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Intramolecular Diels–Alder/Tsuji Allylation Assembly of the Functionalized *trans*-Decalin of Salvinorin A

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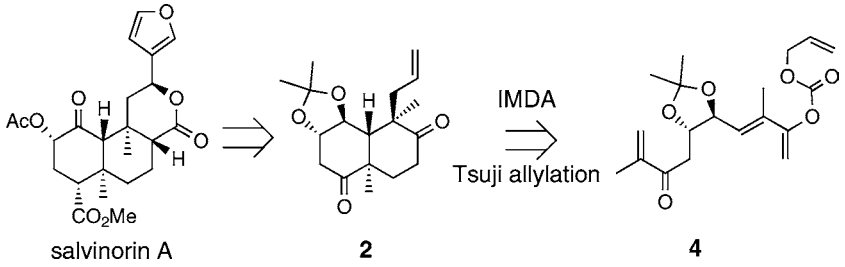
ABSTRACT



An enantioselective synthesis of the highly functionalized *trans*-decalin core (2) of salvinorin A is described. The tetraene 4 was synthesized in six steps from a known L-(+)-tartaric acid derivative. Three contiguous stereocenters, two of them quaternary, on the *trans*-decalin were established asymmetrically by an intramolecular Diels–Alder/Tsuji allylation sequence.

Salvinorin A (**1**) is a potent and selective κ-opiod receptor (KOR) agonist isolated from the hallucinogenic sage *Salvia divinorum*.[1,2] This *neo*-clerodane[3] natural product exhibits unique biological significance, in that it is the only known non-nitrogenous human hallucinogen. No appreciable binding of salvinorin A was observed with 5-HT_{2A} serotonin receptors, which are the main molecular targets responsible for the hallucinogenic properties of classical alkaloid hallucinogens.[2] Evans recently reported a total synthesis of salvinorin A,[4] while several other groups have prepared and evaluated semi-synthetic derivatives in efforts to elucidate its essential pharmacophoric features.[5] The empirical results obtained are largely consistent with Roth's proposed binding mode of salvinorin A at the KOR.[6] However, substantial structural changes that cannot be achieved via semi-synthesis may be required to fully define the minimal pharmacophore of salvinorin A and characterize the basis of its exquisite and modifiable[5] receptor binding specificities. Toward this end, we have embarked upon a versatile total synthesis of salvinorin A that can accommodate deep seated structural variations as well as peripheral modifications.

From a retrosynthetic perspective, salvinorin A can be derived from the highly functionalized *trans*-decalin **2** (Scheme 1). This would involve conversion of the C4,C8-diketone into a bis-single carbon homologated dicarboxylate, the addition of a metalated furan to a C12 aldehyde obtained

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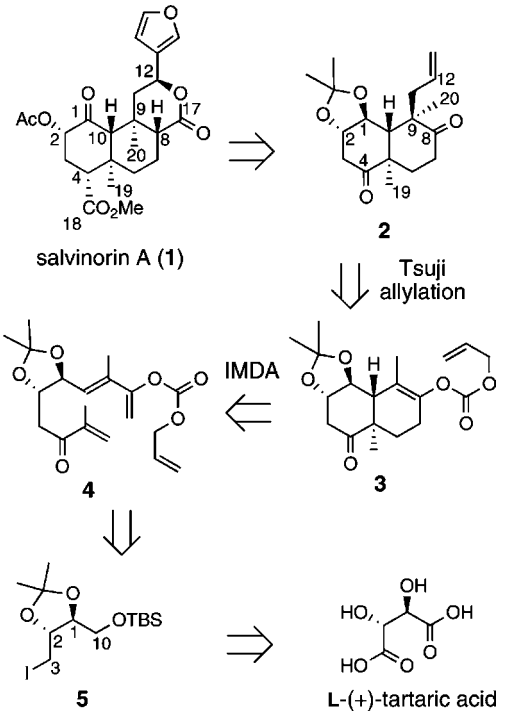
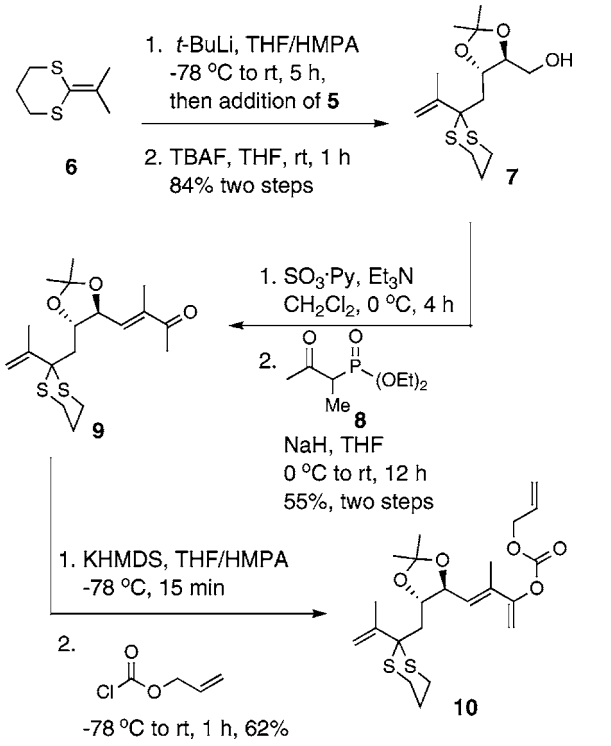
Scheme 1. Retrosynthetic Analysis of Salvinorin A



Scheme 2. Synthesis of Enol Carbonate **10**



from the terminal olefin of **2**, lactonization, and differential functionalization of the installed latent C1,C2-diol. Unmasking of the C1,C2-diol followed by a regioselective acylation[7] and oxidation of the C1 alcohol would complete the synthesis of salvinorin A. Moreover, application of alternative alkene, diol, and diketone functionalizations may offer a wide variety of structural variants emanating from the decalin core of **2**. Versatile intermediate **2** was anticipated to arise from allyl vinyl carbonate **3** by a Tsuji allylation[8] to form an α-keto quaternary stereocenter at C9 (Scheme 1). The *trans*-decalin[9] **3**, bearing a quarternary center stereocenter at the C5 ring fusion could be obtained via a diastereoselective intramolecular Diels−Alder (IMDA) reaction from the enone **4**. The tartaric acid derivative **5**[10] was identified as a useful precursor to **4**. This would involve carbon−carbon bond formation by a regioselective allylic dithiane anion alkylation,[11] Horner−Wadsworth−Emmons (HWE) olefination, and O-acylation of the resultant ketone enolate.

The synthesis of the IMDA substrate enol carbonate **4** shown in Scheme 2 started with 2-(propan-2-ylidene)-1,3-dithiane **6** (synthesized in two steps from 1,3-dithiane)[12] and the known iodide **5**,[10] which was prepared in four steps from L-(+)-tartaric acid. Dithiane **6** was α-alkylated via its lithium anion with iodide **5**, and subsequent silyl ether cleavage with TBAF gave compound **7** with no evidence of *δ*-alkylation. The primary alcohol was oxidized under Parikh−Doering[13] conditions, where the Swern[14] oxidation failed, to give an α-alkoxy aldehyde. HWE olefination with *β*-ketophosphonate **8**[15] afforded the trisubstituted *E*-enone **9** exclusively. O-Acylation of the potassium enolate of **9** with allyl chloroformate gave enol carbonate **10** in useful yield. The use of HMPA here was necessary to reduce C-acylation to approximately 15%, whereas without HMPA, C-acylation occurred to the extent of 33%.

Construction of the *trans*-decalin core was achieved as shown in Scheme 3. Scission of the dithiane moiety of **10** to afford enone **4** was deemed a necessary prelude to accomplishing the desired IMDA reaction. As is often the case with highly functionalized substrates, much difficulty was encountered in attempts to efficiently cleave the dithiane. Among the many reagents and conditions screened, including MeI/$CaCO_3$,[16] Dess−Martin periodinane,[17] IBX,[18] PIFA,[19] $AgNO_3$,[20] $Tl(NO_3)_3$,[21] $Ag(ClO_4)$/NBS,[22] *m*CPBA/

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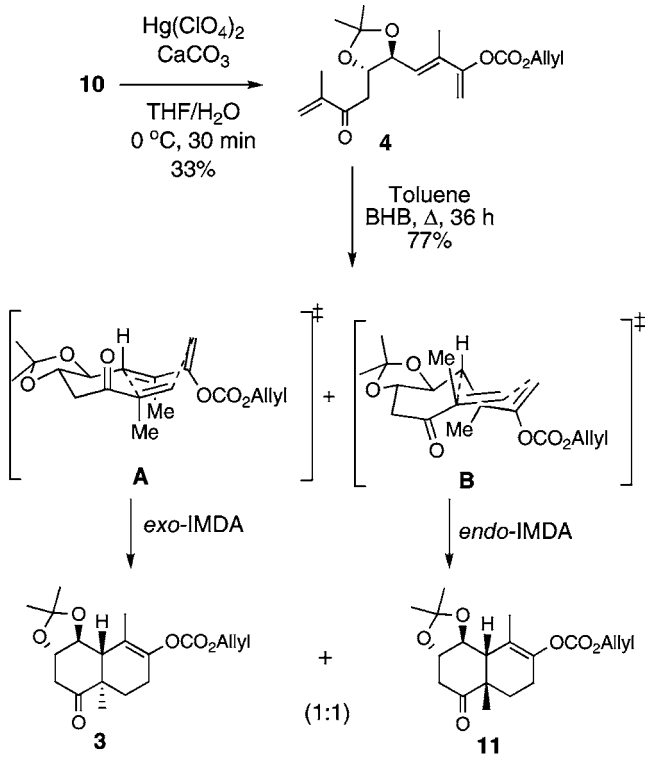
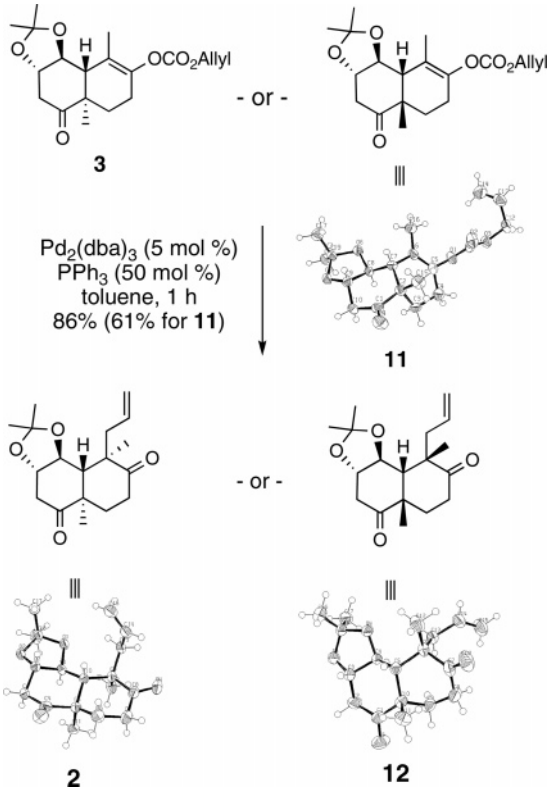
Scheme 3. Intramolecular Diels−Alder Reaction



(BHB=butylated hydroxybenzene)

Scheme 4. Tsuji Allylation of **3** and **11**



Ac_2O/Et_3N,[23] and $HgCl_2/CaCO_3$,[24] the best yield achieved was 33% using $Hg(ClO_4)_2/CaCO_3$[25] to give tetraene **4**. Thereafter, the much anticipated IMDA reaction proceeded to give a (1:1) mixture of the desired *trans*-decalin **3** and a *cis*-decalin **11** in 77% combined yield. The use of a radical inhibitor (BHB) was necessary to obtain useful yields in this transformation. The *cis*-decalin, presumably arising from a boat-like *endo* transition state **B** (Scheme 3), was conveniently separated from the desired noncrystalline product **3** by recrystallization from 95% ethanol. The stereochemistry of **11** was confirmed by single-crystal X-ray analysis (Scheme 4). The stereochemistry of the *trans*-decalin **3**, presumably arising from a chair-like transition state (Scheme 3), was later confirmed by single-crystal X-ray analysis of **2** (Scheme 4).

The next step forward was to install the stereogenic quarternary center at C9 via transposition of the allyl group that was strategically incorporated into the allyl vinyl carbonate of **3**. This was accomplished via a Pd-mediated intramolecular Tsuji allylation using both **3** and **11** (Scheme 4). The latter was employed as a useful model system for later transformations and to generalize our understanding of this type of IMDA−Tsuji allylation (IMDA−TA) sequence for the construction of *cis*- or *trans*-decalins bearing quaternary stereocenters (Scheme 4). Hence, carbonates **3** and **11** were separately subjected to the Tsuji allylation to provide diketones **2** and **12**, respectively. Single-crystal X-ray diffraction analyses of **2** and **12** revealed their complete stereochemistries. Both products reflect the facial selectivity expected to occur in avoiding 1,3-interactions with the bridgehead methyl groups in the respective allylation transition states. Moreover, each product reflects a net equatorial attack of a regioselectively generated (via the IMDA) enolate equivalent upon an allyl species.

The successful stereocontrolled assembly of the salvinorin decalin core **2** was designed to provide a bisketone as functionality for net biscarboxylate installation at C4 and C8. The C4 carboxylate would emerge as an equatorial methyl ester, whereas the C8 carboxylate would ultimately be annulated as a lactone. The most efficient approaches toward accomplishing these one-carbon homologations are currently under study. Thereafter, incorporation of the fufuryl alcohol moiety, lactonization, and differential functionalization of the latent C1,C2-diol will be required to complete a synthesis of **1**.

In summary, a novel approach toward the construction of highly substituted decalin scaffolds bearing asymmetric quaternary stereocenters has been developed in the context of targeting salvinorin A and novel analogues thereof. This involves the use of a diene incorporating an allyl carbonate in an IMDA reaction and exploitation of the resultant allyl vinyl carbonate resident upon a decalin scaffold for a subsequent stereo- and regioselective Tsuji allylation. The

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IMDA reaction establishes the decalin core in a manner that dictates the relative orientation of the Tsuji allylation. Future work includes continued efforts at progressing the key intermediate **2**, or variants thereof, toward salvinorin A and its analogues. Studies to determine the diastereoselectivity of the IMDA process as a function of substitution at C1 and C2 are also being pursued. Finally, the tandem IMDA−TA approach toward generating additional natural and non-natural targets based upon highly functionalized decalin templates will continue to be explored.

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Supporting Information Available: Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for **2**−**4**, **7**, and **9**−**12**, and X-ray crystallographic data for compounds **2**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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