Asymmetric Synthesis of Salvinorin A, A Potent \( \kappa \) Opioid Receptor Agonist

Jonathan R. Scheerer, Jonathan F. Lawrence, Grace C. Wang, and David A. Evans*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received May 18, 2007; E-mail: evans@chemistry.harvard.edu

The neoclerodane diterpene salvinorin A (1) was isolated in 1982 from the rare mint *Salvia divinorum*, indigenous to Oaxaca, Mexico. Recent efforts established salvinorin A as a potent and selective \( \kappa \) opioid receptor agonist, the only non-alkaloid psychoactive substance, and the most potent naturally occurring hallucinogen. As a result of its therapeutic potential, renewed isolation efforts have discovered a number of related salvinorin congeners, and a number of analogues of 1 have been prepared by semisynthesis to probe the pharmacophore and mode of binding. This communication describes the first synthesis of this natural product.

Construction of the tricyclic salvinorin core is predicated on the proposed transannular\(^8\) Michael reaction cascade\(^6\) of bisenone macrocycle 3 (Scheme 1). Conformational analysis\(^7\) of 3 leads to a prediction wherein the resident stereocenters at C\(_2\), C\(_3\), and C\(_{12}\) 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)\(\rightarrow\)(R)-BINAP-catalyzed orthoester alkylation\(^8\) of thiazolidinethione 6, followed by a subsequent Claissen condensation with ethyl hydrogen malonate\(^1\) to give \( \beta \)-ketoester 7 (Scheme 2). Selective formation of the (Z)-enol phosphate permitted an Fe-catalyzed cross-coupling with methyl magnesium chloride\(^10\) to furnish trisubstituted olefin 8. Reduction to the unsaturated aldehyde then allowed a selective aldol addition of acetate-derived chiral auxiliary\(^9\). The derived allylic alcohol was protected as the tert-butyldimethylsilyl (TBS) ether\(^10\). After revealing the terminal aldehyde, an (\(-\)\)-methyl-ephedrine-mediated zinc acetylide addition\(^13\) provided propargylic alcohol 11 in good diastereoselectivity. Alcohol protection as the BOM ether was uniquely effected using NaHMDS and BOMCI at low temperature under Barbier conditions.\(^14\) Semi-hydrogenation, dihydroxylation, and oxidative cleavage furnished fragment 5.

The synthesis of vinyl iodide 4 employed an asymmetric reduction of ketone 12 using (R)-B-Me-oxazaborolidine as catalyst\(^16\) to afford alcohol 13 (Scheme 3). Allyne isomerization\(^17\) of 13 to 14 preceded carbocation\(^18\) 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, desilylation, and oxidation afforded macrocycle 3. Treatment of \( \beta \)-ketalactone 3 with TBAF at \(-78^\circ\)C and warming to \(5^\circ\)C induced the selective transannular reaction cascade to afford tricycle 2 as a single diastereomer. The reaction delivers two quaternary methyl stereocenters at C\(_5\) and C\(_9\) in a 1,3-diaxial alignment from the corresponding \( \beta \)-\( \beta \)-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 reduction\(^22\) to yield 17, epimeric at C\(_6\). Protonation from the \( \alpha \)-face by \(-\)BuOH in situ appears to be under kinetic as well as thermodynamic control, as epimerization studies conducted on 1 (DBU, \(110^\circ\)C in toluene) result in a mixture of C\(_9\)-epimers biased toward 8-\(-\)epi-salvinorin A 19.\(^23\) Deprotection of both the C\(_2\) and C\(_4\) acetals in 17 followed by oxidation and esterification gave 8-\(-\)epi-salvinorin B (18). Epimerization using K\(_2\)CO\(_3\) in oxygen-free methanol followed by acylation produced salvinorin A (1), spectroscopically identical to previous...
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 cycloaddition 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 C₉ stereochemistry, probing the mechanism of the cascade reaction, and synthesizing analogues of 1 that bear modified C₁₂ functionality.

Acknowledgment. Support was provided by the National Institutes of Health (GM-33327-19) and by unrestricted support from Amgen, Merck, and Eli Lilly. The authors wish to thank Dr. Regan Thomson for helpful suggestions.

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.

Supporting Information Available:

Scheme 5. Transannular Cyclization Analysis

Scheme 4. Fragment Coupling and Salvinorin A Synthesis

References