

Short synthesis of a novel class of salvinorin A analogs with hemiacetalic structure

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Abstract

Novel semisynthetic analogs of salvinorin A, a full agonist having extraordinary affinity as well as selectivity for the κ -opioid receptor (KOR), were obtained in good yields. The derivatives are remarkable for their unusual and unique hemiacetal structure in the salvinorin series of compounds. The formation of the hemiacetal occurs with epimerization at C-12, thus preserving the original configuration of salvinorin A. The dimethyl ester derivative of the hemiacetal was found to have an affinity for both KOR and MOR (μ -opioid receptor).

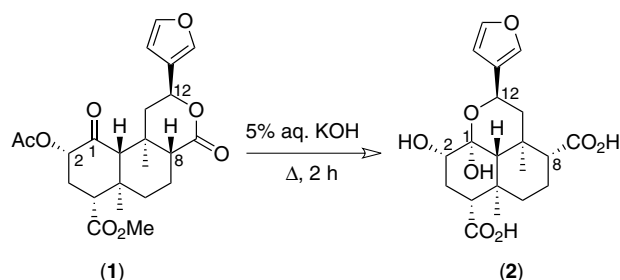
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Salvinorin A, a secondary metabolite isolated from the leaves of *Salvia divinorum*, is a neoclerodane diterpenoid with a strong hallucinogenic activity. It has been shown to have high affinity and selectivity for KOR.¹ Salvinorin A represents an attractive lead compound for drug development due to its strong effects on human mood and low toxicity. In the last two years numerous derivatives and analogs of salvinorin A were synthesized showing a broad range of KOR affinities.² Synthesis of new analogs of salvinorin A is important for generating structure-receptor affinity data and for designing agents with therapeutic potential. Some of the chemical modifications of salvinorin A have produced analogs with changed pharmacological profiles from full κ -agonist to partial δ - or μ -agonists or

antagonists.^{2i,m,3} Recently, modifications of the furan ring yielded the first analogs with κ -antagonistic activity.^{2b}

In this Letter we report the synthesis of the hemiacetal (2) and its derivatives starting from salvinorin A. Refluxing



Scheme 1. Conversion of salvinorin A (1) to hemiacetal (2) under the basic conditions.

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1 with 5% aqueous KOH surprisingly gave only one product according to thin-layer chromatography⁴ (Scheme 1).

¹H and ¹³C NMR analysis of the isolated product showed the typical spectra of salvinorins with an opened lactone moiety, except for the lack of the ketone carbon resonance at δ 200. Instead, a new resonance appeared at δ 97 suggesting the presence of carbon connected to two oxygen atoms (see Fig. 1 for appropriate HMBC and NOESY correlations). Interestingly, under the harsh basic conditions, we did not observe epimerization at C-8, commonly occurring in salvinorins.^{2d,5}

The proposed mechanism of hemiacetal formation with (*R*)-configuration at C-12 includes the formation of acyclic alcohol (**3**), rotation along the C-11–C-12 bond, leading to conformer (**4**), cyclization to the hemiacetal with (*S*)-configuration at C-12 (**5**) and epimerization at C-12 via intermediate **6** to the thermodynamically more stable product (**2**). Although the reaction is performed in an alkaline medium, intermediate **6** is still anticipated to be stabilized by solvation.

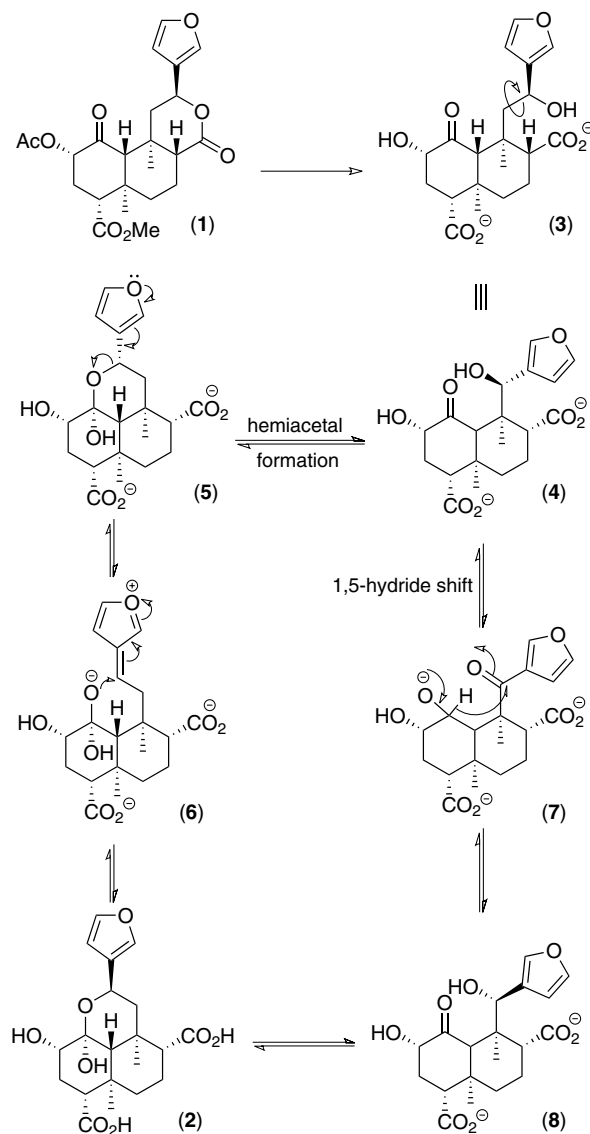
An alternative mechanism assumes a 1,5-hydride shift in hydroxyacid intermediate **4**, followed by a retro 1,5-hydrid shift in **7** to form an epimeric hydroxyacid (**8**) as a precursor to hemiacetal **2** (Scheme 2).

The absolute configuration has been unambiguously determined by X-ray crystallographic analysis⁶ of the corresponding dimethyl ester (**9**)⁷ (Fig. 2).

Considering the importance of the acetoxy group at C-2 for high affinity of salvinorin A to κ -opioid receptor, we synthesized acetate (**10**) using acetic anhydride and a catalytic amount of DMAP⁸ (Scheme 3).

Hemiacetals **2** and **9** are relatively stable under basic and neutral conditions. In the presence of acid diester (**9**) is readily transformed to the corresponding hydroxyketone (**11**).

Compounds **2** and **9–11** were evaluated for KOR and MOR affinities at the NIMH-sponsored Psychoactive Drug Screening Program, University of North Carolina at



Scheme 2. Putative mechanisms for hemiacetal (**2**) formation.

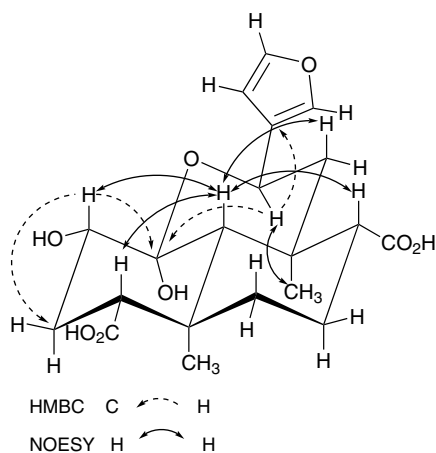


Fig. 1. Key HMBC and NOESY correlations of **2**.

Chapel Hill using radioligand binding assays. The assays were conducted according to the procedure described earlier.¹ The results are presented in Table 1.

Transformation of salvinorin A (**1**) to hemiacetal (**2**) results in a loss of all KOR activity. Compound **9** displays moderate affinity for both κ - and μ -opioid receptors. Surprisingly, the product of acetylation (**10**), despite functional similarity to salvinorin A, is practically devoid of affinity. Conversion of hemiacetal (**9**) into acyclic hydroxyketone (**11**) resulted in the loss of MOR affinity, while retaining a weak KOR activity.⁹

In summary, we have developed a short synthetic approach to new salvinorin A analogs with cyclic hemiacetal structure and dual but rather weak affinity to KOR and MOR. This method offers an attractive strategy to a new and unique class of salvinorin A analogs.

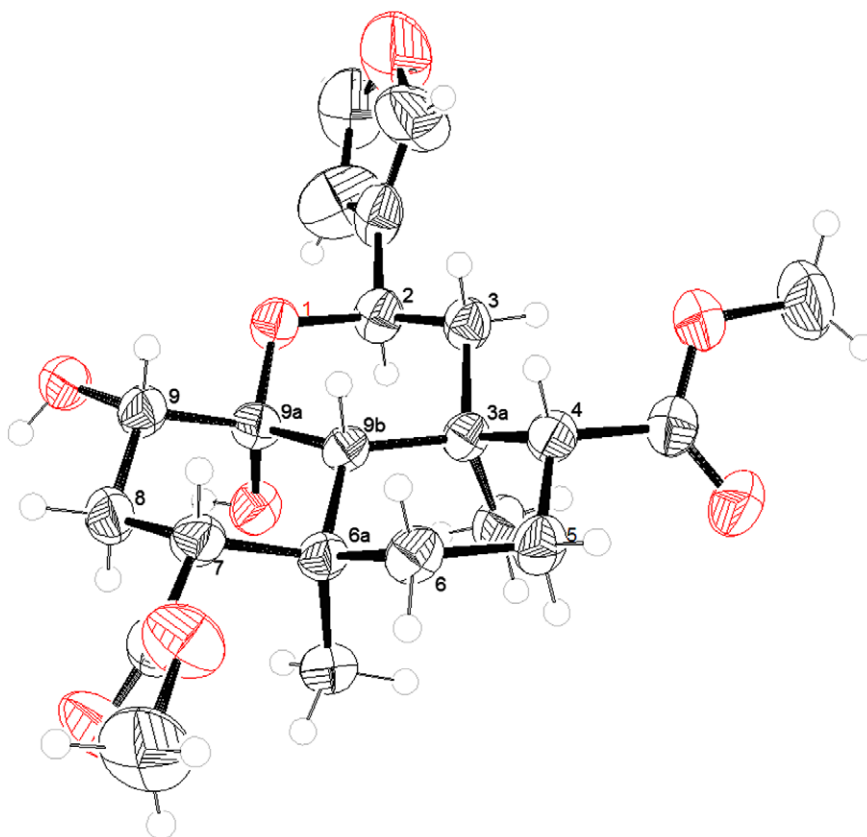
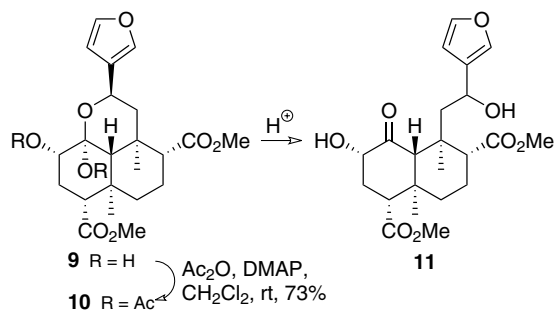


Fig. 2. X-ray crystallographic structure of dimethyl ester (**9**) [dimethyl (2*R*,3*aR*,4*R*,6*aR*,7*R*,9*S*,9*aS*,9*bS*)-2-(3-furyl)-9,9*a*-dihydroxy-3*a*,6*a*-dimethyldodecahydrobenzo[*de*]chromene-4,7-dicarboxylate].



Scheme 3. Derivatives of hemiacetal **2**.

Table 1
Affinity KOR and MOR receptors (for KOR-³H]U69593 and MOR-³H]DAMGO)

Compound	K_i (nM) (KOR)	K_i (nM) (MOR)
Salvinorin A (1)	0.48 ± 0.18	—
Hemiacetal (2)	NA	NA
Diester (9)	219 ± 59	1926 ± 147
Acetate (10)	6003 ± 1242	7487 ± 2141
Hydroxyketone (11)	1991 ± 708	>10,000
DAMGO	—	2.40 ± 0.48

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Supplementary data

Supplementary data (mp, HRMS and ¹³C and ¹H NMR spectra for compounds **2**, **9**, **10**, and **11**) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2007.12.041](https://doi.org/10.1016/j.tetlet.2007.12.041).

References and notes

- 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.
- (a) Holden, K. G.; Tidgewell, K.; Marquam, A.; Rothman, R. B.; Navarro, H.; Prizinsano, T. E. *Biorg. Med. Chem. Lett.* **2007**, *17*, 6111; (b) Simpson, D. S.; Katavic, P. L.; Lozama, A.; Harding, W. W.; Parrish, D.; Deschamps, J. R.; Dersch, C. M.; Partilla, J. S.; Rothman, R. B.; Navarro, H.; Prizinsano, T. E. *J. Med. Chem.* **2007**, *50*, 3596; (c) Beguin, C.; Carlezon, W. A.; Cohen, B. M.; He, M.; Lee, D. Y.-W.; Richards, M. R.; Liu-Chen, L.-Y. U.S. Patent Appl. US 2,007,213,394; AN, 1029945, 2007.; (d) Bikbulatov, R. V.; Yan, F.; Roth, B. L.; Zjawiony, J. K. *Biorg. Med. Chem. Lett.* **2007**, *17*, 2229; (e) Bohn, L. M.;

- Prisinzano, T. E. PCT Int. Appl. WO 2006138589, 2006; *Chem. Abstr.* **2006**, *146*, 100896; (f) Lee, D. Y. W.; He, M.; Liu-Chen, L.-Y.; Wang, Y.; Li, J.-G.; Xu, W.; Ma, Z.; Carlezon, W. A., Jr.; Cohen, B. *Biorg. Med. Chem. Lett.* **2006**, *16*, 5498; (g) Beguin, C.; Richards, M. R.; Li, J.-G.; Wang, Y.; Xu, W.; Liu-Chen, L.-Y.; Carlezon, W. A.; Cohen, B. M. *Biorg. Med. Chem. Lett.* **2006**, *16*, 4679; (h) Stewart, D. J.; Fahmy, H.; Roth, B. L.; Yan, F.; Zjawiony, J. K. *Arzneim.-Forsch. Drug Res.* **2006**, *56*, 269; (i) 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; (j) Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Biorg. Med. Chem. Lett.* **2006**, *16*, 3170; (k) Prisinzano, T. U.S. Patent Appl. 2,006,058,264, 2006; *Chem. Abstr.* **2006**, *144*, 292904; (l) Zjawiony, J.; Fahmy, H.; Stewart, D. J.; Roth, B. PCT Int. Appl. WO 2006012643, 2006; *Chem. Abstr.* **2006**, *144*, 164284; (m) Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Gilmour, B.; Navarro, H.; Rothman, R. B.; Prisinzano, T. E. *J. Nat. Prod.* **2006**, *69*, 107.
3. (a) Harding, W. W.; Tidgewell, K.; Schmidt, M.; Shah, K.; Dersch, C. M.; Snyder, J.; Parrish, D.; Deschamps, J. R.; Rothman, R. B.; Prisinzano, T. E. *Org. Lett.* **2005**, *7*, 3017; (b) Rothman, R. B.; Murphy, D. L.; Xu, H.; Godin, J. A.; Dersch, C. M.; Partilla, J. S.; Tidgewell, K.; Schmidt, M.; Prisinzano, T. E. *J. Pharmacol. Exp. Ther.* **2007**, *320*, 801; (c) Groer, C. E.; Tidgewell, K.; Moyer, R. A.; Harding, W. W.; Rothman, R. B.; Prisinzano, T. E.; Bohn, L. M. *Mol. Pharmacol.* **2007**, *71*, 549.
4. Salvinorin A (**1**) (10 mg, 23 μ mol) was placed in aqueous 5% KOH (5 mL) and refluxed for two hours producing a yellow solution. Upon reaching room temperature, the solution was cooled in an ice bath and neutralized with cold aqueous 0.5 M HCl. The resulting precipitate was collected by vacuum filtration. The product was purified through column chromatography using a short silica column and ethyl acetate. Yield was 6.2 mg (69%).
5. (a) Munro, T. A.; Duncan, K. K.; Staples, R. J.; Xu, W.; Liu-Chen, L.-Y.; Beguin, C.; Carlezon, W. A.; Cohen, B. M. *Beilstein J. Org. Chem.* **2007**, *3*, 1; (b) Valdes, L. J. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716; (c) Brown L. The Stereocontrolled Synthesis of Optically Active Vitamin E Side Chains. II. Benzoyl Triflate and its Application in the Determination of Absolute Configuration of Divinorin A and B, and Terrecyclic Acid. Ph.D. Thesis, University of Michigan, Ann Arbor, MI, 1984, ProQuest Publication Number: AAT 8422201 (Document ID:748992941). See pp 72–75. URL <http://wwwlib.umi.com/dissertations/fullcit/8422201>; (d) Koreeda, M.; Brown, L.; Valdes, L. J. J., III. *Chem. Lett.* **1990**, 2015; (e) Valdes, L. J. J., III. *J. Psychoact. Drugs* **1994**, *26*, 277; (f) Valdes, L. J. J., III; Chang, H. M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935.
6. Carvalho, P.; Bikbulatov, R.; Zjawiony, J. K.; Avery, M. A. *Acta Cryst. E*, in press.
7. Solution of TMSCHN₂ (0.13 mmol) in benzene (1 mL) was added at room temperature to a stirred solution of hemiacetal **2** (20 mg, 0.05 mmol) in methanol (5 mL). The mixture was stirred at room temperature for 30 min and concentrated to give the corresponding dimethyl ester **9**. The product was purified by column chromatography using a short silica column and hexanes/ethyl acetate (2:1). Yield was 18.3 mg (87%).
8. A solution of **9** (10 mg, 24 μ mol), acetic anhydride (10 mg, 98 μ mol) and a catalytic amount of DMAP in CH₂Cl₂ (2 mL) was stirred at room temperature for 2 h. Absolute MeOH (1 mL) was added and the solvent was removed under reduced pressure. CH₂Cl₂ (5 mL) was added to the residue and the solution was washed with 10% HCl (3 \times 3 mL) and saturated NaCl (3 \times 3 mL) and dried (Na₂SO₄). Removal of the solvent under reduced pressure afforded acetate (**10**), which was purified by column chromatography using a short silica column and hexanes/ethyl acetate (2:1). Yield was 8.9 mg (73%).
9. A solution of **9** (10 mg, 24 μ mol) and a catalytic amount of acetic acid (or PTSA, or HCl in MeOH) in CH₂Cl₂ (2 mL) was stirred at room temperature for 3 h. Removal of the solvent under reduced pressure afforded hydroxyketone (**11**), which was purified by column chromatography using a short silica column and hexanes/ethyl acetate (3:2). Yield was 8.1 mg (81%).