Synthesis of Salvinorin A Analogues as Opioid Receptor Probes

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Received March 3, 2006

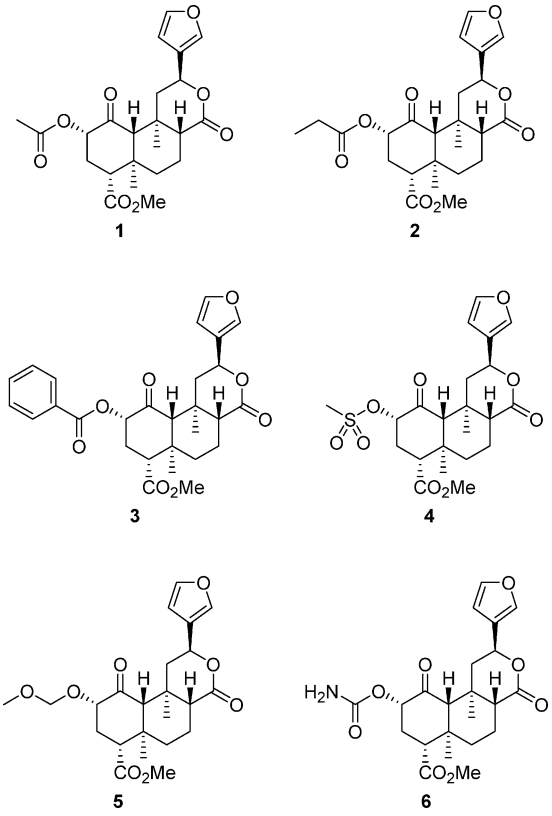
Several neoclerodanes, such as salvinorin A (**1**) and herkinorin (**3**), have recently been shown to possess opioid receptor activity in vitro and in vivo. To explore the structure−affinity relationships of this interesting class of compounds, we have synthesized a series of analogues from **1** isolated from *Salvia divinorum*. Here, we report the semisynthesis of neoclerodane diterpenes and their structure−affinity relationships at opioid receptors. This work will allow the further development of novel opioid receptor ligands.

Salvia divinorum is a plant from the mint family that has been used in the traditional spiritual practices by the Mazatec Indians of Oaxaca, Mexico. Chewing fresh leaves or smoking dried leaves will produce hallucinogenic-like experiences.[1] These experiences last for up to an hour and are reported to be potent and intense.[2−5] These effects, however, appear to be different than other hallucinogenic substances such as LSD or DOB. Recreational use of *S. divinourm* is increasing in part due to its availability for purchase through the Internet.[6]

The main active constituent isolated from the leaves of *S. divinorum* is salvinorin A (**1**), a neoclerodane diterpene.[7,8] Compound **1** was found to be a potent and selective κ opioid receptor (κOR) agonist.[9−11] Interestingly, the pharmacology of **1** appears to be different than other κ agonists.[12] Recent work has shown that **1** decreases dopamine levels in the caudate putamen of mice and that this effect is blocked by the κOR antagonist nor-binaltorphimine.[13] A study has also shown that **1** dose dependently increases immobility in the forced swim test, indicating that **1** has depressive-like effects.[14] Furthermore, **1** disrupts climbing behavior on an inverted screen task.[15] This study showed that there are differences in the susceptibility of **1** and the standard κOR agonist U69,593 to antagonism by nor-binaltorphimine. This finding also indicates that **1** may bind in a manner that is qualitatively different than traditional κOR ligands.

Recently, we described the synthesis of several analogues of **1** that were found to be opioid receptor ligands.[11] Among these compounds described were analogues **2**−**4**. Propionate **2** was found to have approximately the same affinity for the κOR as **1** but was less potent as an agonist. This work also identified herkinorin (**3**), the first neoclerodane diterpene with μ opioid receptor affinity, and WH-1-32 (**4**), an analogue slightly more potent than **1** as a κOR agonist.[11] Recently, methoxymethyl analogue **5**[16] and carbamate **6**[17] were identified as having affinity for κORs similar to **1**. Interestingly, **5** was found to be a full agonist more potent than **1**, and **6** is a partial agonist at κORs. These observations illustrate that substitution at the C-2 position can have profound effects on opioid receptor affinity and activity.

Recently, a model was proposed for the binding of **1** to the κOR.[18] This model was developed through the use of molecular modeling and mutagenesis studies. However, the binding pocket of salvinorin A will not be known until the structure of a κOR-**1** complex is solved. Given the lack of these studies, other methods are needed to elucidate the mode of binding. Here, we describe our additional efforts to more fully understand the manner of the high affinity of **1** for opioid receptors through structure−affinity studies.



Results and Discussion

Synthesis. The synthesis of the salvinorin A analogues is outlined in Scheme 1. Salvinorin B (**7**) was prepared from **1** that was isolated from *S. divinorum* and subjected to methanolysis under basic conditions as described previously.[19] The reaction of **7** with the appropriate alkanoyl chloride and a catalytic amount of DMAP in CH_2Cl_2 gave analogues **8a**−**8c** in 68−74% yield.[17] The coupling of **7** with *N*-Boc glycine using a mixture of (benzotriazol-1-yloxy)-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), *N*-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), and 1-hydroxybenzotriazole hydrate (HOBT) afforded ester **8d** in 58% yield. Treatment of **7** with phenylacetyl chloride and hydro-

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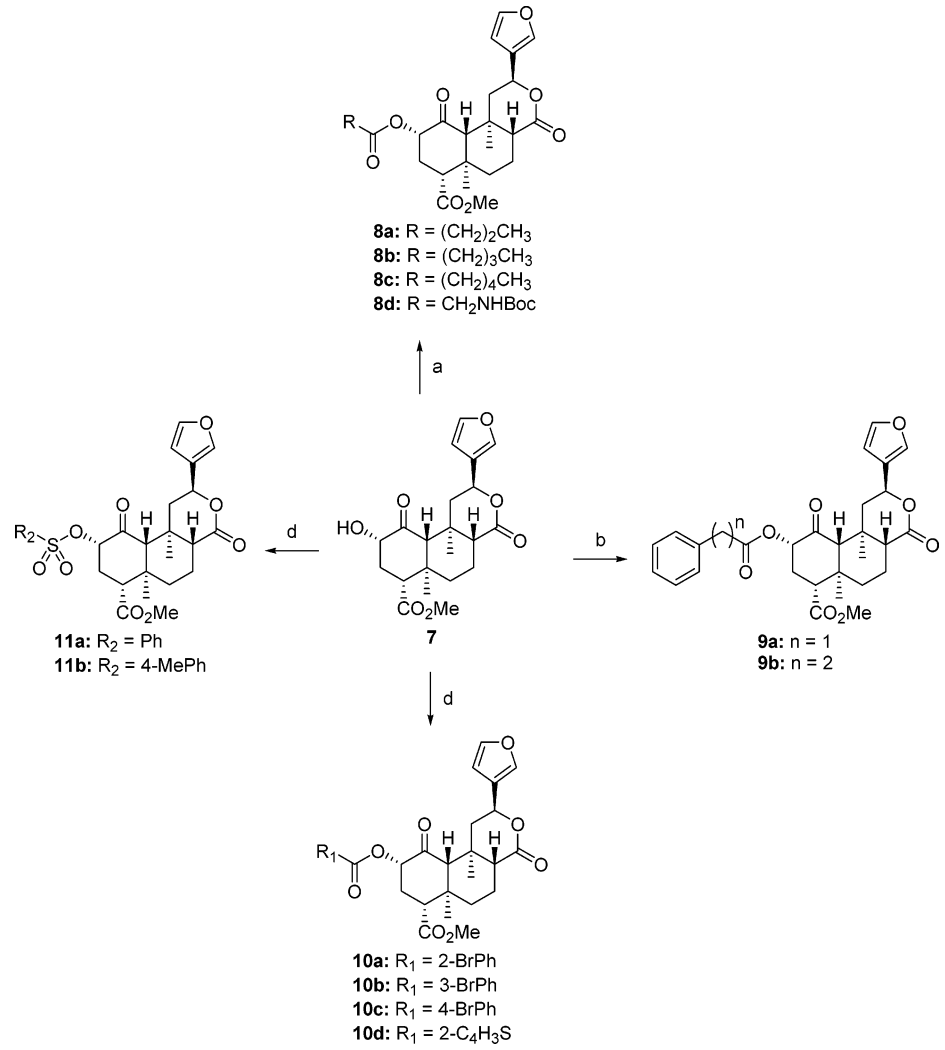
10.1021/np060094b CCC: $33.50
Published on Web 05/26/2006

Scheme 1[a]



[a] Reagents and conditions: (a) appropriate alkanoyl chloride, DMAP, CH_2Cl_2; (b) appropriate alkanoyl chloride, DMAP, CH_2Cl_2 or *N*-Boc glycine, BOP, EDCI, HOBT, pyridine, CH_2Cl_2; (c) appropriate aroyl chloride, DMAP, CH_2Cl_2; (d) appropriate benzenesulfonyl chloride, DMAP, CH_2Cl_2.

cinnamoyl chloride afforded **9a** and **9b**, respectively. The reaction of **7** with 2-bromo and 3-bromobenzoyl chloride afforded analogues **10a** and **10b** in 60 and 70% yield, respectively. Compound **10c** was synthesized as described previously.[20] Similar conditions using 2-thiophenecarbonyl chloride afforded **10d** in 60% yield. Finally, the reaction of **7** with benzenesulfonyl chloride and 4-methylbenzenesulfonyl chloride afforded **11a** and **11b** in 76 and 86% yield, respectively.

Biological Results. Analogues **8**−**11** were then evaluated for affinity at opioid receptors using methodology previously described (Table 1).[21] As shown previously, **1** and **2** have approximately the same affinity and selectivity for κ receptors.[11] This indicated that perhaps chain length might not play an important role. To further explore the role of chain length, we synthesized chain-extended analogues **8a**−**8c**. Increasing the chain length by one carbon (**8a**) had little effect on affinity for κORs compared to **2** (K_i = 4 nM vs K_i = 1.8 nM). This modification also had little effect on affinity for δORs (K_i = 6690 nM vs K_i = 4030 nM). However, affinity for μORs was increased (K_i = 520 nM vs K_i > 1000 nM). The further extension of the carbon chain, **8b** and **8c**, generally decreased affinity for κORs compared to **8a** (K_i = 15 nM and K_i = 70 nM vs K_i = 4 nM). The additional chain length had little effect on affinity for μ and δORs compared to **8a**. The replacement of the acetoxy group in **1** with a 2-*tert*-butoxycarbonylaminoacetoxy group (**8d**) resulted in reduced affinity at κORs compared to **1** (K_i = 90 nM vs K_i = 1.9 nM). This is interesting given the observation that replacement of the acetoxy group in **1** with an 2-acetylaminoacetoxy group abolishes affinity for κORs (K_i > 10 000 nM).[17] This difference is likely due to the different radioligands used ([^{3}H]-diprenorphine vs [^{125}I]IOXY) or the additional steric bulk of the *tert*-butoxycarbonyl moiety compared to the acetyl group.

Table 1. Binding Affinities of Salvinorin A Analogues at Opioid Receptors Using [^{125}I]IOXY as Radioligand[23,24]

	$K_i \pm$ SD, nM			selectivity	
compound	μ	δ	κ	μ/κ	δ/κ
1[a]	>1000[b]	5790 ± 980	1.9 ± 0.2	>530	3050
2[a]	>1000[b]	6690 ± 870	1.8 ± 0.1	>560	2730
3[a]	12 ± 1	1170 ± 60	90 ± 2	0.13	12
4[a]	6820 ± 660	>10 000	2.3 ± 0.1	2750	>4000
8a	520 ± 50	4030 ± 250	4 ± 1	130	1010
8b	310 ± 50	3970 ± 270	15 ± 2	21	265
8c	520 ± 80	4240 ± 290	70 ± 4	7	61
8d	5660 ± 250	>10 000	90 ± 10	63	>100
9a	1090 ± 90	>10 000	290 ± 40	4	>30
9b	280 ± 40	9330 ± 1010	180 ± 10	2	52
10a	110 ± 10	>10 000	90 ± 7	1.2	>100
10b	110 ± 10	>10 000	70 ± 7	1.6	>100
10c	10 ± 1	1410 ± 80	740 ± 40	0.01	2
10d	10 ± 2	1380 ± 130	260 ± 20	0.04	5
11a	>10 000	>10 000	60 ± 6	>150	>150
11b	220 ± 20	3720 ± 400	50 ± 5	4	74

[a] Data from ref 11. [b] Partial inhibitor.

Given the clear effects of chain length in the C-2 position on affinity for opioid receptors, we synthesized **9a** and **9b**, analogues

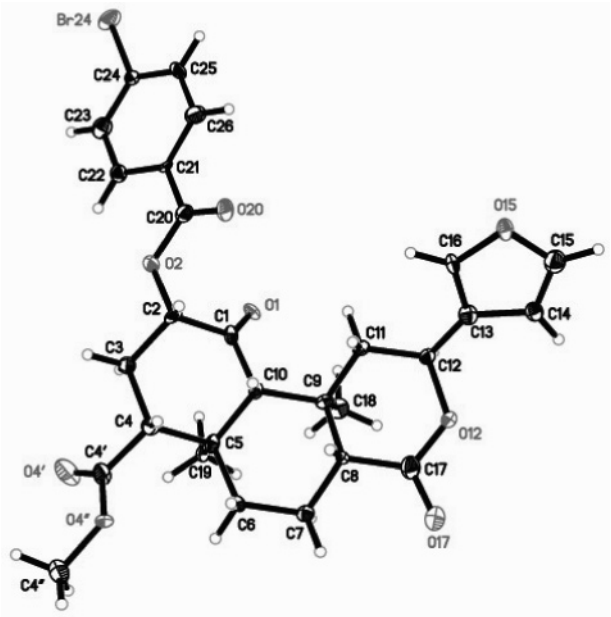


Figure 1. Results from the X-ray analysis on **10c** drawn from the experimentally determined coordinates with thermal parameters at 20% probability.

of herkinorin **3**. The introduction of a one carbon spacer between the carbonyl and phenyl ring (**9a**) led to a decrease in affinity at κORs compared to **3** (K_i = 290 nM vs K_i = 90 nM). This change also resulted in a 90-fold decrease in affinity for μORs (K_i = 1090 nM vs K_i = 12 nM). The addition of a second methylene unit (**9b**) increased affinity for μORs 4-fold compared to **9a** (K_i = 280 nM vs K_i = 1090 nM). This modification also increased affinity for κORs (K_i = 180 nM vs K_i = 290 nM). Generally, however, increasing the spacer between the carbonyl and phenyl ring decreased affinity approximately 10-fold for δORs compared to **3**.

After probing the spacer between the carbonyl and phenyl ring in **3**, we sought to explore the role of ring substitution on affinity and selectivity for opioid receptors. Introduction of a bromo group in the 2-position of the benzene ring in **3** (**10a**) had no effect on κOR affinity (K_i = 90 nM vs K_i = 90 nM). The 2-bromo group, however, decreased affinity for μORs 9-fold (K_i = 110 nM vs K_i = 12 nM). This modification decreased affinity for δORs compared to **3** (K_i > 10 000 nM vs K_i = 1170 nM) and thereby increased selectivity for μ and κ receptors over δ receptors. Parallel effects were seen at all three opioid receptors with 3-bromo analogue **10b**. The presence of a 4-bromo group (**10c**) decreased affinity for κORs 8-fold compared to **3** (K_i = 740 nM vs K_i = 90 nM). To our delight, this modification had no effect on μ or δOR affinity (K_i = 10 nM vs K_i = 12 nM and K_i = 1410 nM vs K_i = 1170 nM, respectively). This result however is in contrast to previous reports. A previous report indicated that **10c** had no affinity (K_i > 10 000 nM) for any opioid receptor.[20] Given the large difference seen in our assay, we sought to further confirm the absolute configuration of **10c** using a single-crystal X-ray diffraction study. Structural analysis was carried out and the absolute stereochemistry of **10c** was determined using the Flack parameter[22] and is as shown (Figure 1). Finally, the bioisosteric replacement of the benzene ring with a 2-thiophene (**10d**) was explored. Diterpene **10d** reduced affinity for κORs 3-fold compared to **3** (K_i = 260 nM vs K_i = 90 nM). This change, however, had no effect on affinity for μ or δORs (K_i = 10 nM vs K_i = 12 nM and K_i = 1,380 nM vs K_i = 1170 nM, respectively).

Given our previous finding that introduction of an aromatic group to the C-2 position increased affinity for μ receptors,[11] we synthesized compounds **11a** and **11b**, analogues of WH-1-32 (**4**). It was envisoned that replacement of the mesylate in **4** with a benzenesulfonate (**11a**) would result in a compound with reduced affinity at κORs and enhanced affinity at μORs compared to **4**. As expected, this structural change reduced affinity at κORs compared to **4** (K_i = 60 nM vs K_i = 2.3 nM). To our surprise, **11a** had no affinity for μORs (K_i > 10 000 nM). In addition, introduction of a 4-methyl group to **11a** (**11b**) had no effect on κOR affinity (K_i = 50 nM vs K_i = 60 nM) and increased affinity for δORs (K_i = 3720 nM vs K_i > 10 000 nM) compared to **11a**. This change, however, increased affinity for μORs compared to **11a** (K_i = 220 nM vs K_i > 10 000 nM). These changes, however, are not parallel to the ester series. This indicates that the previous structure−activity relationships (SAR) may not be applicable to the sulfonate series. It also suggests that these two series are not binding in an identical manner at either the μOR or κOR.

In conclusion, we have synthesized a series of neoclerodane diterpenes (**8**−**11**) from **1** isolated from *S. divinorum*. We have shown that chain length in the C-2 position generally decreases affinity for κORs and increases affinity to μORs. Substitution in the 4-position of the benzene ring in **3** is best tolerated. Furthermore, **3** and mesylate **4** appear to bind in a different manner at both the κOR and the μOR.

Experimental Section

General Experimental Procedures. Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used without further purification. All melting points were determined on a Thomas-Hoover capillary melting apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer or on a Bruker AMX-600 spectrometer using $CDCl_3$ as solvent, δ values in ppm (TMS as internal standard), and J (Hz) assignments of ^{1}H resonance coupling. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel plates. Spots on TLC were visualized with vanillin/H_2SO_4 in EtOH. 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. The systematic name for salvinorin A (**1**) is (2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(acetyloxy)-2-(furan-3-yl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho-[2,1-*c*]pyran-7-carboxylic acid methyl ester.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Butyryloxy)-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (8a). A solution of **7** (60 mg, 0.15 mmol), butyryl chloride (75 μL, 0.72 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (40 mL) was stirred at room temperature for 12 h. The mixture was washed with 2 N HCl (2 × 30 mL), saturated $NaHCO_3$ (2 × 20 mL), and saturated NaCl (30 mL). The organic extract was dried (Na_2SO_4) and filtered and the solvent removed in vacuo to give the crude product as a pale yellow oil. The crude product was purified by flash column chromatography (30−40% ethyl acetate/hexanes) to afford 48 mg (68%) of **8a** as a white solid: mp 158−160 °C; ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, t, J = 7.5); 1.14 (3H, s); 1.47 (3H, s); 1.52−1.66 (3H, m); 1.68−1.76 (2H, m); 1.81 (1H, m); 2.10 (1H, dd, J = 2.7, 11.1); 2.16 (1H, m); 2.19 (1H, s); 2.27−2.34 (2H, m); 2.38−2.46 (2H, ddd, J = 5.7, 7.5, 7.5); 2.52 (1H, dd, J = 5.1, 13.5); 2.77 (1H, dd, J = 9.3, 9.3); 3.74 (3H, s); 5.17 (1H, dd, J = 10.2, 10.2); 5.54 (1H, dd, J = 4.8, 11.4); 6.40 (1H, dd, J = 0.9, 1.2), 7.40 (1H, m); 7.43 (1H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 15.4, 16.6, 18.4, 18.6, 31.1, 35.7, 36.0, 38.4, 42.3, 43.6, 51.6, 52.1, 53.8, 64.3, 72.2, 75.0, 108.6, 125.4, 139.7, 143.9, 171.3, 171.8, 172.8, 202.2; *anal.* C 64.94%, H 7.02%, O 27.63%, calcd for $C_{25}H_{32}O_8$, C 65.20%, H 7.00%, O 27.79%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Pentanoyloxy)-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (8b). 8b was synthesized as described for **8a** from **7** using valeroyl chloride to afford 52 mg (74%) of **8b** as a white solid: mp 159−161 °C; ^{1}H NMR ($CDCl_3$) 0.94 (3H, t, J = 7.2); 1.13 (3H, s); 1.39 (3H, m); 1.46 (3H, s); 1.54−1.72 (7H, m); 1.80 (1H, 3.0, 9.9); 2.09 (1H, dd, J = 2.7, 11.4); 2.14−2.21 (2H, m); 2.27−2.34 (2H, m); 2.44 (2H, dt, J = 4.8, 7.4); 2.52 (1H, dd, J = 4.8, 13.4); 2.77 (1H, t, J = 8.4); 5.16 (1H, dd, J = 10.2, 10.2); 5.53 (1H, dd, J = 5.1, 11.7); 6.39 (1H, dd, J = 0.9, 1.8); 7.40 (1H, dd, J = 1.8, 1.8); 7.42 (1H, dd, J = 0.9, 1.8). ^{13}C NMR ($CDCl_3$) δ 13.9, 15.4, 16.6, 18.4, 22.4, 27.1, 31.1, 33.8, 35.7, 38.4, 42.3, 43.5, 51.6, 52.2, 53.8,

64.2, 72.2, 75.0, 108.6, 125.4, 139.7, 143.9, 171.4, 171.8, 173.0, 202.2; *anal.* C 65.58%, H 7.27%, O 27.21%, calcd for $C_{26}H_{34}O_8$, C 65.81%, H 7.22%, O 26.97%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Hexanoyloxy)-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (8c). 8c was synthesized as described for **8a** from **7** using hexanoyl chloride to afford 53 mg (70%) of **8c** as a white solid: mp 82−85 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 6.9); 1.14 (3H, s); 1.30−1.41 (4H, m) 1.47 (3H, s); 1.55−1.73 (6H, m); 1.81 (1H, dd, J = 3.0, 9.9); 2.10 (1H, dd, J = 3.0, 11.4); 2.19 (1H, s); 2.26−2.37 (2H, m); 2.44 (2H, dt, J = 5.5, 7.8); 2.53 (1H, dd, J = 5.1, 13.2); 2.77 (1H, dd, J = 8.7, 8.7); 3.74 (3H, s); 5.16 (1H, dd, J = 10.5, 10.5); 5.54 (1H, dd, J = 5.1, 11.7); 6.39 (1H, dd, J = 0.9, 1.8); 7.40 (1H, dd, J = 1.8, 1.8); 7.43 (1H, dd, J = 0.9, 1.8); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.4, 16.6, 18.4, 22.5, 24.7, 31.1, 31.5, 34.1, 35.7, 38.4, 42.3, 43.6, 51.6, 52.2, 53.8, 64.3, 72.2, 75.0, 108.6, 125.4, 139.7, 143.9, 171.3, 171.8, 173.0, 202.2; *anal.* C 65.46%, H 7.50%, O 26.91%, calcd for $C_{27}H_{36}O_8$.0.25H_2O, C 65.76%, H 7.46%, O 26.77%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(2-*tert*-Butoxycarbonylaminoacetyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (8d). (Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (244 mg, 0.55 mmol), *N*-Boc glycine (146 mg, 0.83 mmol), *N*-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (160 mg, 0.83 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (112.5 mg, 0.83 mmol), and pyridine (0.23 mL, 2.74 mmol) were added to a solution of **7** (120 mg, 0.31 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred for 4 days at room temperature. The mixture was diluted with CH_2Cl_2 (80 mL) and was washed sequentially with 2 N HCl (2 × 80 mL), 2 N NaOH (2 × 50 mL), and water (2 × 50 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated to give a yellow-brown oil. The crude product was purified by flash column chromatography (30% acetone/hexanes) to give 98 mg (58%) of **8d** as a white foam: mp 124−127 °C; ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, s); 1.46 (12 H, br s); 1.50−1.70 (3H, m); 1.83 (1H, d, J = 2.1 Hz); 2.11 (1H, d, J = 10.5); 2.19 (2H, m); 2.30 (1H, d, J = 4.8); 2.36 (1H, d, J = 9.6); 2.49 (1H, dd, J = 5.4, 13.5); 2.76 (1H, dd, J = 9.3, 9.3); 3.75 (3H, s); 3.99 (1H, dd, J = 5.1, 13.2); 4.13 (1H, dd, J = 6.3, 18.3); 4.99 (1H, br s); 5.20 (1H, dd, J = 10.2, 10.2); 5.53 (1H, dd, J = 5.1, 11.4); 6.39 (1H, br s); 7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.7, 18.4, 28.5(3), 30.9, 35.7(2), 38.4, 42.4, 43.6, 51.6, 52.3, 53.7, 64.3, 72.2, 75.9, 77.4, 108.6, 125.4, 139.6, 144.0, 156.2, 171.2, 171.6(2), 201.6; *anal.* C 61.36%, H 6.86%, O 29.27%, calcd for $C_{28}H_{37}NO_{10}$, C 61.41%, H 6.81%, O 29.22%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Phenylacetyloxy)-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (9a). 9a was synthesized from **7** using phenylacetyl chloride as described for **8a** to afford 70 mg (54%) of **9a** as a white solid: mp 111−114 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, s); 1.40 (3H, s); 1.41−1.52 (2 H, m); 1.61 (1H, m); 1.73 (1H, m); 1.87 (1H, dd, J = 3.0, 11.4); 2.10 (1H, dd, J = 3.0, 13.2); 2.22 (1H, s); 2.31 (2H, m); 2.72 (1H, m); 3.72 (3H, s); 3.75 (2H, s); 5.17 (1H, dd, J = 9.3, 9.3); 5.37 (1H, dd, J = 4.8, 11.7); 6.36 (1H, dd, J = 0.9, 1.5); 7.27−7.36 (6 H, m); 7.38−7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.3, 16.6, 18.2, 30.9, 35.5, 38.2, 40.8, 42.1, 42.9, 51.3, 52.1, 53.6, 63.8, 72.0, 75.6, 108.8, 125.2, 127.4, 128.8(2), 129.6(2), 133.7, 139.9, 143.8, 171.0, 171.3, 171.8, 202.0; *anal.* C 68.74%, H 6.36%, O 24.93%, calcd for $C_{29}H_{32}O_8$, C 68.49%, H 6.34%, O 25.17%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(3-Phenylpropionyl)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (9b). 9b was synthesized from **7** as described for **8a** using hydrocinnamoyl chloride to afford 69 mg (63%) of **9b** as a white solid: mp 155−158 °C; ^{1}H NMR ($CDCl_3$) δ 1.14 (3H, s); 1.47 (3H, s); 1.52−1.74 (3H, m); 1.81 (1H, m); 2.09 (1H, dd, J = 3.0, 11.1); 2.17 (1H, m); 2.19 (1H, s); 2.25−2.34 (2H, m); 2.53 (1H, dd, J = 5.3, 13.7); 2.71−2.76 (1H, m); 2.79 (2H, t, J = 7.5), 3.01 (2H, t, J = 7.5); 3.74 (3H, s); 5.17 (1H, dd, J = 10.1, 10.1); 5.55 (1H, dd, J = 4.8, 11.7); 6.40, (1H, dd, J = 0.9, 1.8), 7.20−7.26 (3H, m); 7.32 (2H, m); 7.43 (2H, m); ^{13}C NMR ($CDCl_3$) 15.4, 16.6, 18.4, 31.0, 35.6, 35.7, 38.4, 42.3, 43.6, 51.6, 52.2, 53.8, 64.3, 72.2, 75.2, 77.4, 108.6, 125.4, 126.6, 128.5(2), 128.7(2), 139.7, 140.4, 143.9, 171.3, 171.7, 172.1, 202.1; *anal.* C 69.23%, H 6.59%, O 24.23%, calcd for $C_{30}H_{34}O_8$, C 68.95%, H 6.56%, O 24.49%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(2-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (10a). 10a was synthesized as described for **8a** from **7** using 2-bromobenzoyl chloride to afforded 70 mg (60%) of **10a** as a white solid: mp 189−191 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, s); 1.45 (3H, s); 1.59−1.67 (3H, m); 1.82 (1H, m); 2.11−2.16 (2H, m); 2.35 (1H, s); 2.40−2.51 (3H, m); 2.86 (1H, dd, J = 8.4, 8.4); 3.73 (3H, s); 5.40−5.50 (2H, m); 6.39 (1H, m); 7.34−7.42 (4H, m); 7.69 (1H, dd, J = 1.8, 7.4); 7.97 (1H, dd, J = 2.4, 7.4); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.7, 18.4, 25.7, 31.0, 38.4, 42.4, 43.6, 51.6, 52.2, 53.8, 64.3, 72.3, 76.1, 108.6, 122.2, 125.4, 127.5, 131.1, 132.1, 133.3, 134.7, 139.7, 143.9, 165.1, 171.3, 171.7, 201.8; *anal.* C 58.46%, H 5.16%, O 22.07%, calcd for $C_{28}H_{29}BrO_8$, C, 58.65%, H, 5.10%, O, 22.32%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(3-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (10b). 10b was synthesized as described for **8a** from **7** using 3-bromobenzoyl chloride to afford 75 mg (70%) of **10b** as a white solid: mp 195−199 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (3H, s); 1.45 (3H, s); 1.28−1.69 (3H, m); 1.82 (1H, m); 2.10 (1H, dd, J = 2.4, 11.1); 2.18 (1H, m); 2.29 (1H, s); 2.42−2.54 (3H, m); 2.83 (1H, dd, J = 6.3, 10.5); 3.75 (3H, s); 5.39 (1H, dd, J = 9.0, 9.0); 5.52 (1H, dd, J = 5.1, 11.7); 6.38 (1H, m); 7.32−7.42 (3H, m); 7.72 (1H, ddd, J = 1.2, 1.8, 7.8); 8.01 (1H, ddd, J = 1.2, 1.2, 7.8); 8.21 (1H, dd, J = 1.8, 1.8); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.7, 18.4, 31.1, 35.7, 38.4, 42.5, 43.7, 51.6, 52.3, 53.8, 64.4, 72.3, 76.0, 108.6, 122.8, 125.4, 128.7, 130.3, 131.2, 133.1, 136.7, 139.7, 143.9, 164.4, 171.3, 171.7, 201.7; *anal.* C 58.54%, H 5.18%, O 22.15%, calcd for $C_{28}H_{29}BrO_8$, C, 58.65%, H, 5.10%, O, 22.32%.

Thiophene-2-carboxylic Acid (2*S*,4a*R*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-7-Carbomethoxy-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-9-yl Ester (10d). A solution of **7** (80 mg, 0.21 mmol), 2-thiophene carbonyl chloride (0.11 mL, 2.73 mmol), Et_3N (0.38 mL, 2.73 mmol), pyridine (0.22 mL, 2.73 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (40 mL) was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with 2 N HCl (2 × 30 mL), saturated $NaHCO_3$ (2 × 30 mL), and water (40 mL). The organic extract was then dried (Na_2SO_4), filtered, and concentrated to give an oil, which was purified by flash column chromatography (30−40% ethyl acetate/hexanes) to give 63 mg (60%) of **10d** as a white solid: mp 143−145 °C; ^{1}H NMR ($CDCl_3$) δ 1.18 (3H, s); 1.48 (3H, s); 1.54−1.77 (3H, m); 1.84 (1H, dd, J = 3.0, 10.2); 2.12 (1H, dd, J = 2.2, 11.1); 2.19 (1H, m); 2.26 (1H, s); 2.47 (2H, m); 2.56 (1H, dd, J = 5.3, 13.4); 2.83 (1H, dd, J = 7.2, 9.6); 3.76 (3H, s); 5.36 (1H, dd, J = 9.9, 9.9); 5.53 (1H, dd, J = 5.4, 11.7); 6.40 (1H, dd, J = 1.2, 1.8); 7.15 (1H, dd, J = 3.8, 5.1); 7.42 (2H, m); 7.63 (1H, dd, J = 1.3, 5.1); 7.89 (1H, dd, J = 1.3, 3.8); ^{13}C NMR ($CDCl_3$) δ 15.4, 16.7, 18.4, 31.1, 35.7, 38.4, 42.4, 43.6, 51.7, 52.2, 53.9, 64.3, 72.3, 75.7, 108.6, 125.4, 128.1, 132.6, 133.5, 134.5, 139.7, 143.9, 161.3, 171.3, 171.8, 201.8; *anal.* C 62.66%, H 5.84%, O 25.67%, calcd for $C_{26}H_{28}O_8S$, C 62.39%, H 5.64%, O 25.57%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(Benzenesulfonyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (11a). A solution of **7** (100 mg, 0.26 mmol), benzenesulfonyl chloride (66 μL, 0.51 mmol), pyridine (0.23 mL, 2.74 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (30 mL) was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2 (40 mL) and washed sequentially with 2 N HCl (2 × 30 mL), saturated $NaHCO_3$ (2 × 30 mL), and water (40 mL). The organic extract was dried (Na_2SO_4), filtered, and concentrated to an oil, which was purified by flash column chromatography (40% ethyl acetate/hexanes) to give 103 mg (76%) of **11a** as a white solid: mp 157−159 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, s); 1.44 (3H, s); 1.47−1.71 (4H, m); 1.82 (1H, m); 2.06 (1H, dd, J = 3.0, 12.0), 2.10 (1H, s); 2.19 (1H, m); 2.26−2.46 (3H, m); 2.72 (1H, dd, J = 4.2, 12.3); 3.73 (3H, s); 5.00 (1H, dd, J = 8.1, 11.7); 5.53 (1H, dd, J = 5.0, 11.6); 6.40 (1H, m); 7.44 (2H, m); 7.58 (2H, m); 7.67 (1H, m). 8.01 (1H, m); ^{13}C NMR ($CDCl_3$) δ 15.3, 16.6, 18.3, 32.4, 35.7, 38.3, 42.2, 43.5, 51.5, 52.3, 53.7, 64.6, 72.1, 80.0, 108.6, 125.4, 126.6, 128.0, 128.1, 129.4-(2), 134.2, 139.6, 144.0, 171.1, 171.2, 200.0; *anal.* C 61.16%, H 5.85%, O 27.06%, calcd for $C_{27}H_{30}O_9S$, C 61.62%, H 5.70%, O 27.14%.

(2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(4-Methylbenzenesulfonyloxy)-2-(3-furanyl)-dodecahydro-6a,10b-dimethyl-4,10-dioxo-2*H*-naphtho-[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (11b). 11b was synthesized as described for **11a** from **7** using 4-methylbenzenesulfonyl chloride to afforded 10 mg (0.22 mmol, 86%) of **11b** as a white solid: mp 163−165 °C (dec); ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, s); 1.44 (3H, s);

1.47−1.67 (4H, m); 1.81 (1H, dd, J = 2.7, 9.9); 2.05−2.08 (1H, dd, obscured); 2.08 (1H, s); 2.17 (1H, dd, J = 3.0, 10.2); 2.32−2.44 (2H, m); 2.41 (3H, s); 2.72 (1H, dd, J = 4.2, 12.3); 3.73 (3H, s); 4.96 (1H, dd, J = 7.5, 11.7); 5.53 (1H, dd, J = 5.1, 11.7); 6.40 (1H, dd, J = 1.2, 1.2); 7.34 (2H, d, J = 7.8); 7.43 (2H, m); 7.84 (2H, d, J = 7.8); ^{13}C NMR ($CDCl_3$) δ 15.3, 16.6, 18.3, 21.8, 32.5, 35.7, 38.3, 42.2, 43.5, 51.6, 52.3, 53.7, 64.6, 72.1, 77.4, 79.8, 108.6, 125.4, 128.1(2), 130.0(2), 139.7, 144.0, 145.4, 171.1, 171.2, 200.1; *anal.* C 61.17%, H 5.84%, O 27.07%, calcd for $C_{28}H_{32}O_9S\cdot0.25H_2O$, C 61.24%, H 5.97%, O 26.95%.

X-ray Crystal Structure of (2*S*,4a*S*,6a*R*,7*R*,9*S*,10a*S*,10b*R*)-9-(4-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,-10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (10c). Single-crystal X-ray diffraction data on compound **10c** were collected at 93 K using Mo Kα radiation and a Bruker SMART 1000 CCD area detector. A 0.32 × 0.04 × 0.02 mm^3 crystal was prepared for data collection coating with high-viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was mounted on a glass rod and transferred immediately to the cold stream (93 K) on the diffractometer. The crystal was orthorhombic in space group $P2_12_12_1$ with unit cell dimensions a = 6.382(2) Å, b = 10.008(7) Å, and c = 20.534(8) Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 99.9% complete to 25.33° θ (approximately 0.83 Å) with an average redundancy of 5.3. The structure was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.14, Bruker AXS Inc., Madison, WI, 2000). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C−H distance set at 0.98 Å. The absolute configuration was determined from the X-ray data (Flack parameter = 0.025(17)). Atomic coordinates for compound **10c** have been deposited with the Cambridge Crystallographic Data Centre (deposition number 299266). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgment. This work was supported by the National Institutes of Health, National Institute on Drug Abuse Grant DA18151 (to T.E.P.), and in part by the Office of Naval Research and the Intramural Research Program of the NIH, NIDA.

Supporting Information Available: CIF file of X-ray data for compound **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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NP060094B