J|A|C|S
COMMUNICATIONS

Published on Web 06/30/2007

Asymmetric Synthesis of Salvinorin A, A Potent κ 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.[1] Recent efforts established salvinorin A as a potent and selective κ opioid receptor agonist, the only non-alkaloid psychoactive substance, and the most potent naturally occurring hallucinogen.[2] As a result of its therapeutic potential, renewed isolation efforts have discovered a number of related salvinorin congeners,[3] and a number of analogues of **1** have been prepared by semisynthesis to probe the pharmacophore and mode of binding.[4] This communication describes the first synthesis of this natural product.

Construction of the tricyclic salvinorin core is predicated on the proposed transannular[5] 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_4, 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.

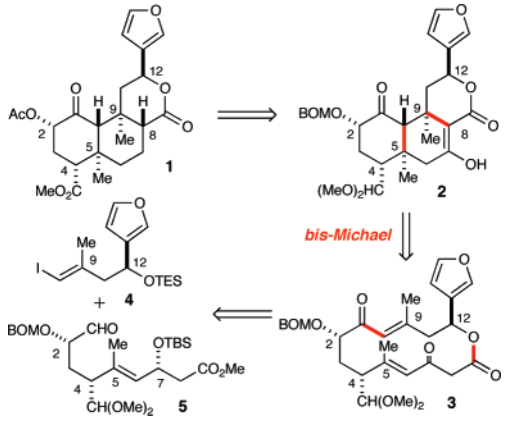
The synthesis of aldehyde **5** began with the Ni(II)−(*R*)-BINAP-catalyzed orthoester alkylation[8] of thiazolidinethione **6**, followed by a subsequent Claisen condensation with ethyl hydrogen malonate[9] to give β-ketoester **7** (Scheme 2). Selective formation of the (*Z*)-enol phosphate permitted an Fe-catalyzed cross-coupling with methylmagnesium chloride[10] to furnish trisubstituted olefin **8**. Reduction to the unsaturated aldehyde then allowed a selective aldol addition of acetate-derived chiral auxiliary **9**.[11,12] The derived allylic alcohol was protected as the *tert*-butyldimethylsilyl (TBS) ether **10**. After revealing the terminal aldehyde, an (−)-*N*-methylephedrine-mediated zinc acetylide addition[13] provided propargylic alcohol **11** in good diastereoselectivity. Alcohol protection as the BOM ether was uniquely effected using NaHMDS and BOMCl at low temperature under Barbier conditions.[14] Semi-hydrogenation, dihydroxylation,[15] and oxidative cleavage furnished fragment **5**.

The synthesis of vinyl iodide **4** employed an asymmetric reduction of ketone **12** using (*R*)-*B*-Me-oxazaborolidene as catalyst[16] to afford alcohol **13** (Scheme 3). Alkyne isomerization[17] of **13** to **14** preceded carboalumination[18] and TES-silyl ether protection.

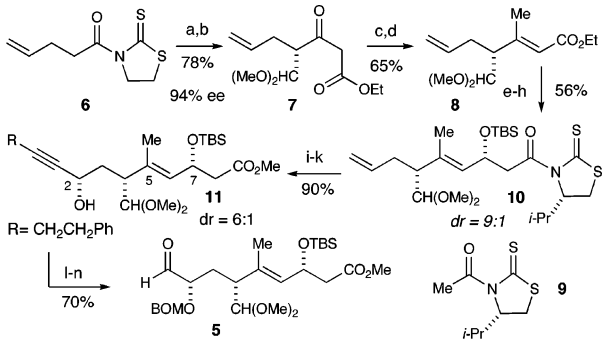
In the coupling event, chelate-controlled addition of the Grignard reagent derived from **4** to aldehyde **5** afforded allylic alcohol **15** (Scheme 4). A series of protecting group manipulations provided seco-acid **16**; subsequent macrolactonization using the Shiina procedure,[19] desilylation, and oxidation afforded macrocycle **3**. Treatment of β-ketolactone **3** with TBAF at −78 °C and warming to 5 °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 β,β-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_8. Protonation from the α-face by *t*-BuOH in situ

Scheme 1. Synthesis Plan for Salvinorin A (**1**)

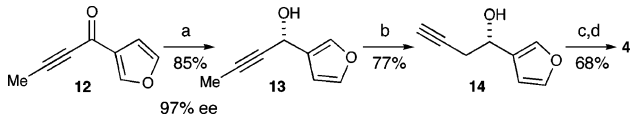


Scheme 2. Aldehyde Fragment Synthesis[a]



[a] Conditions: (a) Ni-(*R*)-BINAP(OTf)$_2$, 2,6-lutidine, BF_3•OEt_2, $HC(OMe)_3$; (b) $HO_2CCH_2CO_2Et$, *i*-PrMgCl, 65 °C; (c) LiHMDS; $ClPO(OEt)_2$; (d) $Fe(acac)_3$, MeMgCl, −20 °C; (e) DIBAL-H, −78 °C; (f) MnO_2; (g) $Sn(OTf)_2$, *N*-ethylpiperdine, **9**, −78 °C; (h) TBSOTf, 2,6-lutidine; (i) K_2CO_3, MeOH; (j) OsO_4, NMO; $NaIO_4$; (k) $Zn(OTf)_2$, (−)-*N*-Me-ephedrine, Et_3N, 4-phenyl-1-butyne; (l) BOMCl, NaHMDS, −78 °C; (m) Lindlar catalyst, H_2; (n) K_2OsO_4, NMO, citric acid, 50 °C; $Pb(OAc)_4$, K_2CO_3.

Scheme 3. Vinyliodide Fragment Synthesis[a]

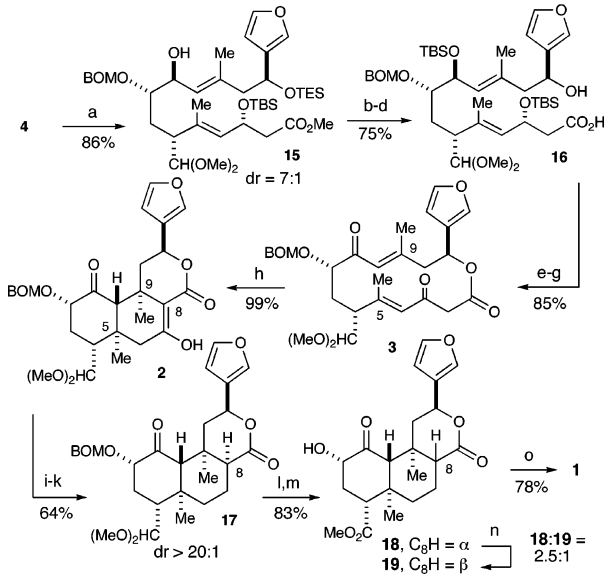


[a] Conditions: (a) (*R*)-*B*-Me-CBS catalyst, BH_3•Me_2S, −30 °C; (b) KH, $H_2N(CH_2)_3NH_2$, 0 °C; (c) Me_3Al, Cp-$_2ZrCl_2$; I_2, −45 °C; (d) TESCl, imidazole.

appears to be under kinetic as well as thermodynamic control, as epimerization studies conducted on **1** (DBU, 110 °C in toluene) result in a mixture of C_8-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_2CO_3 in oxygen-free methanol followed by acylation produced salvinorin A (**1**), spectroscopically identical to previous

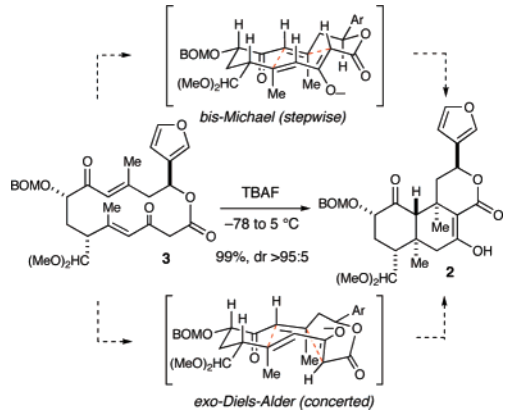
10.1021/ja073590a CCC: $37.00

Scheme 4. Fragment Coupling and Salvinorin A Synthesis[a]



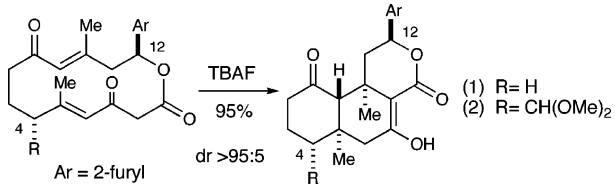
[a] Reaction conditions: (a) *n*-BuLi, $MgBr_2{\bullet}(OEt)_2$, −78 °C, then **5**, $MgBr_2{\bullet}OEt_2$, CH_2Cl_2, −78 to 0 °C; (b) TBSOTf, 2,6-lutidine; (c) PPTS, MeOH; (d) LiOH, *i*-PrOH, H_2O; (e) MNBA, DMAP, [0.0015 M]; (f) TBAF; (g) Dess−Martin periodinane; (h) TBAF, −78 to 5 °C; (i) NaH, Comins reagent; (j) $Pd(OAc)_2$, dppf, Et_3SiH; (k) L-selectride, *t*-BuOH, −78 to −55 °C; (l) $LiBF_4$, $MeCN/H_2O$; (m) $NaClO_2$; $TMSCHN_2$; (n) K_2CO_3, MeOH, quant. mass recovery; (o) Ac_2O, py., DMAP.

Scheme 5. Transannular Cyclization Analysis



reports and having an identical optical rotation (synthetic **1** $[\alpha]^{25}_D$ −40.7 (c = 0.12, $CHCl_3$); natural **1**, $[\alpha]^{25}_D$ −41 (c = 1, $CHCl_3$)).[1]

As a prelude to the pivotal cyclization cascade (**3**→**2**) featured in the synthesis, model systems were designed to probe the influence of the resident stereocenters on the course of the cyclization (eqs 1 and 2). The first cyclization evaluated the role of the C_{12}-furyl moiety and resulted in complete diastereocontrol (eq 1). Subsequent inclusion of the C_4-dimethyl acetal seemingly reinforced the diastereoselection imparted by the C_{12}-substituent (eq 2).



Scheme 5 provides a rationale for the observed selectivity in the **3**→**2** cyclization: conformational analysis of **3** suggests that the three stereocenters, in pseudo-equatorial positions, mutually 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[24] 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 C_8 stereochemistry, probing the mechanism of the cascade reaction, and synthesizing analogues of **1** that bear modified C_{12} 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 ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *10*, 2505−2508.
(2) (a) Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934−11939. (b) For molecular mechanism studies of KOR binding, see: Yan, F.; Mosier, P. D.; Westkaemper, R. B.; Stewart, J.; Zjawiony, J. K.; Vortherms, T. A.; Sheffler, D. J.; Roth, B. L. *Biochemistry* **2005**, *44*, 8643−8651.
(3) Shirota, O.; Nagamatsu, K.; Sekita, S. *J. Nat. Prod.* **2006**, *69*, 1782−1786 and references therein.
(4) (a) Beguin, C.; Richards, M. R.; Li, J.; Wang, Y.; Xu, W.; Liu-Chen, L.; Carlezon, W. A., Jr.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4679−4685 and references therein. (b) Tidgewell, K.; Harding, W. W.; Lozama, A.; Cobb, H.; Shah, K.; Kannan, P.; Dersch, C. M.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *J. Nat. Prod.* **2006**, *69*, 914−918 and references therein.
(5) (a) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787−1790. (b) Evans, D. A.; Scheerer, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 6038−6042.
(6) Ho, T. *Tandem Organic Reactions*; Wiley & Sons: New York, 1992; Chapter 3, pp 33−56.
(7) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.
(8) Evans, D. A.; Thomson, R. J. *J. Am. Chem. Soc.* **2005**, *128*, 10506−10507.
(9) Pollet, P.; Gelin, S. *Synthesis* **1978**, 142−143.
(10) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199−1205.
(11) Nagao, Y.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391−2393.
(12) We targeted the indicated C_7-diastereomer because molecular modeling studies suggested a gearing effect, potentially rendering the macrolactonization of **16** more facile.
(13) Frantz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806−1807.
(14) KHMDS and LiHMDS caused elimination of the allylic silyloxyether. NaH effected heteroconjugate addition of the C_2-alkoxide onto the extended polyene system. Interestingly, treatment of the C_2-diastereomer with NaH cleanly afforded benzyloxymethylated product.
(15) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421−433.
(16) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012 and references therein.
(17) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891−893.
(18) Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* **1979**, *79*, 501−502.
(19) (a) Shiina, I.; Kubota, M.; Ibuka, R.; T*etrahedron Lett.* **2002**, *43*, 7535−7539. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822−1830.
(20) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299−6302.
(21) Kotsuki, H.; Datta, P. K.; Hayakawa, H.; Suenaga, H. *Synthesis* **1995**, 1348−1350.
(22) (a) Ganem, B.; Fortunato, J. M. *J. Org. Chem.* **1975**, *40*, 2846−2848. (b) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194−2200.
(23) This likely is due to the small energy difference between chair and boat δ-lactones. See: (a) Thomas, S. A. *J. Crystallogr. Spectrosc. Res.* **1985**, *15*, 115−131. (b) Stanley, J.; Matallana, A.; Kinsbury, C. A. *J. Phy. Org. Chem.* **1990**, *3*, 419−427.
(24) For a review of TADA reactions in synthesis, see: Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260.

JA073590A