

Synthesis of Salvinorin A Analogues as Opioid Receptor Probes

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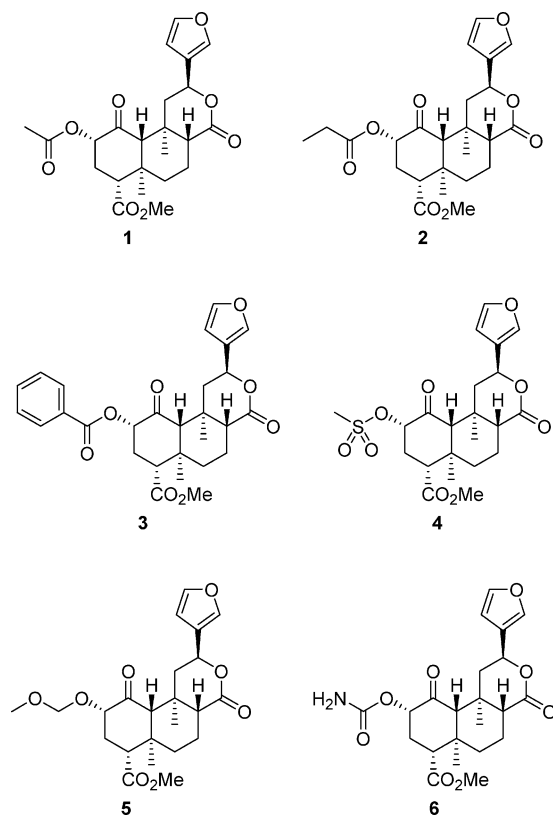
Several neoclerodanes, such as salvinorin A (**1**) and herkinorin (**3**), have recently been shown to possess opioid receptor activity in vitro and in vivo. To explore the structure–affinity relationships of this interesting class of compounds, we have synthesized a series of analogues from **1** isolated 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. divinorum* 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 (κ OR) 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 κ OR 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 κ OR 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 κ OR 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 κ OR 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 κ OR agonist.¹¹ Recently, methoxymethyl analogue **5**¹⁶ and carbamate **6**¹⁷ were identified as having affinity for κ ORs similar to **1**. Interestingly, **5** was found to be a full agonist more potent than **1**, and **6** is a partial agonist at κ ORs. 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 κ OR.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 κ OR–**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

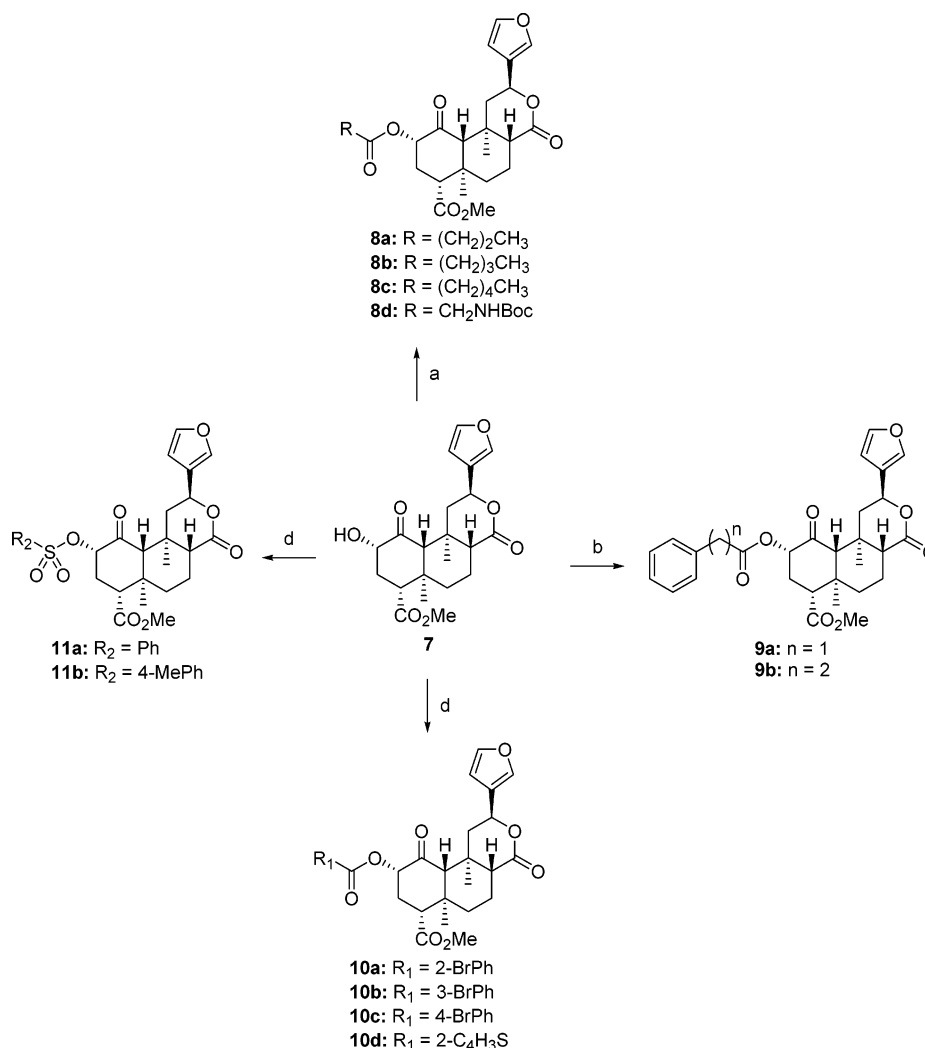
Synthesis. The synthesis of the salvinorin A analogues is outlined in Scheme 1. Salvinorin B (**7**) was prepared from **1** that was isolated from *S. divinorum* and subjected to methanolysis under basic conditions as described previously.¹⁹ The reaction of **7** with the appropriate alkanoyl chloride 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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Scheme 1^a

^a Reagents and conditions: (a) appropriate alkanoyl chloride, DMAP, CH₂Cl₂; (b) appropriate alkanoyl chloride, DMAP, CH₂Cl₂ or *N*-Boc glycine, BOP, EDCI, HOBT, pyridine, CH₂Cl₂; (c) appropriate aroyl chloride, DMAP, CH₂Cl₂; (d) appropriate benzenesulfonyl chloride, DMAP, CH₂Cl₂.

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 κ ORs compared to **2** ($K_i = 4$ nM vs $K_i = 1.8$ nM). This modification also had little effect on affinity for δ ORs ($K_i = 6690$ nM vs $K_i = 4030$ nM). However, affinity for μ ORs 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 κ ORs 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 δ ORs compared to **8a**. The replacement of the acetoxy group in **1** with a 2-*tert*-butoxycarbonylaminoacetoxy group (**8d**) resulted in reduced affinity at κ ORs 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

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

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

^a Data from ref 11. ^b Partial inhibitor.

group abolishes affinity for κ ORs ($K_i > 10 000$ nM).¹⁷ This difference is likely due to the different radioligands used ([³H]-diprenorphine vs [¹²⁵I]IOXY) or the additional steric bulk of the *tert*-butoxycarbonyl moiety compared to the acetyl group.

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

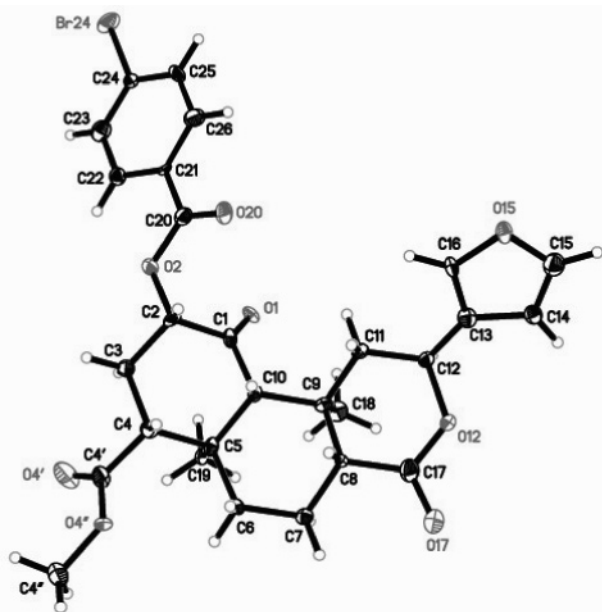


Figure 1. Results from the X-ray analysis on **10c** drawn from the experimentally determined coordinates with thermal parameters at 20% probability.

of herkinorin **3**. The introduction of a one carbon spacer between the carbonyl and phenyl ring (**9a**) led to a decrease in affinity at κ ORs compared to **3** ($K_i = 290$ nM vs $K_i = 90$ nM). This change also resulted in a 90-fold decrease in affinity for μ ORs ($K_i = 1090$ nM vs $K_i = 12$ nM). The addition of a second methylene unit (**9b**) increased affinity for μ ORs 4-fold compared to **9a** ($K_i = 280$ nM vs $K_i = 1090$ nM). This modification also increased affinity for κ ORs ($K_i = 180$ nM vs $K_i = 290$ nM). Generally, however, increasing the spacer between the carbonyl and phenyl ring decreased affinity approximately 10-fold for δ ORs 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 κ OR affinity ($K_i = 90$ nM vs $K_i = 90$ nM). The 2-bromo group, however, decreased affinity for μ ORs 9-fold ($K_i = 110$ nM vs $K_i = 12$ nM). This modification decreased affinity for δ ORs 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 κ ORs 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 δ OR 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 parameter²² 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 κ ORs 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 δ ORs ($K_i = 10$ 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 envisioned that replacement of the mesylate in **4** with a benzenesulfonate (**11a**) would result in a compound with reduced

affinity at κ ORs and enhanced affinity at μ ORs compared to **4**. As expected, this structural change reduced affinity at κ ORs compared to **4** ($K_i = 60$ nM vs $K_i = 2.3$ nM). To our surprise, **11a** had no affinity for μ ORs ($K_i > 10\,000$ nM). In addition, introduction of a 4-methyl group to **11a** (**11b**) had no effect on κ OR affinity ($K_i = 50$ nM vs $K_i = 60$ nM) and increased affinity for δ ORs ($K_i = 3720$ nM vs $K_i > 10\,000$ nM) compared to **11a**. This change, however, increased affinity for μ ORs 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 μ OR or κ OR.

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 κ ORs and increases affinity to μ ORs. 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 κ OR and the μ OR.

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 ¹H NMR and ¹³C NMR spectra were recorded at 300 MHz on a Bruker Avance-300 spectrometer or on a Bruker AMX-600 spectrometer using CDCl₃ as solvent, δ values in ppm (TMS as internal standard), and *J* (Hz) assignments of ¹H resonance coupling. Thin-layer chromatography (TLC) was performed on 0.25 mm Analtech GHLF silica gel plates. Spots on TLC were visualized with vanillin/H₂SO₄ in EtOH. Column chromatography was performed with silica gel (32–63 μ m 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*,4*aR*,6*aR*,7*R*,9*S*,10*aS*,10*bR*)-9-(acetyloxy)-2-(furan-3-yl)dodecahydro-6*a*,10*b*-dimethyl-4,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic acid methyl ester.

(2*S*,4*aS*,6*aR*,7*R*,9*S*,10*aS*,10*bR*)-9-(Butyryloxy)-2-(3-furanyl)-dodecahydro-6*a*,10*b*-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 μ L, 0.72 mmol), and a catalytic amount of DMAP in CH₂Cl₂ (40 mL) was stirred at room temperature for 12 h. The mixture was washed with 2 N HCl (2 \times 30 mL), saturated NaHCO₃ (2 \times 20 mL), and saturated NaCl (30 mL). The organic extract was dried (Na₂SO₄) 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 $^{\circ}$ C; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₅H₃₂O₈, C 65.20%, H 7.00%, O 27.79%.

(2*S*,4*aS*,6*aR*,7*R*,9*S*,10*aS*,10*bR*)-9-(Pentanyloxy)-2-(3-furanyl)-dodecahydro-6*a*,10*b*-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 $^{\circ}$ C; ¹H NMR (CDCl₃) 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). ¹³C NMR (CDCl₃) 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 C₂₆H₃₄O₈, C 65.81%, H 7.22%, O 26.97%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(Hexanoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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; ¹H NMR (CDCl₃) 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, *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); ¹³C NMR (CDCl₃) 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 C₂₇H₃₆O₈, C 65.76%, H 7.46%, O 26.77%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(2-tert-Butoxycarbonylaminoacetoxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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 CH₂Cl₂ (30 mL), and the mixture was stirred for 4 days at room temperature. The mixture was diluted with CH₂Cl₂ (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 (Na₂SO₄), 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₈H₃₇NO₁₀, C 61.41%, H 6.81%, O 29.22%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(Phenylacetoxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₉H₃₂O₈, C 68.49%, H 6.34%, O 25.17%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(3-Phenylpropionyl)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₃₀H₃₄O₈, C 68.95%, H 6.56%, O 24.49%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(2-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-naphtho[2,1-c]py-

ran-7-carboxylic Acid Methyl Ester (10a). **10a** was synthesized as described for **8a** from **7** using 2-bromobenzoyl chloride to afford 70 mg (60%) of **10a** as a white solid: mp 189–191 °C; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₈H₂₉BrO₈, C, 58.65%, H, 5.10%, O, 22.32%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(3-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₈H₂₉BrO₈, C, 58.65%, H, 5.10%, O, 22.32%.

Thiophene-2-carboxylic 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 (10d). A solution of **7** (80 mg, 0.21 mmol), 2-thiophene carbonyl chloride (0.11 mL, 2.73 mmol), Et₃N (0.38 mL, 2.73 mmol), pyridine (0.22 mL, 2.73 mmol), and a catalytic amount of DMAP in CH₂Cl₂ (40 mL) was stirred at room temperature overnight. The mixture was diluted with CH₂Cl₂ (30 mL) and washed with 2 N HCl (2 × 30 mL), saturated NaHCO₃ (2 × 30 mL), and water (40 mL). The organic extract was then dried (Na₂SO₄), 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; ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₆H₂₈O₈S, C 62.39%, H 5.64%, O 25.57%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(Benzenesulfonyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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 CH₂Cl₂ (30 mL) was stirred at room temperature overnight. The mixture was diluted with CH₂Cl₂ (40 mL) and washed sequentially with 2 N HCl (2 × 30 mL), saturated NaHCO₃ (2 × 30 mL), and water (40 mL). The organic extract was dried (Na₂SO₄), 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); ¹H NMR (CDCl₃) 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); ¹³C NMR (CDCl₃) 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 C₂₇H₃₀O₉S, C 61.62%, H 5.70%, O 27.14%.

(2S,4aS,6aR,7R,9S,10aS,10bR)-9-(4-Methylbenzenesulfonyloxy)-2-(3-furanyl)dodecahydro-6a,10b-dimethyl-4,10-dioxo-2H-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 afford 10 mg (0.22 mmol, 86%) of **11b** as a white solid: mp 163–165 °C (dec); ¹H NMR (CDCl₃) 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 $\text{C}_{28}\text{H}_{32}\text{O}_9\text{S} \cdot 0.25\text{H}_2\text{O}$, C 61.24%, H 5.97%, O 26.95%.

X-ray Crystal Structure of (2*S*,4*aS*,6*aR*,7*R*,9*S*,10*aS*,10*bR*)-9-(4-Bromobenzoyloxy)-2-(3-furanyl)dodecahydro-6*a*,10*b*-dimethyl-4-,10-dioxo-2*H*-naphtho[2,1-*c*]pyran-7-carboxylic Acid Methyl Ester (10*c*). Single-crystal X-ray diffraction data on compound **10c** were collected at 93 K using Mo $\text{K}\alpha$ radiation and a Bruker SMART 1000 CCD area detector. A $0.32 \times 0.04 \times 0.02 \text{ mm}^3$ 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 $a = 6.382(2) \text{ \AA}$, $b = 10.008(7) \text{ \AA}$, and $c = 20.534(8) \text{ \AA}$. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 99.9% complete to $25.33^\circ \theta$ (approximately 0.83 \AA) 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 \AA . 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].

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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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