

Asymmetric Synthesis of Salvinorin A, A Potent κ 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.¹ Recent efforts established salvinorin A as a potent and selective κ opioid receptor agonist, the only non-alkaloid psychoactive substance, and the most potent naturally occurring hallucinogen.² As a result of its therapeutic potential, renewed isolation efforts have discovered a number of related salvinorin congeners,³ and a number of analogues of **1** have been prepared by semi-synthesis to probe the pharmacophore and mode of binding.⁴ This communication describes the first synthesis of this natural product.

Construction of the tricyclic salvinorin core is predicated on the proposed transannular⁵ Michael reaction cascade⁶ of bisenone macrocycle **3** (Scheme 1). Conformational analysis⁷ of **3** leads to a prediction wherein the resident stereocenters at C₂, C₄, and C₁₂ 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.

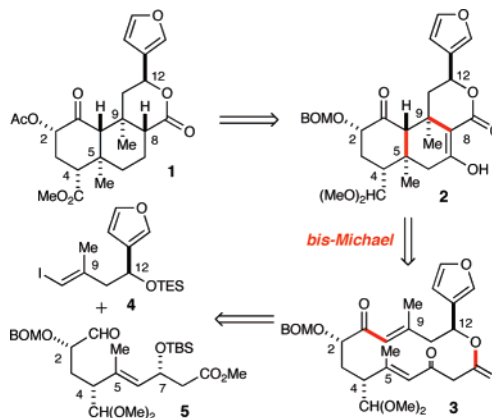
The synthesis of aldehyde **5** began with the Ni(II)–(*R*)-BINAP-catalyzed orthoester alkylation⁸ of thiazolidinethione **6**, followed by a subsequent Claisen condensation with ethyl hydrogen malonate⁹ to give β -ketoester **7** (Scheme 2). Selective formation of the (*Z*)-enol phosphate permitted an Fe-catalyzed cross-coupling with methylmagnesium chloride¹⁰ to furnish trisubstituted olefin **8**. Reduction to the unsaturated aldehyde then allowed a selective aldol addition of acetate-derived chiral auxiliary **9**.^{11,12} 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 addition¹³ 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.¹⁴ Semi-hydrogenation, dihydroxylation,¹⁵ 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 catalyst¹⁶ to afford alcohol **13** (Scheme 3). Alkyne isomerization¹⁷ of **13** to **14** preceded carboalumination¹⁸ and TES-silyl ether protection.

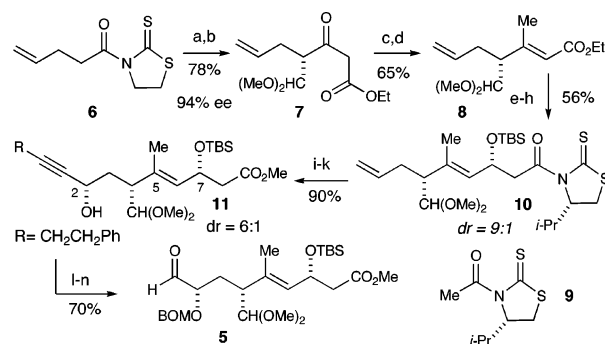
In the coupling event, chelate-controlled addition of the Grignard reagent derived from **4** to aldehyde **5** afforded allylic alcohol **15** (Scheme 4). A series of protecting group manipulations provided seco-acid **16**; subsequent macrolactonization using the Shiina procedure,¹⁹ desilylation, and oxidation afforded macrocycle **3**. Treatment of β -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 C₅ and C₉ in a 1,3-diaxial alignment from the corresponding β,β -disubstituted enones, moieties known to possess poor reactivity toward conjugate addition.

To complete the synthesis, we employed a deoxygenation sequence involving enol triflate formation,²⁰ palladium-catalyzed triflate reduction,²¹ and subsequent conjugate reduction²² to yield **17**, epimeric at C₈. Protonation from the α -face by *t*-BuOH in situ

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

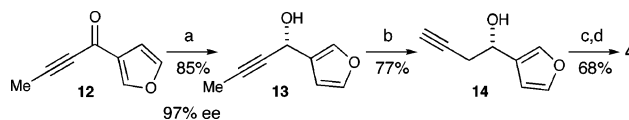


Scheme 2. Aldehyde Fragment Synthesis^a



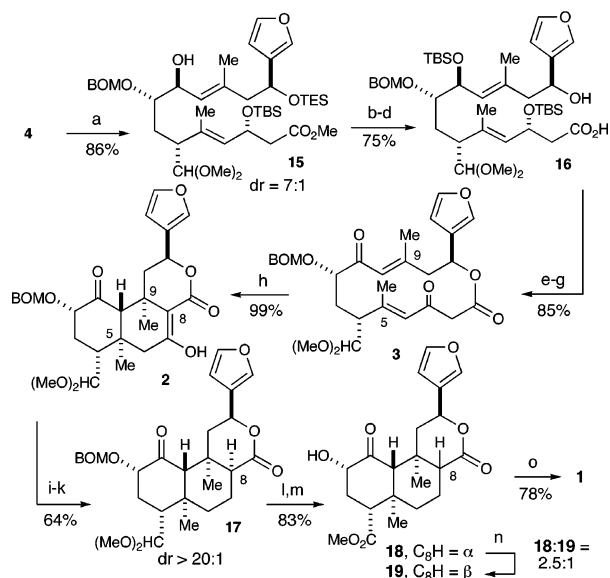
^a Conditions: (a) Ni–(*R*)-BINAP(OTf)₂, 2,6-lutidine, BF₃•OEt₂, HC(OMe)₃; (b) HO₂CCH₂CO₂Et, *i*-PrMgCl, 65 °C; (c) LiHMDS; ClPO(OEt)₂; (d) Fe(acac)₃, MeMgCl, –20 °C; (e) DIBAL-H, –78 °C; (f) MnO₂; (g) Sn(OTf)₂, *N*-ethylpiperidine, **9**, –78 °C; (h) TBSOTf, 2,6-lutidine; (i) K₂CO₃, MeOH; (j) OsO₄, NMO; NaIO₄; (k) Zn(OTf)₂, (–)-*N*-Me-ephedrine, Et₃N, 4-phenyl-1-butene; (l) BOMCl, NaHMDS, –78 °C; (m) Lindlar catalyst, H₂; (n) K₂OsO₄, NMO, citric acid, 50 °C; Pb(OAc)₄, K₂CO₃.

Scheme 3. Vinyl iodide Fragment Synthesis^a

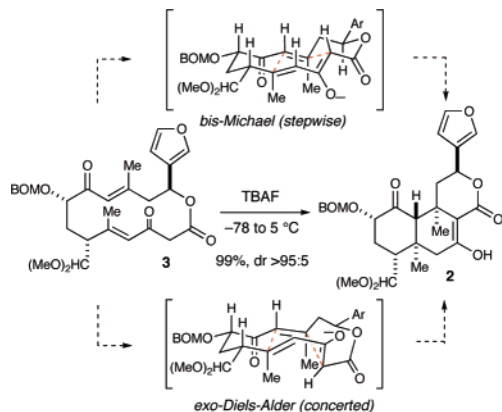


^a Conditions: (a) (*R*)-*B*-Me-CBS catalyst, BH₃•Me₂S, –30 °C; (b) KH, H₂N(CH₂)₃NH₂, 0 °C; (c) Me₃Al, Cp₂ZrCl₂; I₂, –45 °C; (d) TESCl, imidazole.

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 C₈-epimers biased toward 8-*epi*-salvinorin A **19**.²³ Deprotection of both the C₂ and C₄ acetals in **17** followed by oxidation and esterification gave 8-*epi*-salvinorin B (**18**). Epimerization using K₂CO₃ in oxygen-free methanol followed by acylation produced salvinorin A (**1**), spectroscopically identical to previous

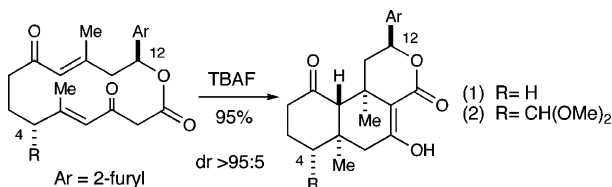
Scheme 4. Fragment Coupling and Salvinorin A Synthesis^a

^a Reaction conditions: (a) *n*-BuLi, MgBr₂•(OEt)₂, -78 °C, then 5, MgBr₂•OEt₂, CH₂Cl₂, -78 to 0 °C; (b) TBSOTf, 2,6-lutidine; (c) PPTS, MeOH; (d) LiOH, *i*-PrOH, H₂O; (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)₂, dppe, Et₃SiH; (k) L-selectride, *t*-BuOH, -78 to -55 °C; (l) LiBF₄, MeCN/H₂O; (m) NaClO₂, TMSCHN₂; (n) K₂CO₃, MeOH, quant. mass recovery; (o) Ac₂O, py., DMAP.

Scheme 5. Transannular Cyclization Analysis

reports and having an identical optical rotation (synthetic **1** [α]_D²⁵, -40.7 (*c* = 0.12, CHCl₃); natural **1**, [α]_D²⁵, -41 (*c* = 1, CHCl₃)).¹

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 C₁₂-furyl moiety and resulted in complete diastereocontrol (eq 1). Subsequent inclusion of the C₄-dimethyl acetal seemingly reinforced the diastereoselection imparted by the C₁₂-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 cycloaddition²⁴ via the derived dipole-minimized enolate of **3** cannot be excluded.

In conclusion, we completed the first synthesis of salvinorin 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 C₈ stereochemistry, probing the mechanism of the cascade reaction, and synthesizing analogues of **1** that bear modified C₁₂ functionality.

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

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