Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1782–1785
Tetrahedron Letters

Synthesis of deacetyl-1,10-didehydrosalvinorin G

Zhongze Ma, David Y. W. Lee *

Bio-Organic and Natural Products Laboratory, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, United States

Received 3 July 2007; revised 10 January 2008; accepted 11 January 2008
Available online 15 January 2008

Abstract

To unambiguously confirm the actual product in autoxidation of salvinorin A under basic conditions, deacetyl-1,10-didehydrosalvinorin G was synthesized from salvinorin C via intermediate salvinorin H. Furthermore, oxidation of salvinorin D with manganese dioxide gave salvinorin G in good yield.

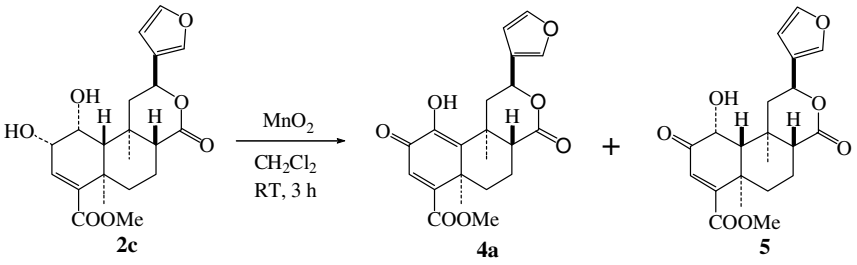
Keywords: Salvinorin A; Oxidation; Manganese dioxide; Synthesis

Salvia divinorum, a Mexican medicinal plant, has been used traditionally for its psychoactive (hallucinogenic) effects in divination rites.[1] Previous phytochemical studies have resulted in the isolation of 34 compounds, including salvinorins A (**1a**), C (**2a**), D (**2b**), G (**3**), and H (**2c**).[2–9] Of those compounds, **1a** was identified as a potent and selective kappa opioid receptor (KOR) agonist.[10,11] Because of the unique non-nitrogenous structure and potent binding activities to KOR, much effort has been directed toward a better understanding of structure–activity relationships (SAR) of **1a**.[12–26] Salvinorin derivatives readily underwent epimerization at C-8 under basic conditions.[3,4,13–17] Surprisingly, treatment of **1a** and its derivative with strong bases, such as $Ba(OH)_2$,[15] KOH,[18,26] and NaOH,[25] yielded corresponding natural salvinorin analogs, and no epimerization at C-8 was observed. It was reported that treatment of **1a** with KOH in methanol produced deacetyl-1,10-didehydrosalvinorin G (**4a**).[18] Recently, we revised the structure of **4a** to its 8-epimer (**4b**) based on comparison of ^{1}H and ^{13}C NMR data with those of **1a** and **1b**, NOESY data, and chemical conversion.[27] To unambiguously confirm the actual product in autoxidation of **1a** under harsh basic conditions,[18] it is necessary to synthesize the natural salvinorin derivative **4a** and to complete its NMR data. In this Letter, we report the synthesis of **4a** from **2a** via intermediate **2c**, and chemical conversion of **3** from **2b**.

Following the published procedure,[18] the diol **2c** was prepared by deacetylation of **2a**. Subsequent oxidation of **2c** with manganese dioxide (Scheme 1) yielded **4a** and deacetylsalvinorin G (**5**).[28] Using 2D NMR techniques, including COSY, NOESY, HMQC, and HMBC, permitted the full assignment of all ^{1}H and ^{13}C NMR chemical shifts of **4a** (Tables 1 and 2), and the key ^{13}C–^{1}H correlations in the HMBC spectrum of **4a** are shown in Figure 1. In the ^{1}H NMR spectrum of **4a**, the C-8-H shifted much upper field to δ 2.42, and the coupling constants (dd, $J = 12.6$ and 3.3 Hz) of H-8 are more suitable for axial orientation than those (δ 2.99, dd, $J = 9.6$ and 5.1 Hz) of **4b** (Table 1). The C-12-H of **4a** shifted low-field slightly compared with that of **4b** (Table 1), and the H-12 of **4a** showed the J values (10.5 and 6.6 Hz) for axial orientation. In addition, the H-11α (δ 3.76) of **4a** shifted much lower field compared with that of **4b** (δ 3.11), and the chemical shift changes are consistent with those of **2a** (δ 2.49)[4] and its 8-epimer (δ 2.14).[29] Comparison of the ^{13}C resonances of C-6, C-8, C-12, C-13, C-17, C-19, and C-20 (Table 2) of **4a** and **4b** also confirms that H-8 in **4a** is the β configuration. In the NOESY spectrum of **4a**, H-12 (δ 5.62) showed cross peaks to H-11α (δ 3.76) and H-20 (δ 1.54), while H-19 (δ 1.76)

* Corresponding author. Tel.: +1 617 855 2038; fax: +1 617 855 2040.
E-mail address: dlee@mclean.harvard.edu (D. Y. W. Lee).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.01.065



Scheme 1.

Table 1
^{1}H NMR data (300 MHz, $CDCl_3$) for **4a** and **4b** [δ (ppm), m, J (Hz)]

Proton	4a	4b
3	6.88 s	7.00 s
6α	2.51 dt (13.2, 3.3)	2.54 dt (13.8, 7.5)
6β	1.46 td (13.5, 3.9)	1.67–1.77 m
7α	1.94 ddt (14.4, 3.3, 13.5)	2.24 ddd (14.4, 7.8, 5.1)
7β	2.27 dq (14.7, 3.6)	1.98 ddd (14.1, 9.6, 6.6)
8	2.42 dd (12.6, 3.3)	2.99 dd (9.6, 5.1)
11α	3.76 dd (14.4, 6.3)	3.11 dd (14.7, 3.0)
11β	2.09 dd (14.4, 10.5)	2.02 dd (14.4, 12.3)
12	5.62 dd (10.5, 6.6)	5.44 dd (12.3, 2.4)
14	6.42 dd (1.2, 0.9)	6.42 dd (1.8, 0.9)
15	7.41 t (1.8)	7.41 t (1.8)
16	7.44 d (0.9)	7.49 d (0.9)
19	1.76 s	1.72 s
20	1.54 s	1.67 s
OH	7.07 s	6.92 s
CO_2CH_3	3.86 s	3.85 s

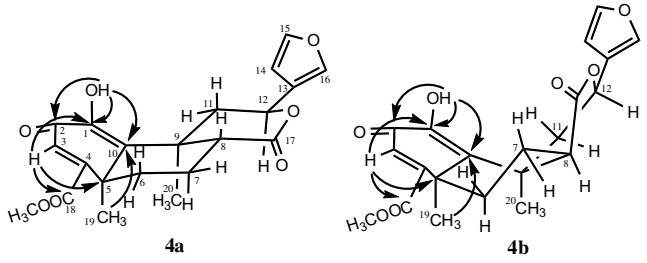


Fig. 1. Key HMBC correlations of **4a** and **4b**.

related to H-6α (δ 2.51), H-7α (1.94), and H-20 (δ 1.54). It should be noted that there is no crossed peak between H-8 and H-12/H-19/H-20. Based on these data, the structure of **4a** was confirmed as deacetyl-1,10-didehydrosalvinorin G.

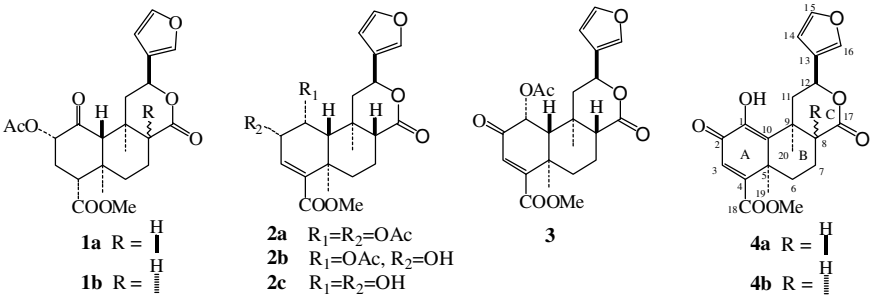
The coupling constants of H-6 and H-7 (Table 1) in **4a** are significantly different from those of **4b**. The J values

Table 2
^{13}C NMR data (75 MHz, $CDCl_3$) for **4a**, **4b**, **6a**, **6b**, **7a**, **7b**, **8a**, **8b**, **9a**, and **9b** [δ (ppm)]

Carbon	4a	4b	6a[a]	6b[b]	7a[b]	7b[b]	8a[b]	8b[b]	9a[c]	9b[c]
1	145.3	145.1	208.9	209.2	201.9	202.3	203.7	204.1	202.2	202.6
2	180.9	180.7	74.4	74.4	74.9	75.1	75.9	76.2	75.2	75.5
3	127.6	128.2	34.5	33.8	30.6	30.5	31.8	31.5	28.3	28.1
4	159.0	157.5	53.1	52.3	53.4	52.6	50.7	50.2	59.7	59.1
5	43.3	42.3	42.6	42.6	42.0	42.1	41.9	42.0	42.5	42.6
6	32.0	28.3	38.1	34.2	38.1	33.8	38.0	33.8	38.0	33.8
7	18.1	21.9	18.1	17.5	18.1	17.5	18.1	17.6	17.9	17.4
8	50.6	44.8	51.3	45.2	51.3	45.2	51.4	45.3	51.2	45.1
9	39.4	37.6	35.3	34.5	35.4	34.7	35.2	34.6	35.4	34.6
10	138.5	140.0	63.8	63.6	63.9	63.9	64.4	64.5	63.6	63.5
11	42.4	36.8	43.5	48.2	43.3	47.9	43.3	48.0	43.2	47.9
12	71.5	70.8	71.9	70.0	72.1	70.1	72.1	70.1	72.0	70.1
13	126.0	124.4	125.3	123.5	125.1	123.3	125.2	123.3	125.1	123.2
14	108.6	108.4	108.3	108.4	108.4	108.5	108.4	108.5	108.3	108.5
15	143.8	143.7	143.8	143.6	143.7	143.6	143.7	143.6	143.8	143.6
16	139.4	139.6	139.3	139.6	139.4	139.7	139.4	139.7	139.4	139.7
17	171.6	173.2	171.0	173.4	171.3	173.7	171.4	173.7	170.9	173.5
18	166.0	165.4	171.8	172.1	175.8	176.2	61.6	61.6	200.6	200.9
19	31.3	30.3	16.5	15.3	16.4	15.3	16.6	15.5	17.9	16.7
20	18.8	24.4	15.2	24.6	15.2	24.6	15.3	24.8	15.1	24.4
CO_2CH_3	52.7	52.6	51.9	51.6	—	—	—	—	—	—
$-CO$CH$_3$	—	—	—	—	170.0	169.9	170.1	169.9	170.0	169.8
$-CO$CH$_3$	—	—	—	—	20.5	20.5	20.6	20.6	20.6	20.6

[a] Compound **6a** was isolated from the leaves of *Salvia divinorum*.[7]
[b] Compounds **6b**, **7a**, **7b**, **8a**, and **8b** were synthesized and reported by our group.[15,16,21]
[c] The chemical shift assignments were based on the comparison with those in **1a** and **1b**.[27]

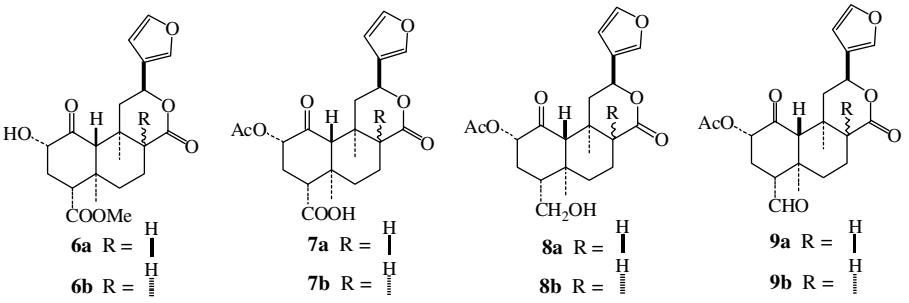
of H-6β (td, 13.5, 3.9) and H-7α (dtd, 14.4, 3.3, 13.5) of **4a** indicate that both protons are axial. It has been reported that the protons in anti-periplanar relationships show stronger correlations in the COSY spectrum.[30] This was also evidenced by the protons (H-7α and H-6β, H-7α and H-8) of **4a** in the COSY spectrum. On the other hand, only H-7β and H-8 of **4b** exhibited stronger correlations in the COSY spectrum. These findings suggest that the B-ring in **4a** should be an identical chair conformation (Fig. 1), which is different from that of **4b**. Obviously, the double bond between C-1 and C-10 in **4a** and **4b** distorts the B-ring conformation to a different extent.

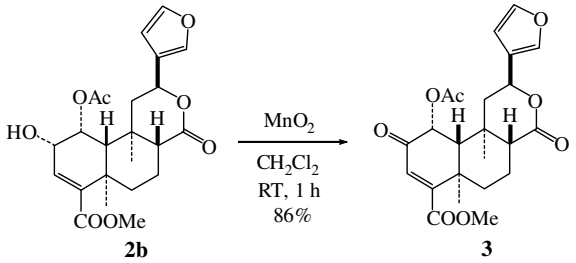


Compounds **4a** and **5** were screened for binding affinity at opioid receptors in vitro, as reported previously.[7] Both compounds were inactive at mu, delta, and kappa opioid receptors at 3 μM.

Salvinorin G (**3**) presents in *S. divinorum* in much lower level than **1a** and **2a**, and it showed a moderate binding affinity at KOR.[7] **3** can be prepared by oxidation of the natural occurring salvinorin D (**2b**)[7] with manganese dioxide in an excellent yield (Scheme 2).[31] This reaction not only confirms the structure of **3** but also demonstrates that no epimerization occurs under the mild oxidation conditions as shown in Scheme 1.

Numerous salvinorin derivatives have been prepared in recent years for SAR study and improvement of KOR binding affinity.[12–26] Compounds **6a**, **6b**, **7a**, **7b**, **8a**, and **8b** have served as key intermediates for C-2 and C-18 SAR studies. Among these compounds, only **6a** and **8a** were reported with full NMR assignments.[30,13] However, **6a** was measured in acetone-d_6 at higher temperature (40 °C).[30] Furthermore, **1b** is the only compound with full ^{1}H and ^{13}C NMR assignments in numerous 8-*epi*-salvinorin derivatives.[13] Therefore, we assigned all ^{13}C NMR chemical shifts of **6a**, **6b**, **7a**, **7b**, **8a**, and **8b** in comparison with those of **1a** and **1b** (Table 2).[27] On the other hand, both aldehydes **9a** and **9b** were synthesized in our laboratory, and the incorrect ^{1}H and ^{13}C NMR data of **9a** were presented in our previous Letter.[21] The ^{13}C NMR data of **9a** were revised and are shown in Table 2.





Scheme 2.

In conclusion, deacetyl-1,10-didehydrosalvinorin G (**4a**) was readily synthesized from salvinorin H (**2c**). The product obtained by the treatment of **1a** with hydroxides in MeOH[18] has been unambiguously identified as 8-*epi*-deacetyl-1,10-didehydrosalvinorin G (**4b**). Finally, the conversion of salvinorin G (**3**) from salvinorin D (**2b**) provides an authentic sample with intact stereochemistry at C-8 for further confirmation of **4a**.

Acknowledgments

The authors wish to thank Ms. Jane F. McNeil for EI-MS determination and Drs. Wei Xu and Lee-Yuan Liu-Chen for the binding assay at opioid receptors. This work was supported by a research grant (R01-DA019688) from NIDA to D.Y.W.L.

Supplementary data

^{1}H and ^{13}C NMR spectra of **4a**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.065.

References and notes

1. Siebert, D. J. *J. Ethnopharmacol.* **1994**, *43*, 53–56.
2. Ortega, A.; Blount, J. F.; Manchand, P. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2505–2508.
3. Valdes, L. J., III.; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 4716–4720.
4. Valdes, L. J., III.; Chang, H.-M.; Visger, D. C.; Koreeda, M. *Org. Lett.* **2001**, *3*, 3935–3937.
5. Munro, T. A.; Rizzacasa, M. A. *J. Nat. Prod.* **2003**, *66*, 703–705.
6. Bigham, A. K.; Munro, T. A.; Rizzacasa, M. A.; Robins-Browne, R. M. *J. Nat. Prod.* **2003**, *66*, 1242–1244.
7. Lee, D. Y. W.; Ma, Z.; Liu-Chen, L.-Y.; Wang, Y.; Chen, Y.; Carlezon, W. A.; Cohen, B. *Bioorg. Med. Chem.* **2005**, *13*, 5635–5639.
8. 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*, 3017–3020.
9. Shirota, O.; Nagamatsu, K.; Sekita, S. *J. Nat. Prod.* **2006**, *69*, 1782–1786.
10. Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D. J.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. *Proc. Natl. Acad. Sci.* **2002**, *99*, 11934–11939.
11. Sheffler, D. J.; Roth, B. L. *Trends Pharmacol. Sci.* **2003**, *24*, 107–109.
12. Chavkin, C.; Sub, S.; Jin, W.; Stewart, J.; Zjawiony, J. K.; Siebert, D. J.; Toth, B. A.; Hufeisen, S. J.; Roth, B. L. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1197–1203.
13. Munro, T. A.; Rizzacasa, M. A.; Roth, B. L.; Toth, B. A.; Yan, F. *J. Med. Chem.* **2005**, *48*, 345–348.
14. Beguin, C.; Richards, M. R.; Wang, Y.; Chen, Y.; Liu-Chen, L.-Y.; Ma, Z.; Lee, D. Y. W.; Carlezon, W. A.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2761–2765.
15. Lee, D. Y. W.; Karnati, V. V. R.; He, M.; Liu-Chen, L.-Y.; Kondaveti, L.; Ma, Z.; Wang, Y.; Chen, Y.; Beguin, C.; Carlezon, W. A.; Cohen, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3744–3747.
16. Lee, D. Y. W.; He, M.; Kondaveti, L.; Liu-Chen, L.-Y.; Ma, Z.; Wang, Y.; Chen, Y.; Li, J.-G.; Beguin, C.; Carlezon, W. A.; Cohen, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4169–4173.
17. Harding, W. W.; Tidgewell, K.; Byrd, N.; Cobb, H.; Dersch, C. M.; Butelman, E. R.; Rothman, R. B.; Prisinzano, T. E. *J. Med. Chem.* **2005**, *48*, 4765–4771.
18. Munro, T. A.; Goetchius, G. W.; Roth, B. L.; Vortherms, T. A.; Rizzacasa, M. A. *J. Org. Chem.* **2005**, *70*, 10057–10061.
19. Harding, W. W.; Schmidt, M.; Tidgewell, K.; Kannan, P.; Holden, K. G.; Dersch, C. M.; Rothman, R. B.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3170–3174.
20. Beguin, C.; Richards, M. R.; Li, J.-G.; Wang, Y.; Xu, W.; Liu-Chen, L.-Y.; Carlezon, W. A.; Cohen, B. M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4679–4685.
21. Lee, D. Y. W.; He, M.; Liu-Chen, L.-Y.; Wang, Y.; Li, J.-G.; Xu, W.; Ma, Z.; Carlezon, W. A.; Cohen, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5498–5502.
22. 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.
23. 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* http://bjoc.beilstein-journals.org/content/pdf/1860-5397-3-1.pdf.
24. Bikbulatov, R. V.; Yan, F.; Roth, B. L.; Zjawiony, J. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2229–2232.
25. Holden, K. G.; Kidgewell, K.; Marquam, A.; Rothman, R. B.; Navarro, H.; Prisinzano, T. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6111–6115.
26. Bikbulatov, R. V.; Stewart, J.; Jin, W.; Yan, F.; Roth, B. L.; Ferreiraa, D.; Zjawiony, J. K. *Tetrhedron Lett.* **2008**, *49*, 937–940.
27. Ma, Z.; Lee, D. Y. W. *Tetrhedron Lett.* **2007**, *48*, 5461–5464.
28. *Synthesis of* **4a**. To a solution of **2c** (12 mg, 31 μmol) in CH_2Cl_2 (3 ml) was added manganese dioxide (50 mg, 575 μmol), and the suspension was stirred at room temperature for 3 h. The solution was filtered and evaporated in vacuo. The residue was purified by silica gel column [CH_2Cl_2/AcOEt (10:1)] to give **4a** (6.2 mg, yield 52%) and **5** (2.5 mg, yield 21%). Data for **4a**: ^{1}H and ^{13}C NMR data, see Tables 1 and 2; EI-MS *m*/*z* 386 (M^+). Data for **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (1H, br s, H-16), 7.43 (1H, br s, H-15), 6.41 (1H, br s, H-14), 6.38 (1H, s, H-3), 5.61 (1H, dd, $J = 11.7$ and 5.4 Hz, H-12), 4.33 (1H, d, $J = 3.3$ Hz, H-1), 3.84 (3H, s, $COOCH_3$), 2.54 (1H, br s, OH), 2.52 (1H, dd, $J = 12.6$ and 5.1 Hz, H-11a), 2.12–2.32 (3H, m, H-6a, H-7a, H-8), 1.70–1.94 (3H, m, H-7b, H-10, H-11b), 1.73 (3H, s, H-19), 1.53 (3H, s, H-20), 1.34 (1H, m, H-6b); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.9 (C-2), 171.4 (C-17), 166.4 (C-18), 162.3 (C-4), 143.9 (C-15), 139.4 (C-16), 127.1 (C-3), 125.4 (C-13), 108.3 (C-14), 71.8 (C-12), 70.1 (C-1), 54.0 (C-10), 52.5 (C-8), 52.0 ($COOCH_3$), 43.2 (C-11), 38.0 (C-5), 37.3 (C-9), 35.1 (C-6), 23.3 (C-19), 18.2 (C-7), 16.8 (C-20); EI-MS *m*/*z* 388 (M^+).
29. Munro, T. A. The Chemistry of *Salvia divinorum*. Ph.D. Thesis, University of Melbourne, Victoria, Australia, 2006; p 212. [http://eprints.infodiv.unimelb.edu.au/archive/00002327].
30. Giner, J. L.; Kiemle, D. J.; Kutrzeba, L.; Zjawiony, J. *Magn. Reson. Chem.* **2007**, *45*, 351–354.
31. The quaternary carbon at C-17 and the carbonyl carbon of the acetyl group in **3** should be reassigned as δ 170.9 and δ 169.7, respectively.