CHEMISTRY
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Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201604853

Link to VoR: http://dx.doi.org/10.1002/chem.201604853

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Total Synthesis of (-)-Salvinorin A

Nathan J. Line,[b] Aaron C. Burns,[d] Sean C. Butler,[c] Jerry Casbohm,[b] and Craig J. Forsyth*[a]

Abstract: Salvinorin A (**1**) is natural hallucinogen that binds the human κ-opioid receptor. A total synthesis has been developed that parlays the stereochemistry of L-(+)-tartaric acid into that of (–)-**1** via an unprecedented allylic dithiane intramolecular Diels-Alder reaction to obtain the *trans*-decalin scaffold. Tsuji allylation set the C9 quaternary center and a late-stage stereoselective chiral ligand-assisted addition of a 3-titanium furan upon a C12 aldehyde / C17 methyl ester established the furanyl lactone moiety. The tartrate diol was finally converted into the C1,C2 keto-acetate.

Salvinorin A (**1**, Figure 1) is a psychoactive natural product isolated from the Mexican sage plant *Salvia divinorum*.[1] This neoclerodane diterpenoid natural product is a potent hallucinogen in humans and a promising lead compound for the development of small molecule modulators of cognition and associated behavioral abnormalities.[2] Because biosynthesis and semi-synthesis provides a limited array of informative structural analogs of **1**, the development of a readily diversifiable laboratory synthetic route to salvinorins and unique analogs is designed to enable the full development of this unique chemotype.

A target of **1** is the κ-opioid G-protein coupled receptor (GPCR) of human brain cells.[2d] A binding model of a derivative of **1** has been proposed based upon X-ray crystallographic data of the human κ-opioid receptor.[3] Key structural features that have been implicated in salvinorin A's specific κ-opioid receptor binding include the spatial display of the C2 acetate, C4 methyl ester, and C12 furan about the rigid all *trans*-fused decalin δ−lactone tricyclic core (Figure 1). However, the specific salvinorin A-bound receptor conformation and the mechanism by which highly selective binding to the κ-opioid GPCR stimulates signal transduction remain to be determined. In addition, **1** is a dopamine D2 receptor partial agonist, suggesting that this receptor may also be relevant in responses to salvinorin A.[4]

Three total syntheses of **1** have been reported[5] and an array of peripheral structural variants have been generated from **1** via semi-synthesis.[2e,6] The provision of further rationally designed analogs of **1** having deep-seated structural changes may enable further understanding of agonist specificity elements and the mechanism of small molecule activation of GPCRs. A versatile total synthesis of **1** is presented that implements a unique intramolecular Diels-Alder (IMDA) reaction of an allylic dithiane and a dienyl allyl carbonate to establish the *trans*-decalin core of 1.[7] Subsequent stereospecific Tsuji allylation[7a] and diastereoselective furan addition[8] enabled facile access to **1** applicable to novel analogs.

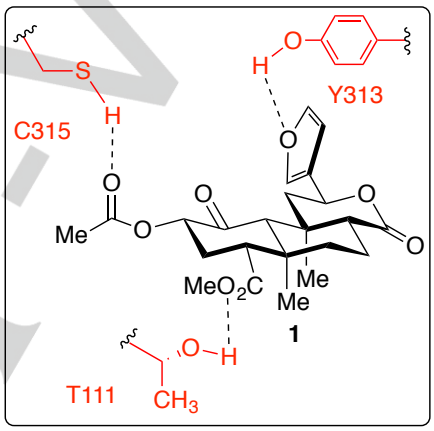

Figure 1. Proposed key binding contacts of human kappa opioid receptor amino acid residues with salvinorin A.[3]

Retrosynthetically, three key processes were planned (Scheme 1): a 3-metallo-furan addition to aldehyde **3** leading to formation of lactone **2**, a Tsuji allylation from enol allyl carbonate **5** to establish the C9 quaternary center in diketone **4**, and an IMDA reaction to convert allylic dithiane **7** into *trans*-decalin **6**. Diketone **4** had been prepared previously, but neither via **6**, nor as efficiently as reported here.[7a] Diels-Alder reaction precursor **7** could be obtained from L-tartrate derived **9**[9] via ketone **8**.

A major challenge was the incorporation of the quaternary centers at C5 and C9. The C5 configuration arose via an exo-selective IMDA reaction of **7** to yield *trans*-decalin **6**. A primary attribute of the IMDA strategy is that the Diels-Alder adduct **5** provides a cyclohexenyl allyl carbonate **6** that is poised to undergo regio- and stereoselective Tsuji allylation to establish the C9 quaternary center.[7a] Studies on IMDA reactions of dienyl carbonates with various allylic substituted dienophiles were performed.[7] But the use of an allylic dithiane for decalin system formation via an IMDA process seems to be unprecedented, although an allylic dithiane has been used in an IMDA reaction with an aryl-substituted diene.[10]

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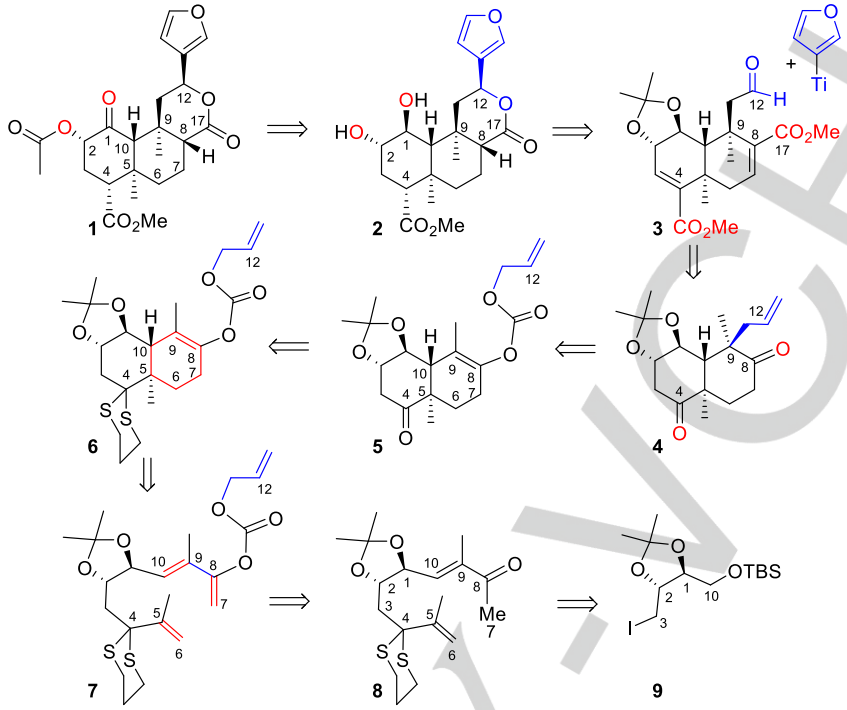
Scheme 1. Retrosynthesis of salvinorin A.



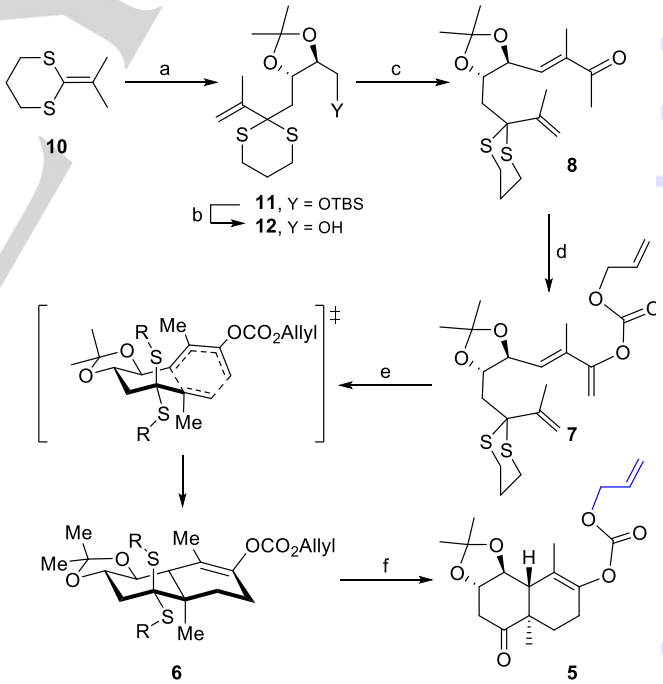
The synthesis of **1** embarked from iodide **9**[9] via conversion into allylic dithiane **11** (Scheme 2). Deprotonation of **10**[11] followed by alkylation with **9** gave **11**. The silyl ether was cleaved, alcohol **12** was oxidized, and a Horner-Wadsworth-Emmons reaction generated (*E*)-enone **8** containing all of the core carbons of salvinorin's decalin system in an acyclic form.

Subjecting **8** to KHMDS and allyl chloroformate in 1,2-dimethoxyethane gave enol allyl carbonate **7** in 80% yield.[12] Heating **7** in 1,2-dichlorobenzene provided *trans*-decalin **6** in 90% yield. The dithiane moiety may incur minimal allylic strain with a cyclic alkyl thio group axial and all substituents but the vinyl methyl group adopting pseudoequatorial positions in a chair-boat transition state. The dithiane moiety of **6** was oxidatively converted into ketone **5**.[13]

The enol allyl carbonate **5** provided a substrate-controlled stereoselective installation of the C9 quaternary center via a palladium mediated decarboxylative allyl transfer (Scheme 3).[7a] Treatment of **5** with $Pd(PPh_3)_4$ in toluene gave ketone **4** in 94% yield via the Tsuji allylation process. The stereoselective formation of the C9 quaternary center in **4** results from enolate α–allylation from the least hindered face. Although **4** had been prepared previously,[7] the route detailed here generates the diketone in a superior 32% overall yield from tartrate derivative **9**.

The attainment of *trans*-decalin **4** left two significant synthetic challenges en route to **1**: installation of ester moieties at C4 and C8, and stereoselective incorporation of the C12 furanyl moiety. Hagiwara and co-workers provided some guidance for the former task,[5c] as did Sibi and He for the latter one.[14] Diketone **4** was transformed into bis-vinyl triflate **13** using KHMDS and Comins' reagent,[15] then **13** was carboxylated[16] to diester **14** (Scheme 3). Selective oxidative cleavage[17] of the exo-cyclic alkene provided aldehyde **3**. Diester-aldehyde **3**

Scheme 2. Preparation of ketone-carbonate **5**.



(i) *n*BuLi,, THF-HMPA, –78 °C, (ii) **9**, 87%; b) NH_4F, CH_3OH, reflux, 3 h, 93%; c) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, (ii) 2-oxo-3-(diethylphosphono)-butane, NaH, THF 85 % (2 steps); d) KHMDS, allyl chloroformate, 1,2-dimethoxyethane, –78 °C, 80%; e) 1,2-dichlorobenzene, reflux, 16 h, 90%; f) PIFA, MeCN, sat. aq. $NaHCO_3$, 67%. PIFA = phenyliodonium perfluoro-diacetate.

then served as the substrate to study stereoselective nucleophilic installation of the furan moiety.

Numerous experiments were performed involving 3-metallo-furan additions to aldehydes such as **3**. These led to a singularly successful asymmetric titanium-furan addition to **3**, as inspired by Gau et al.[8] that gave unsaturated lactone **15** in 74% yield and a 8:1 dr. The selective addition of the 3-titanium furan moiety to aldehyde **3** both set the C12 configuration and the intermediate titanium alkoxide engaged the methyl ester to close the lactone moiety of **1** to give **15**.[14]

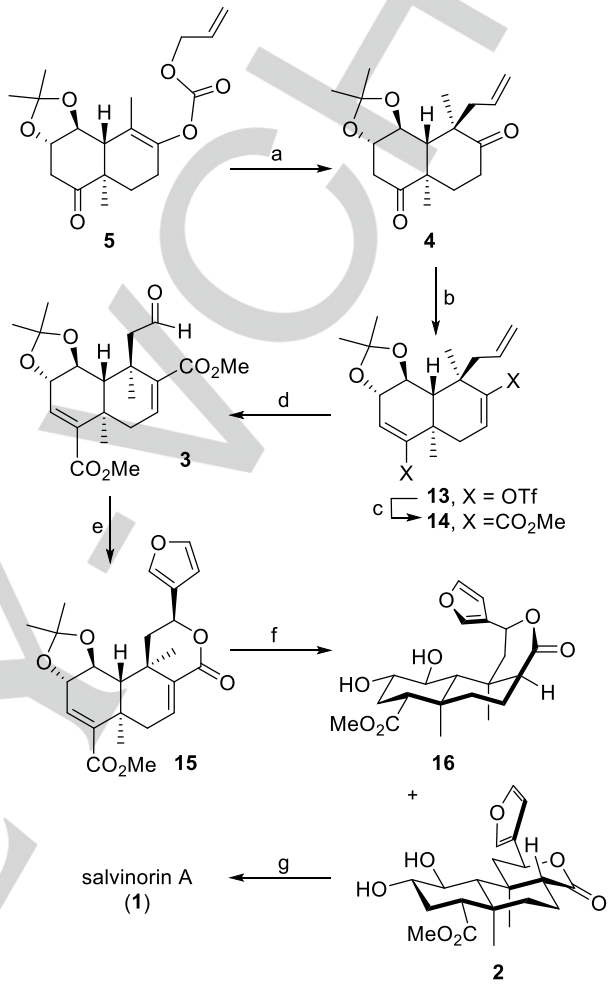
Bis-conjugate reduction of both the α,β-unsaturated methyl ester and lactone of **15** with samarium diiodide in methanol / THF[18,5c] resulted in a 2.5 : 1, (8*S*) : (8*R*) respectively, mixture of C8 α-epimers (Scheme 3).[5,6a] Methanolysis of the acetonide moiety liberated the vicinal diols (8*S*)-**16** and (8*R*)-**2** in 51% combined yield. These diols (8*S*)-**16** and (8*R*)-**2** correspond to the C1 alcohols of 8-*epi*-salvinorin B and salvinorin B, respectively. The structure of 8-*epi*-salvinorin B was established via X-ray crystallography that showed the lactone ring in a boat conformation.[19] The unnatural epimer (8*S*)-**16** can be equilibrated to provide the thermodynamic 2.5 : 1 ratio of (8*S*)-**16** and (8*R*)-**2**, whereas Evans had demonstrated that the ca. 2.5 : 1 ratio of (8*S*) and (8*R*) epimers, respectively, is also kinetically favored in the salvinorin A scaffold.[5a] The preponderance of the unnatural C8 epimer has uniformly been observed in previous total syntheses of **15** and semi-synthesis of salvinorin B.[5,6a]

Completion of **1** from **2** was accomplished by a two-step acylation and oxidation sequence. Exposing **2** to acetic anhydride and 2,6-lutidine in CH_2Cl_2 for 36 h gave selective acylation of the least hindered alcohol at C2. The residual C1 alcohol was subjected to Ley-Griffith oxidation[20] to provide (–)-**1** in 72% yield over two steps.[9]

Highlights of this synthetic approach include an unprecedented allylic dithiane – dienyl carbonate IMDA reaction to establish the salvinorin *trans*-decalin core (**6**) in 90% yield, followed by a 30 min Tsuji allylation reaction to set the C9 quaternary center of **4** in 94 % yield. Hence, the acyclic polyene **7** was converted into the versatile decalin **4** in two steps and 85 % yield. Moreover, **4** was generated from known tartrate derivative **9** in 32% overall yield. The chemo- and stereoselective one step asymmetric addition of a 3-furanyl titanium to aldehyde diester **3** to give furanyl lactone **15** is also notable. An unsolved problem remains, however, in the thermodynamic and kinetic preference for the unnatural C8 configuration among the salvinorins. Strategies to address this latter issue are currently being pursued.

This synthetic route establishes a flexible framework for the generation of previously difficult to obtain structural analogs of the salvinorins. For example, the late-stage asymmetric introduction of the furanyl moiety demonstrated here may be extended to the incorporation of a variety of additional heterocycles to probe and modulate the importance of the proposed hydrogen bonding acceptance of the natural product's furanyl oxygen. The quaternary methyl-bearing centers at C5 and C9 and the readily epimerizable lactone[6a] may also be varied via simple modifications of this synthetic route. The generation and deployment of new rationally designed analogs that are not readily available via semi-synthesis or prior total synthesis approaches is projected to help elucidate numerous aspects of small molecule modulation of GPCRs relevant to human cognition and behavior.

Scheme 3. Stereocontrolled synthesis of salvinorin A.



a) $Pd(PPh_3)_4$, toluene, 23 °C, 30 min, 94%; b) KHMDS, THF, Comins' reagent –78 °C, 72%; c) $Pd(PPh_3)_4$, CO, dppf, Et_3N, CH_3OH / DMF, 60 °C, 73%; d) (i) OsO_4, NMO·H_2O, 2,6-lutidine, acetone/H_2O (10:1, v/v), (ii) bis-acetoxy-iodosobenzene, 75%; e) (3-furyl)Ti(O*i*-Pr)$_3$, (*R*)-BINOL-Ti(O*i*-Pr)$_2$ (10 mol %), THF, 0 °C, 74%, dr = 8:1; f) (i) SmI_2, Et_3N, CH_3OH, THF; (ii) *p*-toluene sulfonic acid, CH_3OH, 51%, **16**:**2** dr = 2.5:1; g) (i) Ac_2O, 2,6-lutidine, CH_2Cl_2 (ii) TPAP, NMO, CH_2Cl_2, 72%.

Experimental Section

Experimental details are provided in the Supporting Information.

Acknowledgements

This research was supported by Bristol-Myers-Squibb, The Ohio State University, and the Forsyth Research Fund.

Keywords: natural prod. • synthesis • Diels-Alder react. • xenobiotics • neurochemistry

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10.1002/chem.201604853

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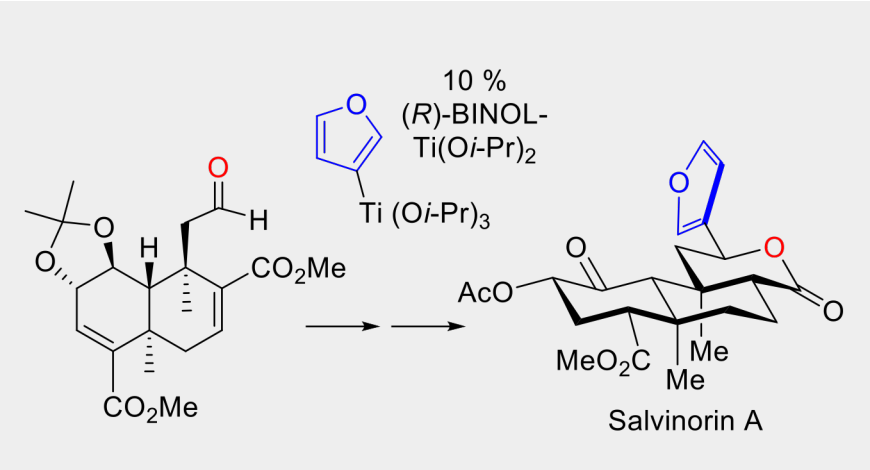

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Total Synthesis of (-)-Salvinorin A

Magic Mint Medley: The total synthesis of the hallucinogenic human kappa-opioid receptor agonist salvinorin A was achieved using a late-stage asymmetric furanyl-lactonization.