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Total Synthesis of the Hallucinogenic Neoclerodane Diterpenoid Salvinorin A

Masato Nozawa,†‡ Yuhki Suka,† Takashi Hoshi,§ Toshio Suzuki,§ and Hisahiro Hagiwara*†

Graduate School of Science and Technology, Niigata University, 8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan, and Faculty of Engineering, Niigata University, 8050, 2-Nocho, Ikarashi, Nishi-ku, Niigata 950-2181, Japan

hagiwara@gs.niigata-u.ac.jp

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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 congener 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−I1b,4 and salvinicins A and B5 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,
chemical transformations of salvinoirs have been achieved extensively to pursue and evaluate more active ingredients for binding affinity to cloned KOR. On the other hand, synthetic studies have been quite limited 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. Another issue is the facile epimerization at C8 (clerodane numbering) under either acidic or basic reaction conditions. Evans et al. utilized this equilibrium at the final stage in their total synthesis, in which salvinoir 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), we investigated independently the total synthesis of salvinoir 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 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.

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 methylation to provide bis-exo-methylene δ-lactone 9. Steric congestion at C4 and C8 at neopentyl positions was so severe that the reaction with methoxyethyltriphenylphosphorane re-

![Scheme 1. Introduction of Carbon Units at C4, C8, and C9 of Hydroxy Enone 5](image-url)
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 trifluoromethane-
sulfonylenol 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 prefer-
entially (Scheme 2).

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
12S-furylalcohol 15 and its 12R-epimer 16 in 2:3 ratio. The
absolute stereochemistry at C12 of less polar 15 was
determined to be S after transformation into deacetoxysalvi-
norin 18 as judged from 10% NOE enhancement between a
proton at C12 and a methyl group at C9.

The resulting 12S-furylalcohol 15 was treated with acid
to give hemiacetal 17. Deprotection of the MPM-ether
followed by threefold oxidation with PDC and subsequent
ersterification with DCC and methanol14 afforded 2-deac-
etoxysalvinorin 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, 12R-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 8S-isomers, which is not solved by the total
synthesis of Evans et al. 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 acetoxy-
methyamine17 and phenylsulfonylphenoxaziridine18 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 subse-
sequently with TES-Cl successfully led to TES-silylenol ether
19 without C8 epimerization (Scheme 3). Prolonged treat-
mant 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-
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 co-workers.4a There was no prominent 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 system20 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 reaction7d,7h to furnish salvinorin A (1). Spectral data of salvinorin A (1) including the value of optical rotation (synthetic [α]D −42; natural [α]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 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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