Neoclerodane Diterpenes as a Novel Scaffold for *μ* Opioid Receptor Ligands[†]

Wayne W. Harding,[‡] Kevin Tidgewell,[‡] Nathan Byrd,[‡] Howard Cobb,[‡] Christina M. Dersch,[§]
Eduardo R. Butelman,[||] Richard B. Rothman,[§] and Thomas E. Prisinzano*,[‡]

*Division of Medicinal & Natural Products Chemistry, College of Pharmacy, The University of Iowa, Iowa City, Iowa 52242,
Clinical Psychopharmacology Section, IRP, NIDA, NIH, DHHS, Baltimore, Maryland 21224, and Laboratory on the Biology of
Addictive Diseases, Rockefeller University, New York, New York 10021*

Structural modification of salvinorin A, the active component of *Salvia divinorum*, has resulted
in the synthesis of novel neoclerodane diterpenes with opioid receptor affinity and activity.
We report in this study a nonnitrogenous neoclerodane diterpene with *μ* opioid receptor affinity
(**13**) that is an agonist at *μ* opioid receptors. This represents the identification of a novel
structural class of *μ* opioid receptor agonists.

Introduction

Intensive research of the last 2 decades has given us a better understanding of the structure, distribution, and pharmacology of the opioid receptors.[1] Three types of opioid receptors known as mu (*μ*), delta (*δ*), and kappa (*κ*) and receptor subtypes have been identified, and the mRNA encoding these receptors has been isolated.[2,3] There is substantial pharmacological evidence for subtypes of each.[4] It has become clear that each receptor mediates unique pharmacological responses[2,5] and is differentially distributed in the central nervous system and periphery.[2,6] Opioid receptors have recently been implicated in the actions of a widely available psychoactive plant, *Salvia divinorum*.[7]

S. divinorum is a plant from the Sage family that has been used in the traditional spiritual practices by the Mazatec Indians of Oaxaca, Mexico, to produce "mystical" or hallucinogenic experiences.[8] The plant has become widely available through the Internet and its recreational use by young adults and adolescents is increasing.[9] Recipes for leaf extracts, elixirs, and tinctures are easily found on the Internet.[10] Due to the recent increase in the popularity of this plant, the DEA has recently placed it on the list of drugs of concern.[9]

Currently, *S. divinorum* is unregulated in most countries and available throughout the world by purchasing it over the Internet. However, it is listed as a controlled substance in Denmark, Australia, and Italy. At present, U.S. laws for controlled substances do not ban the use of *S. divinorum* or its active components. This has resulted in various online botanical companies advertising and selling *S. divinorum* as a legal alternative to other regulated plant hallucinogens. It is predictable that its misuse will increase rapidly.

In the traditional spiritual practices of the Mazatec Indians, fresh *S. divinorum* leaves are chewed as a quid, eaten, or prepared as an infusion.[11] The resulting hallucinatory effects that last for up to 1 h are reported to be potent and intense.[11−13] The active ingredient isolated from the leaves of *S. divinorum* is salvinorin A (**1**) (Figure 1), a neoclerodane diterpene.[14,15] A smoked dose of 200−1000 *μ*g of **1** is effective in humans.[12,13] This potency is similar to the classical hallucinogens lysergic acid diethyl amide (LSD) and 4-bromo-2,5-dimethoxyphenylisopropylamine (DOB), which have effective human doses of 20−250 and 500−1000 *μ*g, respectively.[13] However, unlike LSD and DOB, **1** has no activity at the serotonin 5-HT$_{2A}$ receptor, the presumed molecular target for these compounds.[16−19] Rather, **1** was found to be very selective for *κ* receptors over *μ* and *δ* opioid receptors, as well as over a battery of other receptors.[7,20]

Salvinorin A is a unique opioid receptor ligand. It bears little structural similarity to other structural classes of nonpeptidic opioid receptor ligands, such as morphine (**2**), cyclazocine (**3**), fentanyl (**4**), and SNC 80 (**5**) (Figure 1).[21−23] In addition, **1** has little structural similarity to other *κ* agonists, such as U50,488H (**6**), and 3FLB (**7**). The common structural motif among all of these compounds is the presence of a basic amino group. Until recently it had been assumed that the presence of a positively charged nitrogen atom in opioid compounds represented an absolute requirement for their interaction with opioid receptors.[24] The general assumption was that this cationic amino charge on the opioid ligand would interact with the side chain carboxyl group of an aspartate residue located in TM III of the opioid receptor.[23,25,26] Given the lack of a basic nitrogen in **1**, this interaction is not likely.

The pharmacology of **1** appears to be different than other *κ* agonists.[27] Although **1** and **6** had similar potencies in stimulating [^{35}S]GTP*γ*S binding, **1** was about 40-fold less potent than **6** in promoting *κ* receptor internalization. In addition, **1** was not active in the acetic acid abdominal constriction test. The discrepancy between in vitro and in vivo results is thought to result from in vivo metabolism of **1** and possibly its effects on other pharmacological targets.[27]

Presently, few studies have been initiated to more fully understand the remarkable selectivity of **1** for *κ*

---

‡ The University of Iowa.
§ DHHS.
|| Rockefeller University.
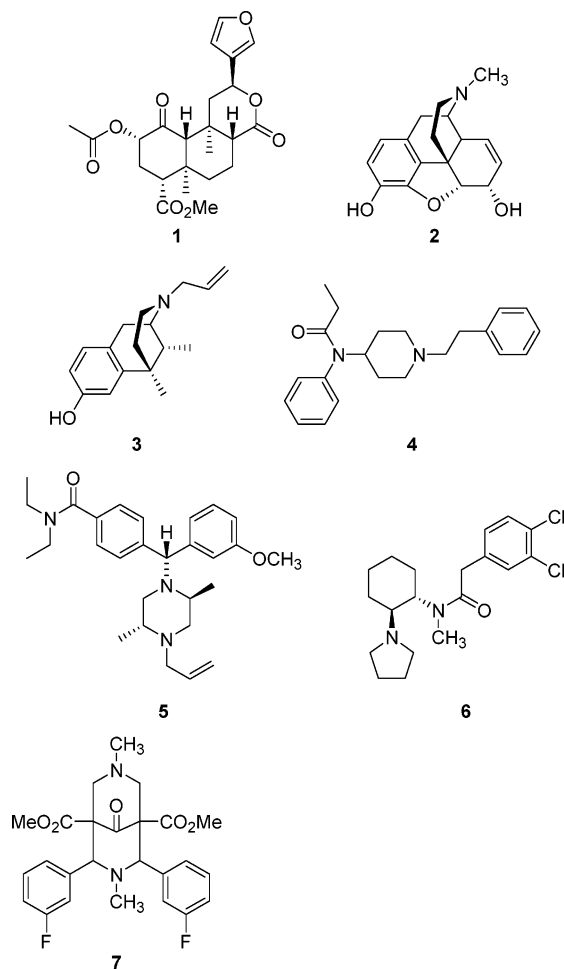
Figure 1. Structures of salvinorin A (**1**), morphine (**2**), cyclazocine (**3**), fentanyl (**4**), SNC 80 (**5**), U50,488H (**6**), and 3FLB (**7**).

opioid receptors. A recent report explored the role of the 2-acetyl group of **1** on affinity and selectivity for κ opioid receptors.[20] Interestingly, replacement of the 2-acetoxy group in **1** with other groups resulted in novel partial agonists at κ opioid receptors.[20] In an effort to further explore this phenomenon, we sought to make additional structural modifications to the 2-position of **1** and determine their effects on opioid receptor affinity and activity. In addition, we also sought to probe the role of several stereocenters in the high affinity and selectivity of **1** for κ opioid receptors.

Chemistry

Recently, we described the synthesis of (*acetyl*-^{2}H$_3$)-salvinorin A from salvinorin A.[28] This compound was needed as an internal standard for the development of an LC−MS method to determine the concentration of **1** in biological fluids.[29] Using this recently described methodology, **1** was isolated from dried *S. divinorum* leaves.[14,15,28,30] Initially, we sought to prepare salvinorin B (**8a**)[15] from **1** using ammonolysis at 0 °C in MeOH (Scheme 1).[31] This method affords **8a** in low yield without the use of chromatography. However, this method leads to significant amounts of the C-8 epimer (**8b**). An alternate method using Na$_2$CO$_3$ in MeOH afforded **8a** in higher yield and produced significantly less **8b**.[28] The reaction of **8a** with the appropriate

Scheme 1[a]
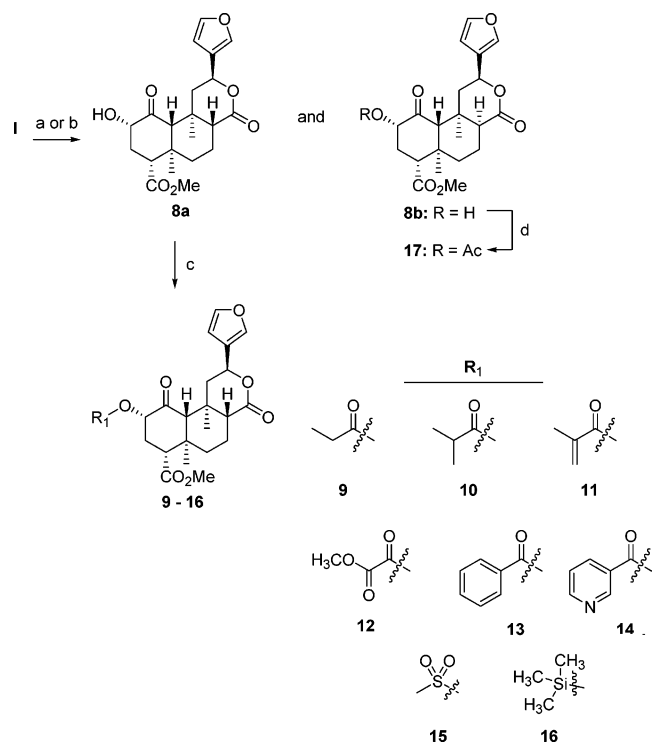
[a] Reagents and conditions: (a) NH$_3$, MeOH, 0 °C; (b) Na$_2$CO$_3$, MeOH; (c) appropriate anhydride or acid chloride, DMAP, CH$_2$Cl$_2$; (d) acetic anhydride, DMAP, CH$_2$Cl$_2$.

Scheme 2[a]
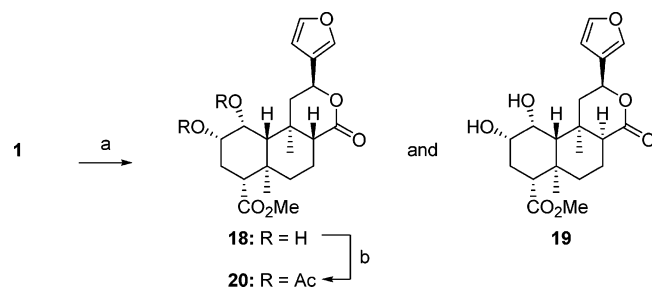
[a] Reagents and conditions: (a) NaBH$_4$, *i*-PrOH, 60 °C; (b) Ac$_2$O, DMAP, NEt$_3$.

anhydride or acid halide and a catalytic amount of DMAP in CH$_2$Cl$_2$ gave analogues **9**−**16** in 26−98% yield. Reacetylation of **8b** using acetic anhydride as previously described gave **17**, the C-8 epimer of **1**.[32]

Additional chemistry associated with **1** is described in Schemes 2 and 3. Reduction of **8a** using sodium borohydride in 2-propanol at 60 °C gave a mixture of diol **18**[15] and its C-8 epimer **19**[33] (Scheme 2). These compounds were readily separated using column chromatography eluting with a mixture of EtOAc/*n*-hexanes. Treatment of diol **18** with an excess of acetic anhydride and a catalytic amount of DMAP in NEt$_3$ afforded diacetate **20**.[33] This method afforded diacetate **20** in one synthetic step rather than the two steps previously described by Valdés et al. The reaction of **8a** with trichloroacetonitrile and diazobicycloundecene at 0 °C afforded trichloroacetimidate **21** in low yield (Scheme 3).[34] Finally, reaction of **8a** with phenylisocyanate and allylisocyanate in the presence of trimethylsilyl chloride in CH$_2$Cl$_2$ gave carbamates **22** and **23**, respectively.[35]

Scheme 3[a]
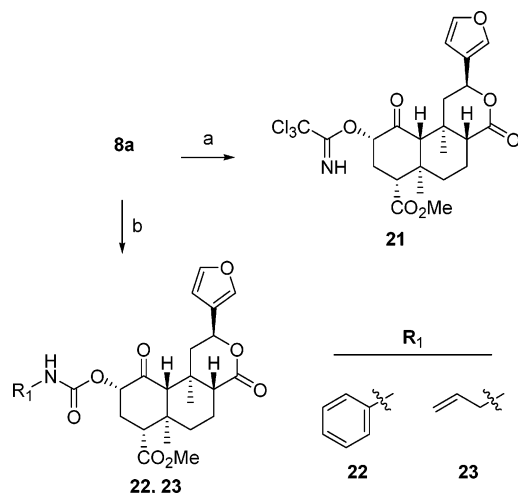
[a] Reagents and conditions: (a) trichloroacetonitrile, DBU, ClCH$_2$CH$_2$Cl, 0 °C; (b) appropriate isocyanate, TMSCl, CH$_2$Cl$_2$.

Table 1. Binding Affinities of Salvinorin A Analogues at Opioid Receptors Using [^{125}I]IOXY as Radioligand[43,44]

| compd | $K_i \pm$ SD, nM | | | selectivity | |
	μ	δ	κ	μ/κ	δ/κ
1	>1000[a]	5790 ± 980	1.9 ± 0.2	ND[b]	3050
9	>1000[a]	6690 ± 870	1.8 ± 0.1	ND	2730
10	2980 ± 110	>10000	19 ± 2	196	ND
11	260 ± 6	8880 ± 390	42 ± 1	7	210
12	>10000	>10000	430 ± 10	>30	>30
13	12 ± 1	1170 ± 60	90 ± 2	0.13	12
14	73 ± 2	4820 ± 300	1930 ± 50	0.04	3
15	6820 ± 660	>10000	2.3 ± 0.1	2750	>4000
16	>10000	>10000	1610 ± 120	>7	>7
17	>10000	>10000	38 ± 2	>33	>33
18	5740 ± 210	>10000	3190 ± 150	2	>3
19	>10000	>10000	>10000	ND	ND
20	>10000	>10000	650 ± 30	>15	>15
21	>10000	6470 ± 310	64 ± 2	>150	95
22	16 ± 1	230 ± 10	93 ± 3	0.2	2
23	640 ± 30	6460 ± 390	120 ± 4	5	55

[a] Partial inhibitor. [b] Not determined.

Results and Discussion

Newly synthesized compounds **10–16** and **21–23** as well as previously assayed compounds **1**, **9**, and **17–20** were then evaluated for affinity at opioid receptors using methodology previously described (Table 1).[36] These analogues were prepared to give insight as to the nature of the high affinity and selectivity of **1** for κ receptors. As shown previously, **1** was found to have high affinity ($K_i = 1.9$ nM) for κ receptors and to have low affinity for δ receptors ($K_i > 10\,000$).[20] Interestingly, **1** was a partial inhibitor at μ receptors.

Initially, propionyl derivative **9**[20] was prepared to probe the effects of an additional methyl group on opioid receptor affinity and selectivity. This also allowed an avenue to compare our results with previously reported data. Propionate **9** had similar affinity compared to **1** at κ receptors ($K_i = 1.8$ nM vs $K_i = 1.9$ nM). To further explore the role of the 2-position on the affinity and selectivity of **1** for κ opioid receptors, we made additional structural modifications. The addition of a methyl group (**10**) reduced affinity 10-fold at κ receptors compared to **9** ($K_i = 19$ nM vs $K_i = 1.8$ nM). Introduction of an alkene (**11**) reduced affinity 3-fold for κ receptors compared to **10** ($K_i = 42$ nM vs $K_i = 19$ nM). Interestingly, this

modification led to an 11-fold increase in affinity at μ receptors compared to **10** ($K_i = 260$ nM vs $K_i = 2,980$ nM). The replacement of the 2-methylacryloyl group with a methyl glyoxyl group (**12**) resulted in a 10-fold loss of affinity at κ receptors compared to **11** ($K_i = 430$ nM vs $K_i = 42$ nM). In addition, this change produced a loss of affinity for μ receptors ($K_i > 10\,000$ nM).

To further explore the role of the size of the 2-position substituent, benzoate **13** and nicotinate **14** were synthesized. Introduction of the benzoyl group (**13**) resulted in a 47-fold loss of affinity at κ receptors compared to **1** ($K_i = 90$ nM vs $K_i = 1.9$ nM). Surprisingly, this modification resulted in a 25-fold increase in affinity at μ receptors compared to **1** ($K_i = 12$ nM vs $K_i > 1000$ nM) and a 5-fold increase in affinity at δ receptors compared to **1** ($K_i = 1170$ nM vs $K_i = 5790$ nM). This represented to the best of our knowledge the first neoclerodane diterpene that binds selectively to the μ opioid receptor. Replacement of the benzoyl group with a nicotinoyl group (**14**) resulted in a 6-fold decrease in affinity at μ receptors compared to **13** ($K_i = 73$ nM vs $K_i = 12$ nM) and a 20-fold loss of affinity for κ receptors ($K_i = 1930$ nM vs $K_i = 90$ nM).

In an effort to gain more information as to the structure–activity relationships of **1**, we probed additional structural changes. Bioisosteric replacement of the acetyl group with a mesylate group, i.e., **15**, resulted in a compound with similar affinity compared to **1** ($K_i = 2.3$ nM vs $K_i = 1.9$ nM). The replacement of the acetyl group with a trimethylsilyl group (**16**) resulted in an almost 850-fold loss in affinity at κ receptors compared to **1** ($K_i = 1610$ nM vs $K_i = 1.9$ nM). Inversion of stereochemistry at the C-8 position (**17**) resulted in a 17-fold loss in affinity at κ receptors compared to **1** ($K_i = 38$ nM vs $K_i = 1.9$ nM). Diol **18** was found to have low affinity at μ and κ receptors ($K_i = 5740$ nM and $K_i = 3190$ nM), whereas **19** was found to have no affinity for any opioid receptors ($K_i > 10\,000$ nM). Replacement of the 1-position carbonyl with an α-acetoxy group (**20**) resulted in a 370-fold decrease in affinity at κ receptors compared to **1** ($K_i = 650$ nM vs $K_i = 1.9$ nM). Substitution of a trichloroacetimidate (**21**) resulted in a 34-fold decrease in affinity for κ receptors compared to **1** ($K_i = 64$ nM vs $K_i = 1.9$ nM). This modification, however, had little effect on affinity for δ receptors ($K_i = 6470$ nM vs $K_i = 5790$ nM). The introduction of a phenylcarbamoyl group (**22**) decreased affinity for κ receptors 49-fold compared to **1** ($K_i = 93$ nM vs $K_i = 1.9$ nM). However, this change resulted in an increase in affinity for μ receptors ($K_i = 16$ nM). It would appear, on the basis of the affinities of **13**, **14**, and **22** for μ receptors, that the introduction of an aromatic moiety in the 2-position increases μ affinity. Compound **22** had the highest affinity for δ receptors of the series ($K_i = 230$ nM). Finally, the presence of an allylcarbamoyl group in **23** resulted in a 63-fold decrease in affinity at κ receptors compared to **1** ($K_i = 120$ nM vs $K_i = 1.9$ nM).

To further explore these developments, **1**, **9**, **10**, **13**, **14**, **15**, and **22** were evaluated for functional activity using a [^{35}S]GTPγS assay (Table 2).[36] As expected, **1** was found to be an agonist at κ receptors (EC$_{50}$ = 40 nM, E_{max} = 120% relative to U50,488H). Interestingly, propionate **9**, isobutyrate **10**, mesylate **15**, and carbamate **22** were also found to be agonists (E_{max} = 110, 105,

Table 2. Results from [^{35}S]GTPγS Functional Assay Carried out in Stably Transfected CHO Cells Containing DNA for Human μ, δ, and κ Receptors

	μ		δ		κ	
	EC$_{50}$ $\pm$ SD		EC$_{50}$ $\pm$ SD		EC$_{50}$ $\pm$ SD	
compd	nM	$E_{max}{}^a$	nM	$E_{max}{}^a$	nM	$E_{max}{}^a$
1	ND^b	ND	ND	ND	40 $\pm$ 10	120 $\pm$ 2
9	ND	ND	ND	ND	140 $\pm$ 20	110 $\pm$ 2
10	ND	ND	ND	ND	360 $\pm$ 50	105 $\pm$ 3
13	500 $\pm$ 140	130 $\pm$ 4	ND	ND	1320 $\pm$ 150	140 $\pm$ 2
14	2100 $\pm$ 300	110 $\pm$ 5	ND	ND	5740 $\pm$ 890	76 $\pm$ 4
15	ND	ND	ND	ND	30 $\pm$ 5	112 $\pm$ 4
22	590 $\pm$ 50	92 $\pm$ 2	2530 $\pm$ 380	82 $\pm$ 3	480 $\pm$ 60	100 $\pm$ 3

^{a} E_{max} is the percentage which compound stimulates binding compared to DAMGO (10 μM) at μ, SNC80 (500 nM) at δ, and (−)-U50,488 (500 nM) at κ receptors, respectively. ^{b} Not determined.

Table 3. Agonist Activity of **1** in Antinociceptive Assays in the Mouse Following Subcutaneous Administration

	ED$_{50}$ (mg/kg)		
compd	PPQ^a	TF^b	HP^c
1	0.59 (0.024−1.43)	1.98 (1.02−3.82)	inactive at 1, 28% at 10, and inactive at 30
2^d	0.23	5.8	0.8
enadoline^e	0.0015 (0.0004−0.006)	0.015 (0.003−0.059)	0.01 (0.004−0.04)

^{a} PPQ = *p*-phenylquinone writhing test. ^{b} TF = tail flick test. ^{c} HP = hot plate test. ^{d} Taken from ref 45. ^{e} Taken from ref 40.

112, and 103, respectively) at κ receptors. However, **9** and **10** were less potent than **1** (EC$_{50}$ = 140 nM and EC$_{50}$ = 360 nM vs EC$_{50}$ = 40 nM). Mesylate **15** was found to be more potent than **1** (EC$_{50}$ = 30 nM vs EC$_{50}$ = 40 nM). Benzoate **13** was found to be 30-fold less potent as a κ agonist compared to **1** (EC$_{50}$ = 1320 nM vs EC$_{50}$ = 40 nM) and to have no agonist activity at δ receptors. Surprisingly, **13** was found to be an agonist at μ receptors (EC$_{50}$ = 500 nM and E_{max} = 130%). This represents to the best of our knowledge the first example of a nonnitrogenous μ agonist. This also identifies a new structural class of μ opioid receptor ligands for further investigation. Similarly, **14** and **22** were also found to be μ agonists, but these are not as potent as **13** (EC$_{50}$ = 2100 nM and EC$_{50}$ = 590 nM vs EC$_{50}$ = 500 nM).

Compound **1** was further evaluated for its in vivo opioid receptor activity in mice using three assays, *p*-phenylquinone (PPQ) writhing, tail-flick (TF), and hot-plate (HP) (Table 3).[37-39] In the TF and PPQ tests, potent opioid agonist activity was evident. The ED$_{50}$ value in the TF and PPQ tests were 1.98 and 0.59 mg/kg sc, respectively. Interestingly, **1** was more potent than **2** in the TF but less potent in the PPQ test. However, **1** was less potent than the κ agonist enadoline.[40] Curiously, significant HP activity was not seen.

A recent report has shown that **1** produces a discriminative stimulus effect similar to the high efficacy κ agonist U69,593 in nonhuman primates.[41] In an effort to further understand the in vivo pharmacology of these derivatives, propionate **9** was evaluated for behavioral effects in nonhuman primates in a pilot study. Preliminary results indicate that **9** acts behaviorally as a partial κ agonist. Propionate **9** generalized to U69,593 in only one of two rhesus monkeys tested, up to the highest dose that could be administered (0.1 mg/kg sc).

Conclusions

Various neoclerodane diterpenes have been prepared in several steps from salvinorin A (**1**) isolated from the dried leaves of *Salvia divinorum*. Structure−activity relationship studies have shown that a C-8 hydrogen in the β position is favored over the α position. Intro-

duction of an aromatic group into the 2 position results in increased μ opioid receptor affinity. Propionate **9** and mesylate **15** were found to be selective κ agonists. Benzoate **13** was identified as the first nonnitrogenous μ agonist identified to date. The antinociceptive activity of **1** and **13** are currently under investigation and will be presented in due course.

Experimental Section

Unless otherwise indicated, all reagents were purchased from commercial suppliers and are used without further purification. All melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer using CDCl$_3$ as solvent, δ values are reported in ppm (TMS as internal standard), and ^{1}H resonance coupling constants, J, are reported in hertz. Thin-layer chromatography (TLC) was performed on 0.25 mm plates Analtech GHLF silica gel plates using *n*-hexanes/EtOAc, 1:1 as the solvent system. Spots on TLC were visualized with vanillin/H$_2$SO$_4$ in ethanol. Column chromatography was performed with silica gel (32−63 μm particle size) from Bodman Industries (Atlanta, GA). Elemental analyses were performed by Atlantic Microlabs, Norcross, GA and were within ±0.4% of the theoretical values. No attempt was made to optimize yields reported. Absolute stereochemistry has been assigned on the basis of comparison with previously reported data.[42]

Ammonolysis of 1. A mixture of NH$_3$ (6 mL of a 7 N solution in MeOH) and **1** (0.4 g, 1.12 mmol) in absolute MeOH (100 mL) was stirred at room-temperature overnight. The resulting precipitate was collected by filtration and washed with cold *n*-hexanes (250 mL) and dried to afford 0.2 g of salvinorin B (**8a**) as a white solid, mp 211−214 °C (lit.[15] mp 213−216 °C). The combined filtrate was evaporated to dryness under reduced pressure and the residue was subjected to column chromatography. Eluting in gradient fashion (20% EtOAc/*n*-hexanes to 60% EtOAc/*n*-hexanes) afforded **8a** (0.06 g) and **8b** (0.06 g) as an oil.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-Hydroxy-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho-[2,1-c]pyran-7-carboxylic Acid Methyl Ester (8b). ^{1}H NMR (CDCl$_3$): δ 1.18 (3H, s, H-19), 1.47 (3H, s, H-20), 1.59−1.66 (3H, m, H-7α, β and H-11β), 1.84 (1H, ddd, J = 3.0, 3.0, 9.9 Hz, H-6α), 2.11 (1H, dd, J = 2.4, 10.8 Hz, H-8), 2.21 (1H, s, H-10), 2.26 (1H, m, H-6β), 2.47 (2H, m, H-3 α, β), 2.55 (1H, dd, J = 5.1, 13.5 Hz, H-11 α), 2.84 (1H, dd, J = 6.9, 9.9 Hz, H-4), 3.63 (1H, d, J = 3.3 Hz, OH), 3.75 (3H, s, CO$_2$CH_3), 4.13

(1H, ddd, J = 3.2, 7.5, 11.2 Hz, H-2), 5.28 (1H, d, J = 10.5 Hz, H-12), 6.39 (1H, dd, J = 0.9, 1.8 Hz, H-14), 7.40 (1H, dd, J = 1.5, 1.8 Hz, H-15), 7.42 (1H, dd, J = 0.9, 1.5 Hz, H-16).

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(Propionyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-7-carboxylic Acid Methyl Ester (9). A solution of **8a** (0.05 g, 0.13 mmol), propionic anhydride (0.09 g, 0.66 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. Absolute MeOH (15 mL) was added and the solvent was removed under reduced pressure. CH_2Cl_2 (25 mL) was added to the residue and the solution was washed with 10% HCl (3 × 20 mL) and saturated NaCl (3 × 20 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded 0.04 g (78%) of **9** as a white solid, mp 217−221 °C. ^{1}H NMR (CDCl$_3$): δ 1.12 (3H, s, H-19), 1.18 (3H, t, J = 7.5 Hz, CH_3CH$_2$CO$_2$), 1.46 (3H, s, H-20), 1.47−1.70 (4H, m, H-6β, H-7α,β and H-11β), 1.80 (1H, ddd, J = 3.0, 3.0, 9.9 Hz, H-6α), 2.07 (1H, dd, J = 3.0, 11.1 Hz, H-8), 2.17 (1H, s, H-10), 2.30 (2H, q, J = 7.5 Hz, CH$_3$CH_2CO$_2$), 2.47 (2H, m, H-3α,β), 2.53 (1H, dd, J = 5.4, 13.2 Hz, H-11α), 2.76 (1H, dd, J = 8.1, 8.7 Hz, H-4), 3.73 (3H, s, CO$_2$CH_3), 5.16 (1H, dd, J = 9.9, 10.5 Hz, H-2), 5.53 (1H, dd, J = 5.4, 11.7 Hz, H-12), 6.38 (1H, dd, J = 0.6, 1.8 Hz, H-14), 7.39 (1H, dd, J = 1.5, 1.8 Hz, H-15), 7.41 (1H, dd, J = 0.6, 1.5 Hz, H-16). Anal. (C$_{24}$H$_{30}$O$_{10}$·0.25H$_2$O): C, H, O.

(2S,4aR,6aR,7R,9S,10aS,10bR)-9-(Isobutyryloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-7-carboxylic Acid Methyl Ester (10). **10** was synthesized as described for **9** from **8a** using isobutyryl chloride to afford 0.04 g (62%) of **10** as a white solid, mp 209−211 °C. ^{1}H NMR (CDCl$_3$): δ 1.13 (3H, s, H-19), 1.24 (3H, d, J = 6.9 Hz, CH$_3$CH(CH$_3$)CO$_2$), 1.26 (3H, d, J = 6.9 Hz CH$_3$CH(CH_3)CO$_2$), 1.46 (3H, s, H-20), 1.52−1.78 (3H, m, H-7α,β and H-11β), 1.80 (1H, ddd, J = 3.0, 3.0, 9.9 Hz, H-6α), 2.12 (2H, m, H-3α and H-8), 2.20 (1H, s, H-10), 2.25−2.35 (2H, m, H-3β and H-6β), 2.51 (1H, dd, J = 5.1, 13.2 Hz, H-11α), 2.68 (1H, sept, J = 6.9 Hz, CH$_3$CH(CH$_3$)CO$_2$), 2.77 (1H, dd, J = 8.4, 8.4 Hz, H-4), 3.74 (3H, s, CO$_2$CH_3), 5.15 (1H, dd, J = 9.9, 10.3 Hz, H-2), 5.52 (1H, dd, J = 5.3, 11.9 Hz, H-12), 6.39 (1H, dd, J = 0.9, 1.5 Hz, H-14), 7.40 (1H, dd, J = 1.5, 1.5 Hz, H-15), 7.42 (1H, dd, J = 0.9, 1.5 Hz, H-16). Anal. (C$_{25}$H$_{32}$O$_8$·0.25H$_2$O): C, H, O.

(2S,4aR,6aR,7R,9S,10aS,10bR)-9-(2-Methylacryloyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-7-carboxylic Acid Methyl Ester (11). **11** was synthesized as described for **9** from **8a** using methacrylic anhydride to afford 0.03 g (56%) of **11** as a white solid, mp 196−199 °C. ^{1}H NMR (CDCl$_3$): δ 1.15 (3H, s, H-19), 1.47 (3H, s, H-20), 1.50−1.75 (4H, m, H-6β, H-7α,β and H-11β), 1.82 (1H, ddd, J = 3.0, 3.0, 10.2 Hz, H-6α), 1.99 (3H, s, CH$_2$=C(CH_3)CO$_2$), 2.04−2.21 (2H, m, H-3α and H-8), 2.23 (1H, s, H-10), 2.40 (1H, m, H-3β), 2.53 (1H, dd, J = 5.1, 13.5 Hz, H-11α), 2.80 (1H, dd, J = 8.4, 8.4 Hz, H-4), 3.75 (3H, s, CO$_2$CH_3), 5.22 (1H, dd, J = 9.9, 9.9 Hz, H-2), 5.53 (1H, dd, J = 5.1, 11.7 Hz, H-12), 5.69 (1H, d, J = 1.5 Hz, H-CH=C(CH$_3$)CO$_2$), 6.24 (1H, d, J = 1.5 Hz, H-CH=C(CH$_3$)CO$_2$), 6.39 (1H, dd, J = 0.9, 1.5 Hz, H-14), 7.41 (1H, dd, J = 1.5, 1.5 Hz, H-15), 7.42 (1H, dd, J = 0.9, 1.5 Hz, H-16). Anal. (C$_{25}$H$_{30}$O$_8$·0.25H$_2$O): C, H, O.

Oxalic Acid (2S,4aR,6aR,7R,9S,10aS,10bR)-7-Carbomethoxy-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-9-yl Methyl Diester (12). **12** was synthesized as described for **9** from **8a** using methyl chlorooxoacetate to afford (26%) of **12** as a white solid, mp 241−244 °C. ^{1}H NMR (CDCl$_3$): δ 1.16 (3H, s, H-19), 1.47 (3H, s, H-20), 1.56−1.81 (4H, m, H-3α, H-6β, H-7β and H-11β), 1.84 (1H, ddd, J = 3.0, 3.0, 10.1 Hz, H-6α), 2.11 (1H, dd, J = 3.0, 11.3 Hz, H-8), 2.19 (1H, m, H-7α), 2.22 (1H, s, H-10), 2.46 (1H, dd, J = 4.5, 8.1 Hz, H-3β), 2.52 (1H, dd, J = 5.6, 12.8 Hz, H-11α), 2.79 (1H, dd, J = 5.1, 12.0 Hz, H-4), 3.76 (3H, s, CO$_2$CH_3), 3.96 (3H, s, COCO$_2$CH_3), 5.26 (1H, dd, J = 8.5, 11.9 Hz, H-2), 5.54 (1H, dd, J = 5.1, 11.7 Hz, H-12), 6.39 (1H, dd, J = 0.9, 1.5 Hz, H-14), 7.42 (2H, m, H-15 and H-16). Anal. (C$_{24}$H$_{28}$O$_{10}$·0.25H$_2$O): C, H.

(2S,4aR,6aR,7R,9S,10aS,10bR)-9-(Benzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho-[2,1-c]pyran-7-carboxylic Acid Methyl Ester (13). **13** was synthesized as described for **9** from **8a** using benzoyl chloride to afforded 0.06 g (98%) of **13** as a white solid, mp 165−170 °C. ^{1}H NMR (CDCl$_3$): δ 1.18 (3H, s, H-19), 1.47 (3H, s, H-20), 1.50−1.75 (4H, m, H-6β, H-7α,β and H-11β), 1.84 (1H, ddd, J = 3.0, 3.0, 9.9 Hz, H-6α), 2.11 (1H, dd, J = 2.4, 10.8 Hz, H-8), 2.26 (1H, s, H-10), 2.47 (2H, m, H-3α,β), 2.55 (1H, dd, J = 5.1, 13.5 Hz, H-11α), 2.84 (1H, dd, J = 6.9, 9.9 Hz, H-4), 3.75 (3H, s, CO$_2$CH_3), 5.40 (1H, dd, J = 9.6, 10.5 Hz, H-2), 5.52 (1H, dd, J = 2.1, 11.7 Hz, H-12), 6.39 (1H, dd, J = 0.9, 1.8 Hz, H-14), 7.40 (1H, dd, J = 1.5, 1.8 Hz, H-15), 7.42 (1H, dd, J = 0.9, 1.5 Hz, H-16), 7.48 (2H, dt, J = 7.2, 7.5 Hz, Ar-*m*-H), 7.60 (1H, tt, J = 1.2, 7.5 Hz, Ar-*p*-H), 8.09 (2H, dt, J = 1.2, 7.2 Hz, Ar-*o*-H). Anal. (C$_{28}$H$_{30}$O$_8$): C, H.

Nicotinic Acid (2S,4aR,6aR,7R,9S,10aS,10bR)-7-Carbomethoxy-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-9-yl Ester (14). **14** was synthesized as described for **13** from **8a** using nicotinoyl chloride hydrochloride to afford 0.03 (56%) of **14** as a white solid, mp 200−204 °C. ^{1}H NMR (CDCl$_3$): δ 1.18 (3H, s, H-19), 1.47 (3H, s, H-20), 1.50−1.72 (4H, m, H-6β, H-7α,β and H-11β), 1.84 (1H, ddd, J = 3.0, 3.0, 9.9 Hz, H-6α), 2.11 (1H, dd, J = 2.4, 10.5 Hz, H-8), 2.27 (1H, s, H-10), 2.49 (2H, m, H-3α,β), 2.54 (1H, dd, J = 5.1, 13.2 Hz, H-11α), 2.85 (1H, dd, J = 6.2, 10.7 Hz, H-4), 3.76 (3H, s, CO$_2$CH_3), 5.41 (1H, dd, J = 10.1, 10.1 Hz, H-2), 5.53 (1H, dd, J = 5.1, 11.7 Hz, H-12), 6.39 (1H, d, J = 0.9 Hz, H-14), 7.42 (3H, m, H-15, H-16 and Ar−H), 8.34 (1H, ddd, J = 1.5, 3.9, 7.8 Hz, Ar−H), 8.82 (1H, ddd, J = 1.8, 3.9 Hz, Ar−H), 9.27 (1H, d, J = 1.5 Hz, Ar−H). Anal. (C$_{27}$H$_{29}$NO$_8$·0.25H$_2$O): C, H, N.

(2S,4aR,6aR,7R,9S,10aS,10bR)-9-(Methanesulfonyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-7-carboxylic Acid Methyl Ester (15). A solution of **8a** (0.05 g, 0.13 mmol), methanesulfonyl chloride (1 mL, 12.9 mmol), and NEt$_3$ (2 mL, 14.3 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature overnight and then the mixture was washed with saturated NaHCO$_3$ (20 mL) and saturated NaCl (2 × 15 mL) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure. The resulting crude solid was purified by column chromatography (eluent EtOAc/*n*-hexanes) to afford 0.02 g (32%) of **15** as a white solid, mp 147−150 °C. ^{1}H NMR (CDCl$_3$): δ 1.14 (3H, s, H-19), 1.47 (3H, s, H-20), 1.50−1.70 (3H, m, H-7α,β and H-11β), 1.81 (1H, m, H-6α), 2.11 (1H, dd, J = 2.9, 11.3 Hz, H-8), 2.16 (1H, s, H-10), 2.19 (1H, m, H-6β), 2.42 (1H, dd, J = 13.2, 13.2 Hz, H-3α), 2.50 (1H, m, H-3β), 2.52 (1H, dd, J = 4.8, 13.2 Hz, H-11α), 2.75 (1H, dd, J = 3.6, 13.2 Hz, H-4), 3.25 (3H, s, CH_3SO$_2$), 3.74 (3H, s, CO$_2$CH_3), 5.07 (1H, dd, J = 8.0, 12.2 Hz, H-2), 5.55 (1H, dd, J = 5.1, 11.7 Hz, H-12), 6.41 (1H, dd, J = 0.9, 1.8 Hz, H-14), 7.42 (1H, dd, J = 1.8, 1.8 Hz, H-15), 7.45 (1H, br d). Anal. (C$_{22}$H$_{28}$O$_9$S): C, H, O.

(2S,4aR,6aR,7R,9S,10aS,10bR)-9-(Trimethylsilanyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]pyran-7-carboxylic Acid Methyl Ester (16). A solution of **8a** (0.08 g, 0.20 mmol), NEt$_3$ (0.1 mL, 0.72 mmol), and chlorotrimethylsilane (0.1 mL, 0.79 mmol) in CH_2Cl$_2$ (30 mL) was stirred at room temperature overnight. The mixture was washed with saturated NaHCO$_3$ (2 × 10 mL) and H$_2$O (50 mL) and dried (Na$_2$SO$_4$), and the solvent was removed under reduced pressure. The resulting crude solid was purified by column chromatography (eluent EtOAc/*n*-hexanes) to afford 0.06 g (68%) of **16** as a white solid, mp 197−200 °C. ^{1}H NMR (CDCl$_3$): δ 0.14 (9H, s, (CH_3)$_3$SiO), 1.11 (3H, s, H-19), 1.48 (3H, s, H-29), 1.50−1.73 (3H, m, H-7α,β and H-11β), 1.79 (1H, ddd, J = 3.0, 3.0, 10.5 Hz, H-6α), 2.03 (1H, dd, obscured, H-8), 2.06 (1H, s, H-10), 2.10−2.38 (3H, m, H-3α,β and H-6β), 2.57 (1H, dd, J = 5.1, 10.5 Hz, H-11α), 2.69 (1H, dd, J = 3.9, 12.9 Hz, H-4), 3.72 (3H, s, CO$_2$CH_3), 4.12 (1H, dd, J = 7.5, 11.7 Hz, H-2), 5.56 (1H, dd, J = 5.1, 11.4 Hz, H-12), 6.38 (1H, dd, J = 0.8, 1.7 Hz, H-14), 7.40 (1H, m, H-15), 7.42 (1H, m, H-16). Anal. (C$_{24}$H$_{34}$O$_7$Si): C, H.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10*R*,10a*S*,10b*R*)-9,10-Diacetoxy-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4-oxo-2*H*-naphtho-[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (20). A solution of **18**[15] (0.02 g, 0.05 mmol), acetic anhydride (2 mL, 21.2 mmol), NEt$_3$ (4 mL, 28.7 mmol), and a catalytic amount of DMAP was stirred at room temperature for 3 h. The solution was then poured into 2 N NaOH (20 mL) and the resulting mixture was extracted with CH$_2$Cl$_2$ (30 mL). The CH$_2$Cl$_2$ portion was washed with 2N HCl (10 mL) and H$_2$O (2 × 20 mL) and dried (Na$_2$SO$_4$). Removal of the solvent under reduced pressure afforded a brown oil that was purified by column chromatography (eluent ethyl acetate/*n*-hexanes) to afford 0.01 g (60%) of **20** as a colorless oil. ^{1}H NMR (CDCl$_3$): δ 1.19 (3H, s, H-19), 1.39 (3H, s, H-20), 1.58−1.90 (5H, m, H-6α,β, H-7α,β and H-11β), 1.99 (3H, s, C*H*$_3$CO$_2$), 2.01−2.13 (2H, m, H-8 and H-10), 2.15 (3H, s, C*H*$_3$CO$_2$), 2.20−2.38 (3H, m, H-3α,β and H-11α), 2.44 (1H, dd, *J* = 5.4, 13.2 Hz, H-4), 3.71 (3H, s, CO$_2$C*H*$_3$), 4.77 (1H, m, H-2), 5.47 (1H, dd, *J* = 5.6, 11.6 Hz, H-12), 5.68 (1H, br s, H-1), 6.43 (1H, dd, *J* = 0.8, 1.7 Hz, H-14), 7.42 (1H, m, H-15), 7.46 (1H, m, H-16). Anal. (C$_{25}$H$_{32}$O$_9$·0.25H$_2$O): C, H, O.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(2,2,2-Trichloroacetimidoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (21). A solution of **8a** (0.05 g, 0.13 mmol), trichloroacetonitrile (0.1 mL, 1.0 mmol), and 1,8-diazobicylo-[5.4.0]undec-7-ene (0.05 mL, 0.3 mmol) in dichloroethane (20 mL) was stirred at 0 °C for 24 h. The reaction mixture was then washed with saturated NaHCO$_3$ (10 mL) and H$_2$O (10 mL) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to give a crude oil. The oil was purified by column chromatography (eluent EtOAc/*n*-hexanes) to afford 0.02 g (37%) of **21** as a white solid, mp 120−123 °C. ^{1}H NMR (CDCl$_3$): δ 1.18 (3H, s, H-19), 1.50 (3H, s, H-20), 1.52−1.76 (4H, m, H-7α,β and H-11α,β), 1.85 (1H, ddd, *J* = 2.6, 2.6, 10.1 Hz, H-6α), 2.10 (1H, dd, *J* = 2.9, 11.6 Hz, H-8), 2.20 (1H, m, H-6β), 2.24 (1H, s, H-10), 2.35−2.58 (3H, m, H-2 and H-3α,β), 2.80 (1H, dd, *J* = 4.1, 12.5 Hz, H-4), 3.75 (3H, s, CO$_2$C*H*$_3$), 5.34 (1H, dd, *J* = 7.7, 12.2 Hz, H-12), 6.40 (1H, dd, *J* = 0.9, 1.5 Hz, H-14), 7.41 (1H, dd, *J* = 1.5, 1.5 Hz, H-15), 7.43 (1H, dd, *J* = 0.9, 1.5 Hz, H-16), 8.38 (1H, s, NH). Anal. (C$_{23}$H$_{26}$Cl$_3$NO$_7$·0.5H$_2$O): C, H, N.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Phenylcarbamoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (22). A solution of **8a** (0.06 g, 0.14 mmol), trimethylsilyl chloride (0.01 mL, 0.08 mmol), and phenylisocyanate (0.1 mL, 0.92 mmol) in CH$_2$Cl$_2$ was stirred at room temperature for 5 d. The reaction mixture was then washed with saturated NaHCO$_3$ (10 mL) and H$_2$O (10 mL) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to give a crude oil. The oil was purified by column chromatography (eluent EtOAc/*n*-hexanes) to afford 0.01 g (14%) of **22** as a clear oil. ^{1}H NMR (CDCl$_3$): δ 1.15 (3H, s, H-19), 1.48 (3H, s, H-20), 1.52−1.72 (3H, m, H-7α,β and H-11β), 1.82 (1H, ddd, *J* = 2.7, 2.7, 10.2 Hz, H-6α), 2.03−2.20 (1H, m, H-8), 2.22 (1H, s, H-10), 2.24−2.48 (2H, m, H-3α,β), 2.54 (1H, dd, *J* = 5.1, 13.5 Hz, H-4), 2.80 (1H, dd, *J* = 3.6, 13.2 Hz, H-11α), 3.75 (3H, s, CO$_2$C*H*$_3$), 5.21 (1H, dd, *J* = 7.8, 12.3 Hz, H-2), 5.54 (1H, dd, *J* = 5.7, 11.7 Hz, H-12), 6.40 (1H, m, H-14), 6.69 (1H, br s, NH), 6.87 (1H, br s, Ar−H), 7.12 (2H, m, Ar−H's), 7.28−7.45 (5H, m, H-14, H-15 and Ar−H's). Anal. (C$_{28}$H$_{31}$NO$_8$·1.25H$_2$O): C, H, N.

(2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Allylcarbamoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (23). 23 was synthesized as described for **22** from **8a** using allyl isocyanate to afford 0.01 g (17%) of **23** as a white solid, mp 196−199 °C. ^{1}H NMR (CDCl$_3$): δ 1.13 (3H, s, H-19), 1.48 (3H, s, H-20), 1.50−1.76 (4H, m, H-6β, H-7α,β and H-11β), 1.80 (1H, ddd, *J* = 2.7, 2.7, 9.9 Hz, H-6α), 2.10 (1H, dd, *J* = 3.1, 11.1 Hz, H-8), 2.19 (1H, s, H-10), 2.20−2.40 (2H, m, H-3α,β), 2.55 (1H, dd, *J* = 5.4, 13.5 Hz, H-4), 2.76 (1H, dd, *J* = 3.9, 13.2 Hz, H-11α), 3.74 (3H, s, CO$_2$C*H*$_3$), 3.84 (2H, dd, *J* = 5.4,

5.4 Hz, CH$_2$=CHC*H*$_2$NH), 4.98 (1H, t, *J* = 5.4 Hz, NH), 5.12 (1H, dd, *J* = 7.8, 12.3 Hz, H-2), 5.18 (1H, dd, *J* = 1.2, 10.2 Hz, *H*-CH=CHCH$_2$NH), 5.25 (1H, dd, *J* = 1.2, 17.1 Hz, *H*-CH=CHCH$_2$NH), 5.54 (1H, dd, *J* = 5.4, 11.4 Hz, H-12), 5.86 (1H, ddt, *J* = 5.4, 10.2, 17.1 Hz, CH$_2$=C*H*CH$_2$NH), 6.40 (1H, dd, *J* = 1.5, 1.8 Hz, H-14), 7.41 (1H, dd, *J* = 0.9, 1.5 Hz, h-15), 7.43 (1H, dd, *J* = 0.9, 1.5 Hz, H-16). Anal. (C$_{25}$H$_{31}$NO$_8$·0.75H$_2$O): C, H, N.

Supporting Information Available: Table of analysis data for **1** and **9**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Calderon, S. N.; Coop, A. SNC 80 and related delta opioid agonists. *Curr. Pharm. Des.* **2004**, *10*, 733−742.

(2) Mansour, A.; Fox, C. A.; Akil, H.; Watson, S. J. Opioid-Receptor mRNA Expression in the Rat CNS: Anatomical and Functional Implications. *Trends Neurosci.* **1995**, *18*, 22−29.

(3) Waldhoer, M.; Bartlett, S. E.; Whistler, J. L. Opioid receptors. *Annu. Rev. Biochem.* **2004**, *73*, 953−990.

(4) Reisine, T. Neurotransmitter Receptors V: Opiate Receptors. *Neuropharmacology* **1995**, *34*, 463−472.

(5) Goldstein, A.; Naidu, A. Multiple Opioid Receptors: Ligand Selectivity Profiles and Binding Site Signatures. *Mol. Pharmacol.* **1989**, *36*, 265−272.

(6) Bagnol, D.; Mansour, A.; Akil, H.; Watson, S. J. Cellular localization and distribution of the cloned mu and kappa opioid receptors in rat gastrointestinal tract. *Neuroscience* **1997**, *81*, 579−591.

(7) Roth, B. L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K. C.; Steinberg, S.; Ernsberger, P.; Rothman, R. B. Salvinorin A: A Potent Naturally Occurring Nonnitrogenous Kappa Opioid Selective Agonist. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11934−11939.

(8) Valdes, L. J., III; Diaz, J. L.; Paul, A. G. Ethnopharmacology of Ska-Maria-Pastora (Salvia, Divinorum, Epling and Jativa-M.). *J. Ethnopharmacol.* **1983**, *7*, 287−312.

(9) National, D. I. C. *Salvia divinorum*. In *Information Bulletin*; U.S. Department of Justice: Johnstown, PA, 2003.

(10) Giroud, C.; Felber, F.; Augsburger, M.; Horisberger, B.; Rivier, L.; Mangin, P. *Salvia divinorum*: An Hallucinogenic Mint Which Might Become a New Recreational Drug in Switzerland. *Forensic Sci. Int.* **2000**, *112*, 143−150.

(11) Valdes III, L. J. Salvia Divinorum and the Unique Diterpene Hallucinogen, Salvinorin (Divinorin) A. *J Psychoact. Drugs* **1994**, *26*, 277−283.

(12) Siebert, D. J. Salvia-Divinorum and Salvinorin-a−New Pharmacological Findings. *J. Ethnopharmacol.* **1994**, *43*, 53−56.

(13) Sheffler, D. J.; Roth, B. L. Salvinorin A: The 'Magic Mint' Hallucinogen Finds a Molecular Target in the Kappa Opioid Receptor. *Trends Pharmacol. Sci.* **2003**, *24*, 107−109.

(14) Ortega, A.; Blount, J. F.; Manchand, P. S. Salvinorin, a New Trans-Neoclerodane Diterpene from Salvia-Divinorum (Labiatae). *J. Chem. Soc., Perkin Trans. 1* **1982**, 2505−2508.

(15) Valdes, L. J., III; Butler, W. M.; Hatfield, G. M.; Paul, A. G.; Koreeda, M. Divinorin A, a Psychotropic Terpenoid, and Divinorin B from the Hallucinogenic Mexican Mint *Salvia divinorum*. *J. Org. Chem.* **1984**, *49*, 4716−4720.

(16) Glennon, R. A.; Titeler, M.; McKenney, J. D. Evidence for 5-HT$_2$ Involvement in the Mechanism of Action of Hallucinogenic Agents. *Life Sci.* **1984**, *35*, 2505−2511.

(17) Titeler, M.; Lyon, R. A.; Glennon, R. A. Radioligand Binding Evidence Implicates the Brain 5-HT2 Receptor as a Site of Action for LSD and Phenylisopropylamine Hallucinogens. *Psychopharmacology* **1988**, *94*, 213-216.

(18) Egan, C. T.; Herrick-Davis, K.; Miller, K.; Glennon, R. A.; Teitler, M. Agonist Activity of LSD and Lisuride at Cloned 5HT2A and 5HT2C Receptors. *Psychopharmacology* **1998**, *136*, 409−414.

(19) Nichols, D. E. Hallucinogens. *Pharmacol. Ther.* **2004**, *101*, 131−181.

(20) Chavkin, C.; Sud, S.; Jin, W.; Stewart, J.; Zjawiony, J. K.; Siebert, D. J.; Toth, B. A.; Hufeisen, S. J.; Roth, B. L. Salvinorin A, an Active Component of the Hallucinogenic Sage *Salvia divinorum* Is a Highly Efficacious κ-Opioid Receptor Agonist: Structural and Functional Considerations. *J. Pharmacol. Exp. Ther.* **2004**, *308*, 1197−1203.

(21) Kaczor, A.; Matosiuk, D. Non-peptide opioid receptor ligands−Recent advances. Part I−Agonists. *Curr. Med. Chem.* **2002**, *9*, 1567−1589.

(22) Kaczor, A.; Matosiuk, D. Non-peptide opioid receptor ligands−Recent advances. Part II−Antagonists. *Curr. Med. Chem.* **2002**, *9*, 1591−1603.

(23) Eguchi, M. Recent advances in selective opioid receptor agonists and antagonists. *Med. Res. Rev.* **2004**, *24*, 182−212.

(24) Rees, D. C.; Hunter, J. C. *Comprehensive Medicinal Chemistry*; Pergammon: New York, 1990; pp 805−846.

(25) Surratt, C.; Johnson, P.; Moriwaki, A.; Seidleck, B.; Blaschak, C.; Wang, J.; Uhl, G. μ Opiate receptor. Charged transmembrane domain amino acids are critical for agonist recognition and intrinsic activity. *J. Biol. Chem.* **1994**, *269*, 20548−20553.

(26) Lu, Y.; Weltrowska, G.; Lemieux, C.; Chung, N. N.; Schiller, P. W. Stereospecific Synthesis of (2S)-2-Methyl-3-(2′,6′-dimethyl-4′-hydroxyphenyl)propionic acid (Mdp) and its Incorporation into an Opioid Peptide. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 323−325.

(27) Wang, Y.; Tang, K.; Inan, S.; Siebert, D.; Holzgrabe, U.; Lee, D. Y.; Huang, P.; Li, J. G.; Cowan, A.; Liu-Chen, L. Y. Comparison of Pharmacological Activities of Three Distinct κ Ligands (Salvinorin A, TRK-820 and 3FLB) on κ Opioid Receptors in Vitro and Their Antipruritic and Antinociceptive Activities in Vivo. *J. Pharmacol. Exp. Ther.* **2005**, *312*, 220−230.

(28) Tidgewell, K.; Harding, W. W.; Schmidt, M.; Holden, K. G.; Murry, D. J.; Prisinzano, T. E. A facile method for the preparation of deuterium labeled salvinorin A: Synthesis of [2,2,2-²H₃]-salvinorin A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5099−5102.

(29) Schmidt, M. S.; Prisinzano, T. E.; Tidgewell, K.; Harding, W. W.; Butelman, E. R.; Kreek, M. J.; Murry, D. J. Determination of salvinorin A in body fluids by high proformance liquid chromatography−Atmospheric pressure chemical ionization. *J. Chromatogr. B* **2005**, *818*, 221−225.

(30) Munro, T. A.; Rizzacasa, M. A. Salvinorins D−F, New Neoclerodane Diterpenoids from *Salvia divinorum*, and an Improved Method for the Isolation of Salvinorin A. *J. Nat. Prod.* **2003**, *66*, 703−705.

(31) Valdes, L. J., III. Personal communication, 2003.

(32) Munro, T. A.; Rizzacasa, M. A.; Roth, B. L.; Toth, B. A.; Yan, F. Studies toward the Pharmacophore of Salvinorin A, a Potent kappa Opioid Receptor Agonist. *J. Med. Chem.* **2005**, *48*, 345−348.

(33) Valdes, L. J., III; Chang, H. M.; Visger, D. C.; Koreeda, M. Salvinorin C, a New Neoclerodane Diterpene from a Bioactive Fraction of the Hallucinogenic Mexican Mint *Salvia divinorum*. *Org. Lett.* **2001**, *3*, 3935−3937.

(34) Barton, D. H. R.; Fontana, G. The invention of radical reactions. Part XXXVII. A convenient radical synthesis of dialkyl diselenides from carboxylic acids. *Tetrahedron* **1996**, *52*, 11163−11176.

(35) Villhauer, E. B.; Brinkman, J. A.; Naderi, G. B.; Burkey, B. F.; Dunning, B. E.; Prasad, K.; Mangold, B. L.; Russell, M. E.; Hughes, T. E. 1-[[(3-hydroxy-1-adamantyl)amino]acetyl]-2-cyano-(S)-pyrrolidine: A potent, selective, and orally bioavailable dipeptidyl peptidase IV inhibitor with antihyperglycemic properties. *J. Med. Chem.* **2003**, *46*, 2774−2789.

(36) Xu, H.; Hashimoto, A.; Rice, K. C.; Jacobson, A. E.; Thomas, J. B.; Carroll, F. I.; Lai, J.; Rothman, R. B. Opioid peptide receptor studies. 14. Stereochemistry determines agonist efficacy and intrinsic efficacy in the [³⁵S]GTP-γ-S functional binding assay. *Synapse* **2001**, *39*, 64−69.

(37) Pearl, J.; Harris, L. S. Inhibition of writhing by narcotic antagonists. *J. Pharmacol. Exp. Ther.* **1966**, *154*, 319−323.

(38) Eddy, N. B.; Leimbach, D. Synthetic analgesics: II. Dithienyl-butenyl- and dithienylbutylamines. *J. Pharmacol. Exp. Ther.* **1953**, *107*, 385−393.

(39) Aceto, M. D.; Harris, L. S.; Bowman, E. R. Etorphines: μ-Opioid receptor-selective antinociception and low physical dependence capacity. *Eur. J. Pharmacol.* **1997**, *338*, 215−223.

(40) Husbands, S. M.; Neilan, C. L.; Broadbear, J.; Grundt, P.; Breeden, S.; Aceto, M. D.; Woods, J. H.; Lewis, J. W.; Traynor, J. R. BU74, a complex oripavine derivative with potent kappa opioid receptor agonism and delayed opioid antagonism. *Eur. J. Pharmacol.* **2005**, *509*, 117−125.

(41) Butelman, E. R.; Harris, T. J.; Kreek, M. J. The plant-derived hallucinogen, salvinorin A, produces kappa-opioid agonist-like discriminative effects in rhesus monkeys. *Psychopharmacology* **2004**, *172*, 220−224.

(42) Koreeda, M.; Brown, L.; Valdes, L. J. The Absolute Stereochemistry of Salvinorins. *Chem. Lett.* **1990**, 2015−2018.

(43) Ni, Q.; Xu, H.; Partilla, J. S.; de Costa, B. R.; Rice, K. C.; Rothman, R. B. Selective labeling of κ₂ opioid receptors in rat brain by [¹²⁵I]IOXY: Interaction of opioid peptides and other drugs with multiple κ₂ₐ binding sites. *Peptides* **1993**, *14*, 1279−1293.

(44) de Costa, B. R.; Iadarola, M. J.; Rothman, R. B.; Berman, K. F.; George, C.; Newman, A. H.; Mahboubi, A.; Jacobson, A. E.; Rice, K. C. Probes for narcotic receptor mediated phenomena. 18. Epimeric 6α- and 6β-iodo-3,14-dihydroxy-17-(cyclopropylmethyl)-4,5α-epoxymorphinans as potential ligands for opioid receptor single photon emission computed tomography (SPECT): Synthesis, evaluation, and radiochemistry of [¹²⁵I]-6β-iodo-3,14-dihydroxy-17-(cyclopropylmethyl)-4,5α-epoxymorphinan ([¹²⁵I]-Ioxy). *J. Med. Chem.* **1992**, *35*, 2826−2835.

(45) Coop, A. Biological Evaluation of Compounds for Their Physical Dependence Potential and Abuse Liability. XXVII. Drug Evaluation Committee of the College on Problems of Drug Dependence 2003. *NIDA Res. Monogr.* **2004**, *184*, 135−151.