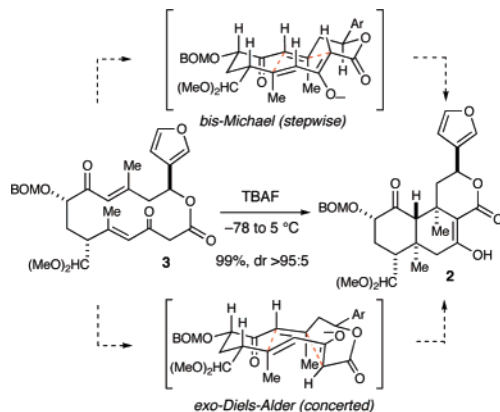


<sup>a</sup> Conditions: (a) (*R*)-*B*-Me-CBS catalyst, BH<sub>3</sub>•Me<sub>2</sub>S, –30 °C; (b) KH, H<sub>2</sub>N(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>, 0 °C; (c) Me<sub>3</sub>Al, Cp<sub>2</sub>ZrCl<sub>2</sub>; I<sub>2</sub>, –45 °C; (d) TESCl, imidazole.

appears to be under kinetic as well as thermodynamic control, as epimerization studies conducted on **1** (DBU, 110 °C in toluene) result in a mixture of C<sub>8</sub>-epimers biased toward 8-*epi*-salvinorin A **19**.<sup>23</sup> Deprotection of both the C<sub>2</sub> and C<sub>4</sub> acetals in **17** followed by oxidation and esterification gave 8-*epi*-salvinorin B (**18**). Epimerization using K<sub>2</sub>CO<sub>3</sub> in oxygen-free methanol followed by acylation produced salvinorin A (**1**), spectroscopically identical to previous

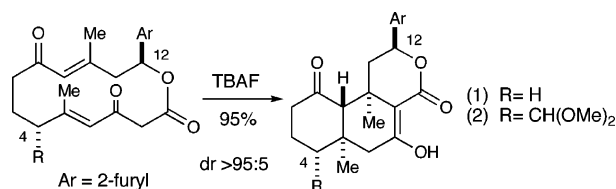
**Scheme 4.** Fragment Coupling and Salvignorin A Synthesis<sup>a</sup>

<sup>a</sup> Reaction conditions: (a) *n*-BuLi, MgBr<sub>2</sub>•(OEt)<sub>2</sub>, -78 °C, then 5, MgBr<sub>2</sub>•OEt<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 to 0 °C; (b) TBSOTf, 2,6-lutidine; (c) PPTS, MeOH; (d) LiOH, *i*-PrOH, H<sub>2</sub>O; (e) MNBA, DMAP, [0.0015 M]; (f) TBAF; (g) Dess–Martin periodinane; (h) TBAF, -78 to 5 °C; (i) NaH, Comins reagent; (j) Pd(OAc)<sub>2</sub>, dppe, Et<sub>3</sub>SiH; (k) L-selectride, *t*-BuOH, -78 to -55 °C; (l) LiBF<sub>4</sub>, MeCN/H<sub>2</sub>O; (m) NaClO<sub>2</sub>, TMSCHN<sub>2</sub>; (n) K<sub>2</sub>CO<sub>3</sub>, MeOH, quant. mass recovery; (o) Ac<sub>2</sub>O, py., DMAP.

**Scheme 5.** Transannular Cyclization Analysis

reports and having an identical optical rotation (synthetic **1** [ $\alpha$ ]<sub>D</sub><sup>25</sup> -40.7 (*c* = 0.12, CHCl<sub>3</sub>); natural **1**, [ $\alpha$ ]<sub>D</sub><sup>25</sup> -41 (*c* = 1, CHCl<sub>3</sub>)).<sup>1</sup>

As a prelude to the pivotal cyclization cascade (**3**→**2**) featured in the synthesis, model systems were designed to probe the influence of the resident stereocenters on the course of the cyclization (eqs 1 and 2). The first cyclization evaluated the role of the C<sub>12</sub>-furyl moiety and resulted in complete diastereocontrol (eq 1). Subsequent inclusion of the C<sub>4</sub>-dimethyl acetal seemingly reinforced the diastereoselection imparted by the C<sub>12</sub>-substituent (eq 2).



Scheme 5 provides a rationale for the observed selectivity in the **3**→**2** cyclization: conformational analysis of **3** suggests that the three stereocenters, in pseudo-equatorial positions, mutually

reinforce the desired diastereoselectivity, a fact borne out by the experiments. This analysis also suggests that enolization favors the *Z*-enolate. While this analysis presumes a stepwise process, a concerted mechanism involving *exo*-selective Diels–Alder cycloaddition<sup>24</sup> via the derived dipole-minimized enolate of **3** cannot be excluded.

In conclusion, we completed the first synthesis of salvignorin A and demonstrated the utility of a transannular reaction cascade in the construction of polycyclic architectures. Current efforts are directed toward finding epimerization conditions that favor the natural C<sub>8</sub> stereochemistry, probing the mechanism of the cascade reaction, and synthesizing analogues of **1** that bear modified C<sub>12</sub> functionality.

**Acknowledgment.** Support was provided by the National Institutes of Health (GM-33327-19) and by unrestricted support from Amgen, Merck, and Eli Lilly. The authors wish to thank Dr. Regan Thomson for helpful suggestions.

**Supporting Information Available:** Experimental procedures, spectroscopic data, and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA073590A