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Total Synthesis of the Hallucinogenic Neoclerodane Diterpenoid Salvinorin A

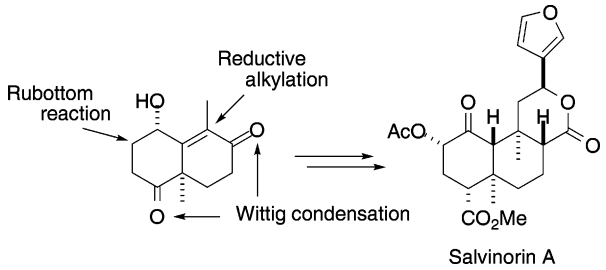
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ABSTRACT



Total synthesis of salvinorin A (1), a neoclerodane diterpenoid having the most potent hallucinogenic activity and a selective κ-opioid agonist, was completed in 20 steps starting from enantiomerically pure hydroxy-Wieland–Miescher ketone 5.

Salvinorin A (**1**), a neoclerodane diterpenoid, isolated from the Mexican hallucinogenic plant *Salvia divinorum*,[1] is a selective κ-opioid receptor (KOR) agonist.[2] Its hallucinogenic activity is the most potent among any other known non-nitrogenous and nitrogenous compounds such as tetrahydrocannabinol (THC) or lysergic acid diethylamide (LSD), respectively.[1b,3] Since a different mechanism from LSD or mescaline is anticipated for its activity, salvinorin A (**1**) and its congeners are expected to be lead compounds for drug development for the treatment of many disorders including pain, opesity, pruritis, and so on. Due to their fascinating physiological properties, investigation of salvinorins from natural sources have been carried out, and eight congeners, salvinorins B−I[1b,4] and salvinicins A and B,[5] have been isolated to date. The biosynthetic pathway has recently been unveiled to be the 1-deoxy-D-xylulose phosphate pathway,[6] instead of the common mevalonic acid pathway. In addition,

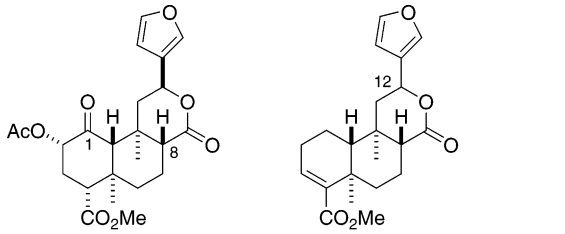


Figure 1. Neoclerodane furolactone natural products.

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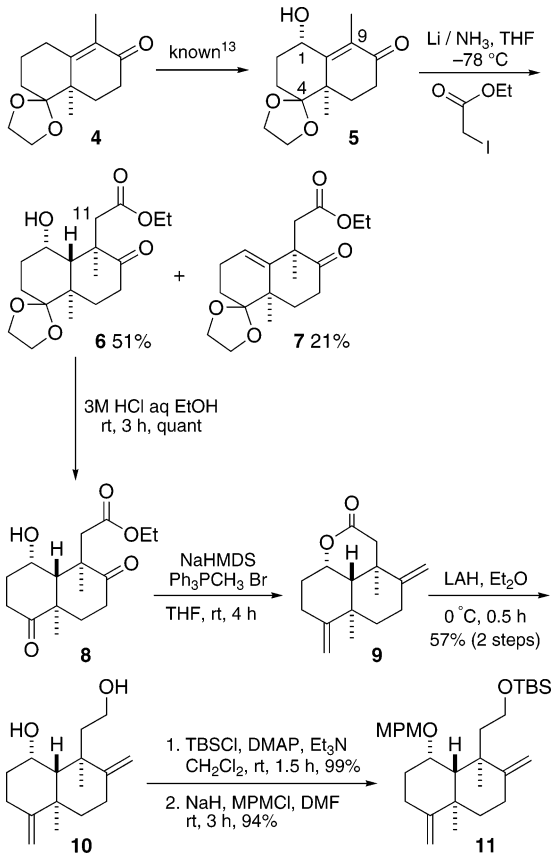
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chemical transformations of salvinorins have been achieved extensively to pursue and evaluate more active ingredients for bindng affinity to cloned KOR.[7] On the other hand, synthetic studies have been quite limited[8] probably due to difficulties associated with issues on construction of chemical architectures having seven asymmetric centers and five oxygenated functionalities, until the recent first total synthesis by Evans et al. in 29 steps based on the transannular sequential Michael strategy of 14-membered macrocyclic lactone.[9] Another issue is the facile epimerization at C8 (clerodane numbering) under either acidic or basic reaction conditions.[1b,7c,f,h,10] Evans et al. utilized this equilibrium at the final stage in their total synthesis,[9] in which salvinorin A (**1**) was furnished via partial isomerization of the corresponding 8-*epi*-precursor.

Intrigued by its very characteristic biological activity and highly oxygenated chemical architecture, along with our recent results on the first total synthesis of a neoclerodane diterpenoid, methyl barbascoate (**2**),[11] we investigated independently the total synthesis of salvinorin A (**1**), and delineate herein an alternative total synthesis of **1** starting from enantiomerically pure hydroxy enone **5**.

Hydroxy enone **5** was chosen as the starting material because of difficulty in introducing the hydroxy group at C1 of 12-*epi*-barbascoate **3**, which was readily obtained from enantiomerically pure (*R*)-(−)-Wieland-Miescher ketone **4**[12] according to a known procedure (Scheme 1).[13] We initially envisaged convergent connection of the C9−C11 bond by reductive alkylation of hydroxy enone **5** with 2-alkoxy-2-(3-furyl)ethyl iodide and its derivatives with lithium in liquid ammonia. However, all attempts failed probably due to steric congestion, which made us take the linear synthetic approach. Reductive alkylation with ethyl iodoacetate provided alkylation product **6** having three requisite contiguous asymmetric centers and four requisite functionalities for further transformations. Formation of dehydration product **7** could be suppressed by keeping the reaction temperature low, while protection of the hydroxyl group at C1 of enone **5** as a silyl ether increased the amount of **7**.

Scheme 1. Introduction of Carbon Units at C4, C8, and C9 of Hydroxy Enone **5**



To introduce two α-carboxy moieties at C4 and C8, acetal **6** was hydrolyzed to give diketone **8**. Two carbon units at C4 and C8 were introduced by double Wittig methylenation to provide *bis*-*exo*-methylene *δ*-lactone **9**. Steric congestion at C4 and C8 at neopentyl positions was so severe that the reaction with methoxymethylene triphenylphosphorane re-

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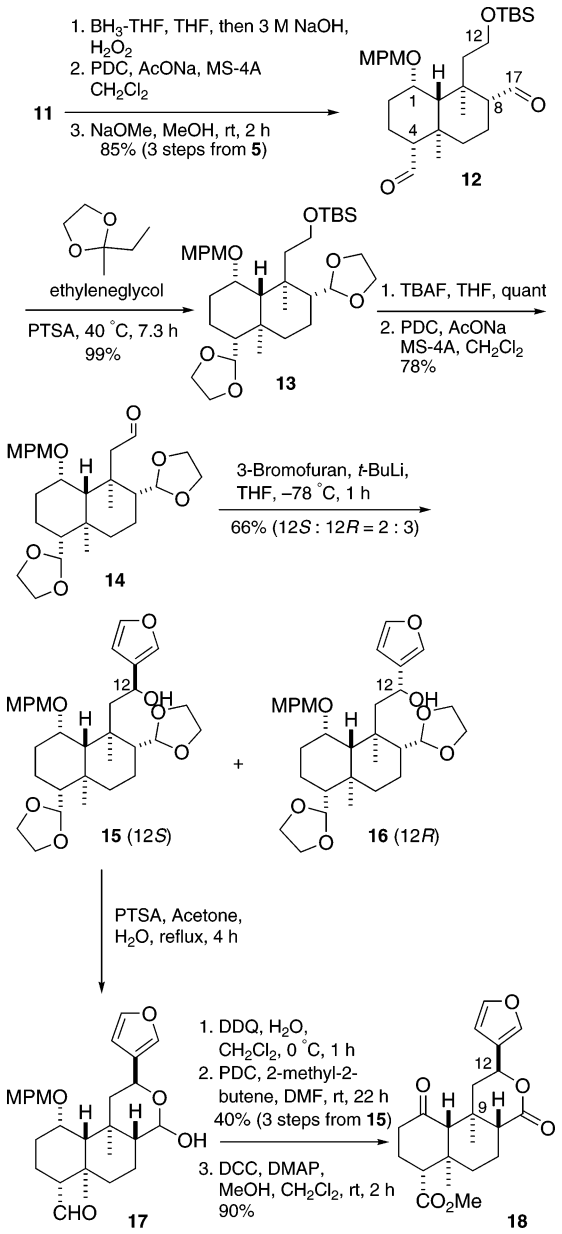
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sulted in complete recovery of **8**. Attempts to introduce α,β-unsaturated ester groups at C4 and C8 by palladium-catalyzed carbonyl insertion of the corresponding trifluoromethanesulfonylenol ether were not fruitful, probably also due to the same steric hindrance. The lactonic portion was reduced with lithium aluminum hydride and the resulting diol **10** was selectively protected as TBS-ether at first and then as MPM-ether to provide **11** for future selective transformations of two alcohols.

Hydroboration of *bis*-olefin **11**, oxidation of the resulting diol with PDC and subsequent treatment with base afforded thermodynamically more stable *bis*-α-aldehyde **12** preferentially (Scheme 2).

Scheme 2. Introduction of Furolactone Moiety

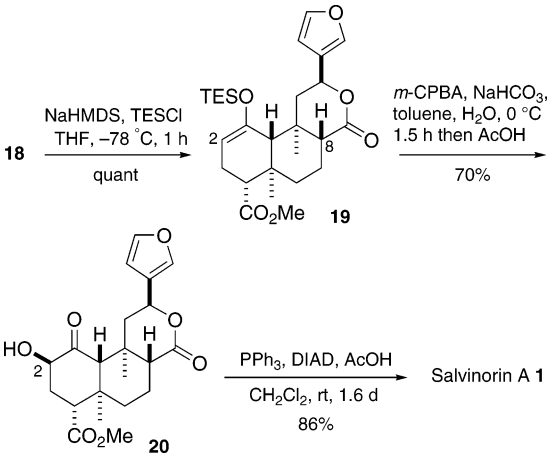


Prior to arranging the oxidation state of functional groups at C1, C4, and C8, the furyl unit was installed, because in the presence of a carboxy moiety at C8, undesirable lactonization between C12 and C17 was anticipated during deprotection of TBS-ether at C12. Thus, formyl groups were protected as acetals to give *bis*-acetal **13**. Deprotection of TBS-ether and subsequent PDC oxidation provided aldehyde **14**, which was reacted with 3-furyllithium to give the desired 12*S*-furylalcohol **15** and its 12*R*-epimer **16** in 2:3 ratio. The absolute stereochemistry at C12 of less polar **15** was determined to be *S* after transformation into deacetoxysalvinorin **18** as judged from 10% NOE enhancement between a proton at C12 and a methyl group at C9.

The resulting 12*S*-furylalcohol **15** was treated with acid to give hemiacetal **17**. Deprotection of the MPM-ether followed by threefold oxidation with PDC and subsequent esterification with DCC and methanol[14] afforded 2-deacetoxysalvinorin A **18**, whose spectral data were consonant with those of **18** derived from naturally occurring salvinorin A **1** according to the method by Prisinzano employing samarium diiodide.[15] In a similar manner, 12*R*-deacetoxysalvinorin A was obtained.

The final task is the introduction of the α-acetoxy group at C2. The major issue at this stage is the facile epimerization at C8 of salvinorin A (**1**) as well as 2-deacetoxysalvinorin (**18**) into 8*S*-isomers, which is not solved by the total synthesis of Evans et al.[9] As anticipated, various preliminary studies to introduce the 2-acetoxy group directly into 2-deacetoxysalvinorin (**18**) were troublesome by employing reagents such as (diacetoxyiodo)benzene,[16] acetoxymethylamine[17] and phenylsulfonylphenyloxaziridine[18] under either a variety of acidic or basic reaction conditions. After screening a wide variety of reagents and reaction conditions furthermore, this crucial problem was resolved by the Rubottom method,[19] in which brief treatment of deacetoxysalvinorin A (**18**) with NaHMDS at −78 °C and subsequently with TES-Cl successfully led to TES-silylenol ether **19** without C8 epimerization (Scheme 3). Prolonged treatment with base resulted in partial epimerization at C8 even under −78 °C. TMS-enol ether was not suitable due to its instability for subsequent epoxidation. Although the config-

Scheme 3. Total Synthesis of Salvinorin A **1**



uration at C8 of *trans*-clerodane furolactonic compound epimerize under basic condition either in the presence or absence of the carbonyl group at C1, the carbonyl group at C1 of salvinorin A (**1**) may play some role to facilitate epimerization at C8 as proposed by Koreeda and coworkers.[4a] There was no promiment difference in heat of formations between salvinorin A (**1**) and its C8 epimer according to energy calculations.[7f] Oxidation of TES-enol ether **19** with MCPBA in the two-phase system[20] proceeded sterically with less hindered β-face of the molecule selectively, and subsequent hydrolysis of the resulting TES-ether provided 2-*epi*-salvinorin A (**20**). Finally, inversion at C2 was carried out by the Mitsunobu reaction[7d,7h] to furnish salvinorin A (**1**). Spectral data of salvinorin A (**1**) including the value of optical rotation (synthetic **1** $[\alpha]_D$ −42; natural **1** $[\alpha]_D$ −41)[1a] were identical to those of the sample kindly supplied by Professor Koreeda.

In summary, we have completed an alternative total synthesis of hallucinogenic neoclerodane diterpenoid, salvinorin A (**1**) in 20 steps starting from optically pure Wieland−Miescher ketone **5**. The present protocol offers a method to afford 12-episalvinorin A, which is expected for evaluating hallucinogenic activity.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}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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