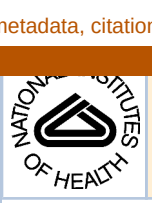


Published in final edited form as:

Tetrahedron Lett. 2008 February 4; 49(6): 937–940.

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

Ruslan V. Bikbulatov[a], **Jeremy Stewart**[a], **Wentao Jin**[a], **Feng Yan**[b], **Bryan L. Roth**[b], **Daneel Ferreira**[a,c], and **Jordan K. Zjawiony**[a,c,*]

a *Department of Phamacognosy, School of Pharmacy, University of Mississippi, University, MS 38677-1848, USA*

b *Department of Pharmacology, School of Medicine and Division of Medicinal Chemistry and Natural Products, School of Pharmacy, NIMH Psychoactive Drug Screening Program, University of North Carolina, Chapel Hill, NC 27599, USA*

c *National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University, MS 38677-1848, USA*

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).

Keywords

salvinorin A; KOR ligands; hemiacetal; dual afinity

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 design of 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,2m,3] Recently, modifications of the furan ring yielded the first analogs with κ-antagonistic activity.[2b]

In this paper we report the synthesis of the hemiacetal (**2**) and its derivatives starting from salvinorin A. Refluxing **1** with 5% aqueous KOH surprisingly gave only one product according to thin-layer chromatography.[4] (Scheme 1).

*Corresponding author. Tel.: +1-662-915-7290; fax: +1-662-915-6975; e-mail: jordan@olemiss.edu.

^{1}H and ^{13}C 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. Interestingly, under the harsh basic conditions, we did not observe epimerisation at C-8, commonly occurring in salvinorins.[2d,5]

The proposed mechanism of hemiacetal formation with (*R*)-configuration at C-12 includes 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, the intermediate **6** is still anticipated to be stabilized by solvation.

An alternative mechanism assumes a 1,5-hydride shift in the 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 analysis[6] of the corresponding dimethyl ester (**9**)[7] (Figure 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 DMAP.[8] (Scheme 3)

Hemiacetals **2** and **9** are relatively stable under basic and neutral conditions. In the presence of acids 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 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 the hemiacetal (**9**) into the acyclic hydroxyketone (**11**) resulted in the loss of MOR affinity, while retaining a weak KOR activity.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to acknowledge Lukasz Kutrzeba for help in extraction of salvinorin A from plant material, and Dr. Paulo Carvalho for providing crystallographic data. This work was supported by NIH grant R01 DA017204, and conducted in a facility constructed with support from research facilities improvement program grant C06 RR-14503-01 from National Center for Research Resources, National Institutes of Health, Bethesda, MD, USA.

References and notes

1. Roth BL, Baner K, Westkaemper R, Siebert D, Rice KC, Steinberg S, Ernsberger P, Rothman RB. Proc Natl Acad Sci 2002;99:11934. [PubMed: 12192085]
2. (a) Holden KG, Tidgewell K, Marquam A, Rothman RB, Navarro H, Prizinsano TE. Biorg Med Chem Lett 2007;17:6111. (b) Simpson DS, Katavic PL, Lozama A, Harding WW, Parrish D, Deschamps JR, Dersch CM, Partilla JS, Rothman RB, Navarro H, Prisinzano TE. J Med Chem 2007;50:3596. [PubMed: 17580847]Beguin, C.; Carlezon, WA.; Cohen, BM.; He, M.; Lee, DY-W.; Richards, MR.; Liu-Chen, L-Y. US Pat Appl US 2007213394, AN 2007:1029945. (d) Bikbulatov RV, Yan F, Roth BL, Zjawiony JK. Biorg Med Chem Lett 2007;17:2229.Bohn, LM.; Prisinzano, TE. PCT Int. Appl. WO 2006138589, 2006. Chem Abstr 2006. p. 100896 (f) Lee DYW, He M, Liu-Chen L-Y, Wang Y, Li J-G, Xu W, Ma Z, Carlezon WA Jr, Cohen B. Biorg Med Chem Lett 2006;16:5498. (g) Beguin C, Richards MR, Li JG, Wang Y, Xu W, Liu-Chen LY, Carlezon WA, Cohen BM. Biorg Med Chem Lett 2006;16:4679. (h) Stewart DJ, Fahmy H, Roth BL, Yan F, Zjawiony JK. Arzneimittel Forschung Drug Research 2006;56:269. [PubMed: 16724512] (i) Tidgewell K, Harding WW, Lozama A, Cobb H, Shah K, Kannan P, Dersch CM, Parrish D, Deschamps JR, Rothman RB, Prisinzano TE. J Nat Prod 2006;69:914. [PubMed: 16792410] (j) Harding WW, Schmidt M, Tidgewell K, Kannan P, Holden KG, Dersch CM, Rothman RB, Prisinzano TE. Biorg Med Chem Lett 2006;16:3170.Prisinzano, T. U.S. Patent Appl. 2006058264, 2006. Chem Abstr 2006. p. 292904Zjawiony, J.; Fahmy, H.; Stewart, DJ.; Roth, B. PCT Int. Appl. WO 2006012643, 2006. Chem Abstr 2006. p. 164284 (m) Harding WW, Schmidt M, Tidgewell K, Kannan P, Holden KG, Gilmour B, Navarro H, Rothman RB, Prisinzano TE. J Nat Prod 2006;69:107. [PubMed: 16441078]
3. (a) Harding WW, Tidgewell K, Schmidt M, Shah K, Dersch CM, Snyder J, Parrish D, Deschamps JR, Rothman RB, Prisinzano TE. Org Lett 2005;7:3017. [PubMed: 15987194] (b) Rothman RB, Murphy DL, Xu H, Godin JA, Dersch CM, Partilla JS, Tidgewell K, Schmidt M, Prisinzano TE. J Pharmacol Exp Ther 2007;320:801. [PubMed: 17060492] (c) Groer CE, Tidgewell K, Moyer RA, Harding WW, Rothman RB, Prisinzano TE, Bohn LM. Molecular Pharmacology 2007;71:549. [PubMed: 17090705]
4. Salvinorin A (1) (10 mg, 23 μmol) 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 0.5M 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 TA, Duncan KK, Staples RJ, Xu W, Liu-Chen LY, Beguin C, Carlezon WA, Cohen BM. Beilstein Journal of Organic Chemistry 2007;3:1. [PubMed: 17212822] (b) Valdes LJJ III, Butler WM, Hatfield GM, Paul AG, 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. PhD Thesis, University of Michigan, Ann Arbor, MI 1984, Pro-Quest 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 LJJ III. Chem Lett 1990:2015. (e) Valdes LJJ III. J Psychoact Drugs 1994;26:277. (f) Valdes LJJ III, Chang HM, Visger DC, Koreeda M. Org Lett 2001;3:3935. [PubMed: 11720573]
6. X-ray data in press
7. Solution of $TMSCHN_2$ (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 μmol), acetic anhydride (10 mg, 98 μmol) and a catalytic amount of DMAP in CH_2Cl_2 (2mL) was stirred at room temperature for 2h. Absolute MeOH (1 mL) was added and the solvent was removed under reduced pressure. CH_2Cl_2 (5 mL) was added to the residue and the solution was washed with 10% HCl (3×3 mL) and saturated NaCl (3×3mL) and dried (Na_2SO_4). 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 μmol) and a catalytic amount of acetic acid (or PTSA, or HCl in MeOH) in CH_2Cl_2 (2mL) was stirred at room temperature for 3h. 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%).

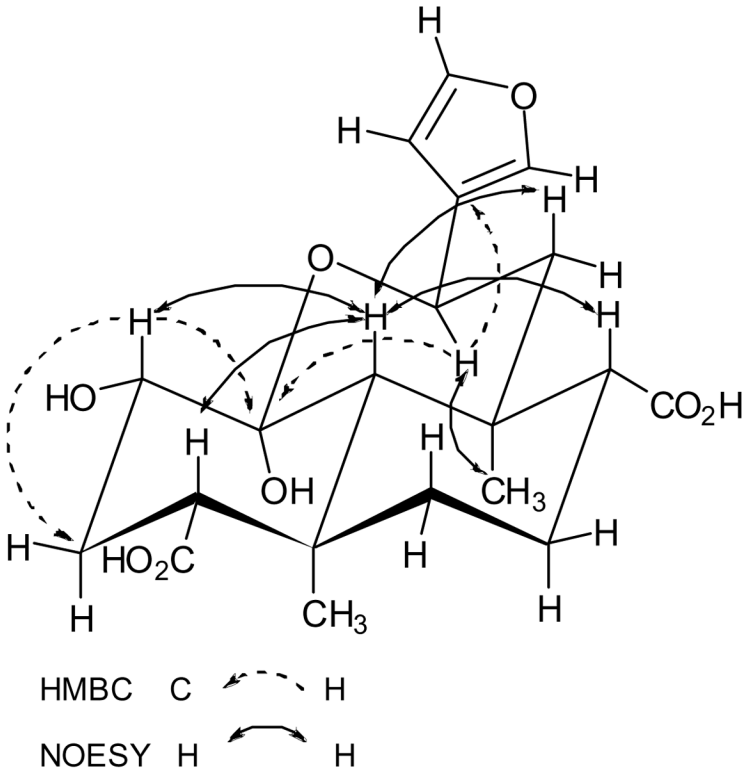


Figure 1.
Key HMBC and NOESY correlations of **2**

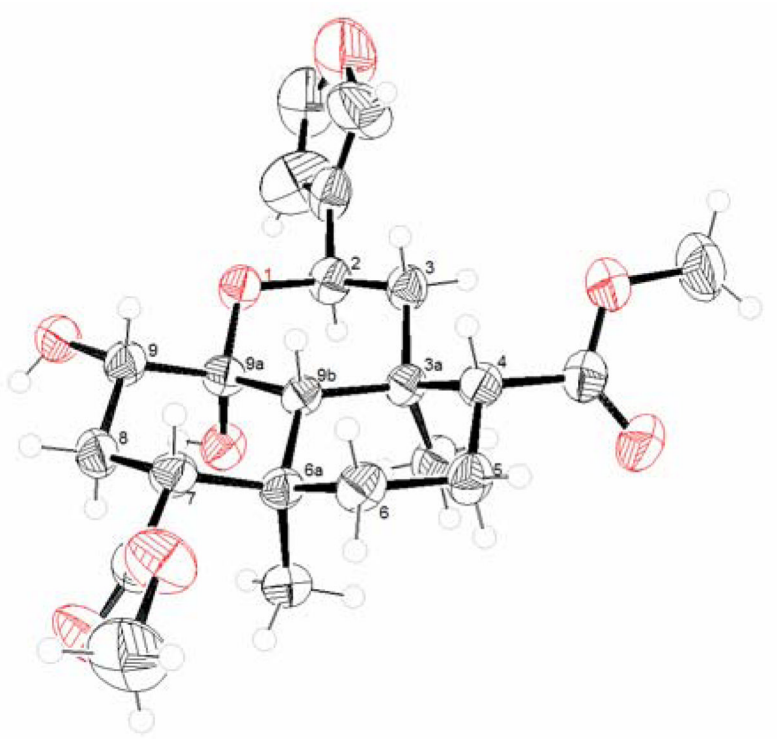
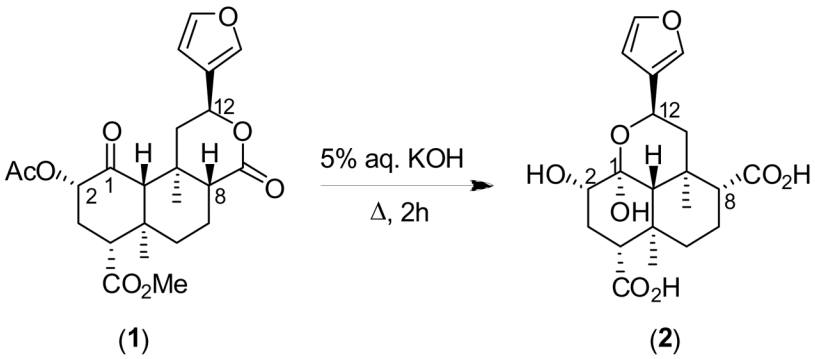
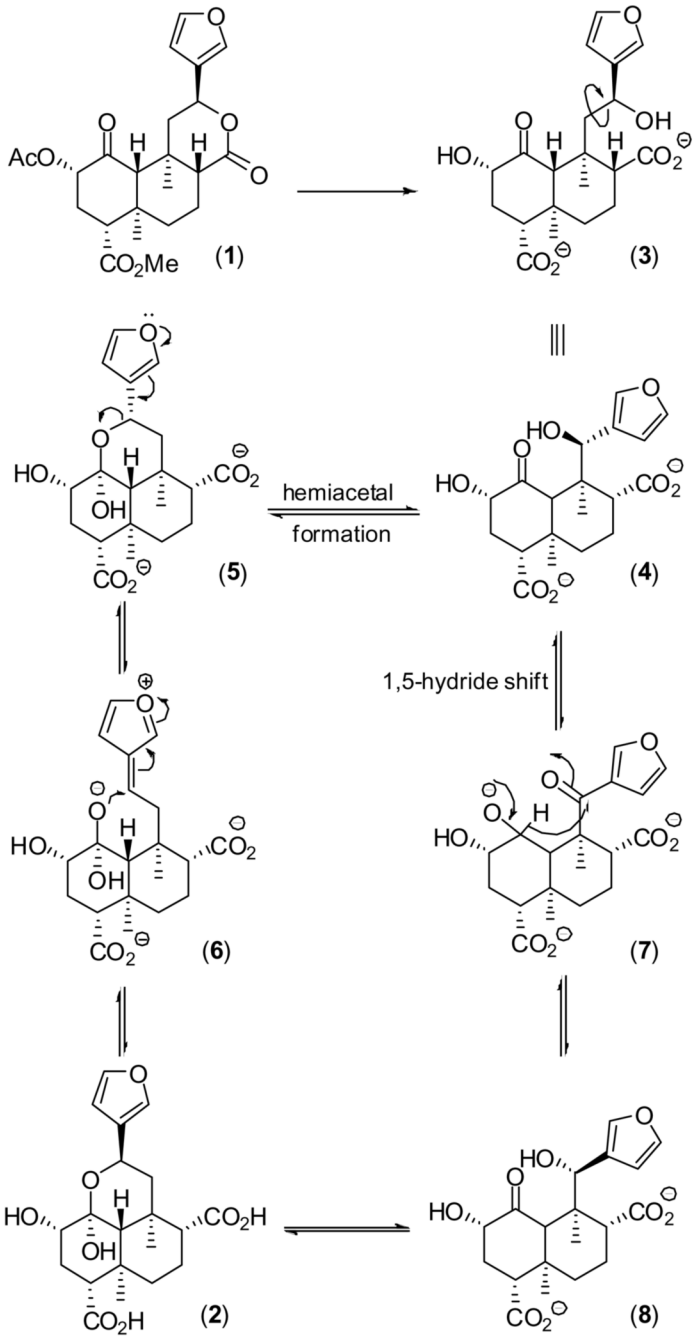


Figure 2.
X-ray crystallographic structure of the dimethyl ester (**9) [**dimethyl (2*R*,3a*R*,4*R*,6a*R*,7*R*,9*S*, 9a*S*,9b*S*)-2-(3-furyl)-9,9adihydroxy-3a,6a-dimethyldodecahydrobenzo[*de*]chromene-4,7-dicarboxylate]

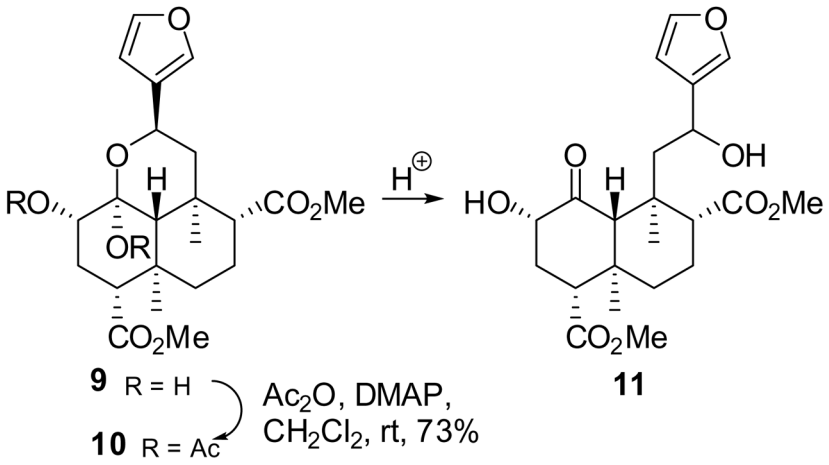


(**1**) (**2**)

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



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



Scheme 3.
Derivatives of hemiacetal **2**

Table 1

Affinity KOR and MOR receptors (for KOR-[^{3}H]U69593 and MOR-[^{3}H] DAMGO)

Compound	K_i (nM) (KOR)	K_i (nM) (MOR)
Salvinorin A (**1**)	0.48+/− 0.18	--
Hemi-acetal (**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