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Catalyst-Free sp^3 C−H Acyloxylation: Regioselective Synthesis of 1-Acyloxy Derivatives of the Natural Product Tanshinone IIA

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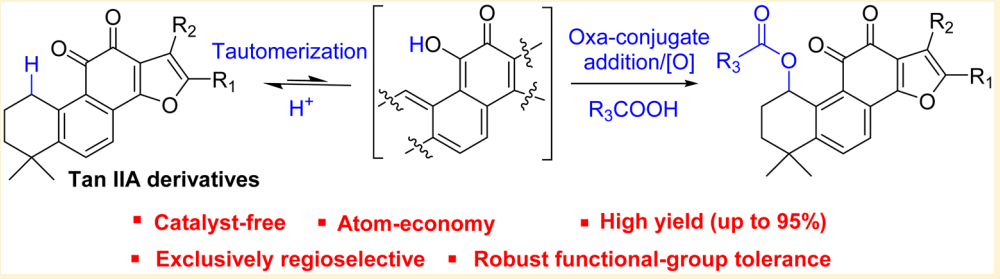
Supporting Information



ABSTRACT: Tanshinone IIA is a valuable bioactive natural product isolated from the well-known Chinese herb Danshen. Structural manipulation of the A-ring of tanshinone IIA is rather limited. In this study, a substrate tautomerization-induced catalyst-free benzylic sp^3 C−H acyloxylation approach is reported that allows the direct introduction of various acyloxy groups at the A-ring benzylic methylene of various tanshinone IIA substrates, thus avoiding the use of expensive transition metal catalysts and the production of harmful byproducts. This approach features a unique acid-induced reversible enolization/oxa-conjugate addition process followed by oxidation to exclusively give a series of diverse 1-acyloxylated derivatives under simple conditions in a regioselective manner. Compared with the literature procedures, this protocol demonstrates a higher efficiency, a more robust functional-group tolerance, atom economy, and lower cost.

Tanshinone IIA (Tan-IIA, **1**, Scheme 1) is a pharmacologically valuable natural product isolated from the well-known Chinese herb Danshen that has been used for more than 2000 years for the treatment of cardiovascular disease in Asian countries.[1] Structurally, Tan-IIA features a benzofuran-4,5-dione (C-/D-ring) fused to a tetrahydronaphthalene framework (A-/B-ring),[2] and it possesses a broad range of biological activities, including antitumor activities.[3] However, further clinical development of Tan-IIA is hampered by its poor drug-like properties,[4] thus making this natural product an ideal lead compound for further structural modifications. Currently, most of the Tan-IIA derivatives are obtained by modifying the 3-methylbenzofuran-4,5-dione moiety,[5] whereas structural manipulation of the A-ring is rather limited. In 2012, Wu and co-workers reported the synthesis of a small series of Tan-IIA A-ring derivatives using a Diels−Alder reaction;[6] however, the yields were low and the substrates were relatively limited. Direct oxidation or halogenation of the A-ring of Tan-IIA was also reported, but low yields and poor regioselectivity were obtained due to competitive reactions of the furan benzylic methyl moiety.[7] For example, Liu and co-workers synthesized a series of vasodilatory C-1 Tan-IIA benzoates through the bromination of Tan-IIA followed by nucleophilic substitution with aromatic acids (Scheme 1b).[7c] However, this two-step method has a low overall efficacy (~26%) and suffered from the instability of 1-bromo Tan-IIA.[7b] Therefore, the development of efficient and economically attractive synthetic approaches to readily modify the A-ring of Tan-IIA is required.

Recent years have witnessed an explosive development of C−H activation/functionalization,[8] among which transition-metal-catalyzed sp^3 C−H bond activation/acyloxylation has become an intriguing approach to functionalize inactive C−H bonds (Scheme 1a).[9] However, most currently reported metal-catalyzed acyloxylations of benzylic sp^3 C−H bonds encounter limitations, such as sensitivity to the environment, the use of expensive catalysts, and the difficult removal of toxic metal residues from the products. As a result, increased attention has been focused on metal-free catalytic processes.[10] Recently, benzylic C−H acetoxylations catalyzed by the nonmetal *n*-Bu_4NI have been developed by several groups (Scheme 1a).[11] However, catalyst-free acyloxylation of benzylic sp^3 C−H bonds under mild reaction conditions, especially as a late-stage strategy to modify complex bioactive natural products such as Tan-IIA, remains a challenge. In our ongoing efforts to chemically diversify tanshinone natural products,[12] a catalyst-

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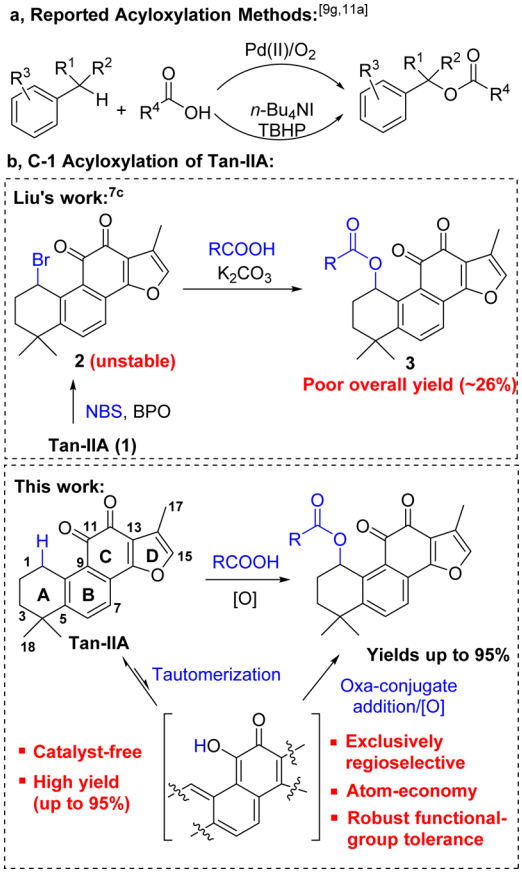
Scheme 1. Various Acyloxylation Approaches to the Synthesis of Benzylic Esters

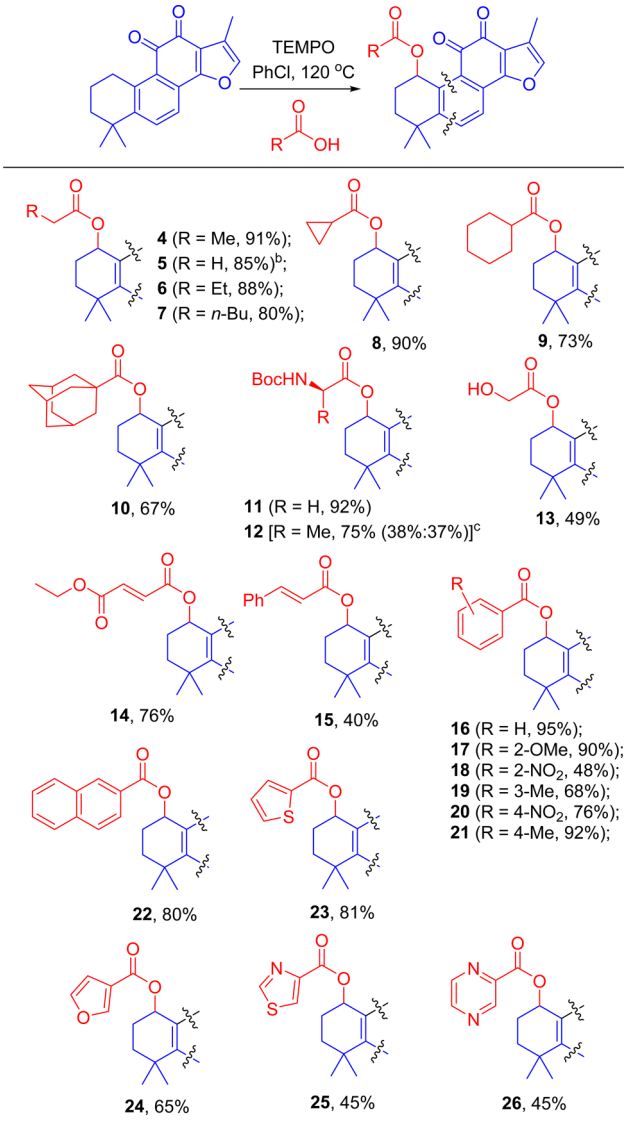


free benzylic sp^3 C−H acyloxylation approach has been developed that leads to a late-stage structural modification of Tan-IIA with low cost, high selectivity, and high efficiency.

RESULTS AND DISCUSSION

Tan-IIA was chosen as the model substrate, and the corresponding acyloxylation reaction was initially conducted using *n*-Bu_4NI as the catalyst and *tert*-butyl hydroperoxide (TBHP) as the co-oxidant.[11a] However, the formation of propanoate **4** was not observed (Scheme 2, entry 1). Interestingly, the reaction proceeded gradually in the air without the addition of both *n*-Bu_4NI and TBHP, providing product **4** in 36% yield after 24 h, along with some unreacted Tan-IIA (Table 1, entry 2). A control experiment was performed in the absence of oxygen, but no reaction was detected (Table 1, entry 3), suggesting that an oxidant was essential for the acyloxylation reaction. Encouraged by this result, various oxidants were screened to improve the yield. Moderate yields could be achieved when silver salts, such as Ag_2CO_3 and Ag_2O, were employed as the oxidant (Table 1, entries 4, 5). $Cu(OAc)_2$ promoted this reaction as well, but the yield was very low (Table 1, entry 6). $FeCl_3$ failed to catalyze the formation of any targeted product, except for decomposition of the substrate (Table 1, entry 7). Next, various organic oxidants were tested, and gratifyingly, TEMPO was found to be an optimal oxidant, leading to the targeted ester **4** in 95% yield (Table 1, entry 10). Poor yields or decomposition was observed when 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), 1,4-benzoquinone (BQ), and TBHP were utilized as

Scheme 2. Substrate Scope of Carboxylic Acids[a]



[a]Reaction conditions: Tan-IIA (0.1 mmol), acid (0.2 mmol), TEMPO (0.12 mmol), PhCl (1 mL), 120 °C, 24 h. [b]Acetic acid was used as the solvent. [c]Two isomers were isolated.

the oxidants (Table 1, entries 8, 9, 11). Because the use of an excessive amount of propionic acid as the solvent leads to a mixture of products when other carboxylic acids are employed as the acyloxylating partner, alternative solvents were screened to replace propionic acid. It was found that *t*-BuOH, DMF, and DCE failed to facilitate this reaction, leading to decreased yields (Table 1, entries 12−14). Nonpolar solvents, such as PhCl, toluene, and mesitylene, were compatible with the reaction in the presence of 2 equiv of propionic acid (Table 1, entries 15−17). Among the nonpolar solvents, PhCl was the best solvent, affording product **4** in 91% isolated yield (Table 1, entry 15).

With the optimized conditions in hand, the substrate scope of this new C−H acyloxylation reaction was explored with respect to various carboxylic acids, as shown in Scheme 2. Both acyclic and cyclic alkyl carboxylic acids efficiently reacted with Tan-IIA to give the corresponding acyloxylated products **4**−**10** in 67−91% yields. Among the carboxylic acids, adamantane-carboxylic acid gave the lowest yield (67% for compound **10**), which was most likely due to the increased steric hindrance.

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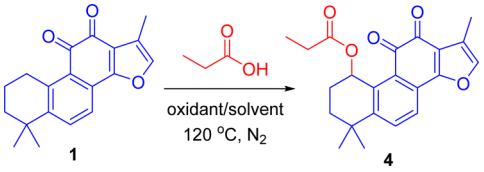
Table 1. Optimization of the Reaction Conditions for the Synthesis of 4[a]



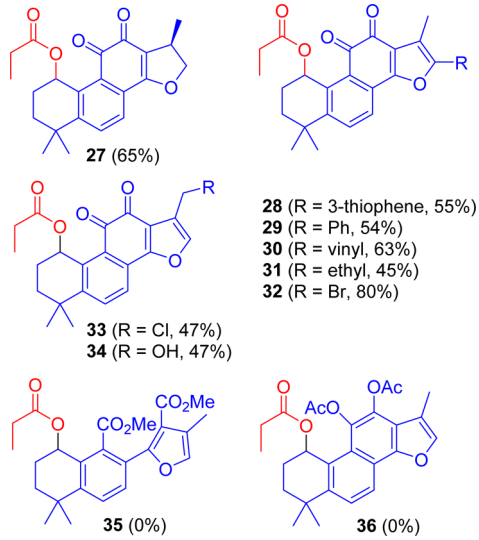
entry	solvent	oxidant	yield (%)[b]
1	propionic acid	*n*-Bu_4NI/TBHP	0
2	propionic acid	O_2	36
3	propionic acid	no oxidant[c]	0
4	propionic acid	Ag_2CO_3	48
5	propionic acid	Ag_2O	50
6	propionic acid	$Cu(OAc)_2$	12
7	propionic acid	$FeCl_3$	0
8	propionic acid	DDQ	0
9	propionic acid	BQ	24
10	propionic acid	TEMPO	95
11	propionic acid	TBHP	0
12	*t*-BuOH	TEMPO	11
13	DMF	TEMPO	21
14	DCE	TEMPO	69
15	PhCl	TEMPO	94 (91[d])
16	toluene	TEMPO	86
17	mesitylene	TEMPO	89

[a]Reaction conditions: Tan-IIA (0.1 mmol), propionic acid (0.2 mmol), oxidant (0.12 mmol), solvent (1 mL), 120 °C, 24 h. [b]Yields determined by ^1H NMR analysis using 1, 2-dibromoethane as the internal standard. [c]The reaction was performed under a N_2 atmosphere without oxidant. [d]Isolated yield.

Interestingly, this new method was also suitable for *N*-Boc-protected amino acids. Acyloxylation with *N*-Boc-2-aminoacetic acid afforded the amino ester **11** in 92% yield, whereas the reaction with (*R*)-*N*-Boc-2-aminopropanoic acid produced the ester **12** as a mixture of two diastereoisomers with a ratio of approximately 1:1 that could be separated using a silica gel column. When 2-hydroxyacetic acid was employed as the acyloxylating agent, the yield of product **13** decreased to 49%, likely due to the excessively oxidized or decomposed side products resulting from the hydroxy functional group. *α*,*β*-Unsaturated aliphatic carboxylic acids, such as monoethyl fumarate and cinnamic acid, participated amicably in this reaction to furnish products **14** and **15** in good and moderate yields, respectively. Meanwhile, a wide array of aromatic carboxylic acids was found to give high yields; among these, benzoic acid was the best acyloxylating agent, affording product **16** in the highest yield (95%). Variously substituted benzoic acids were also tolerated in the reaction to provide the corresponding acyloxylated products **17**−**21** in moderate to excellent yields. *β*-Naphthoic acid was also compatible in the reaction to give the ester **22** in 80% yield. Remarkably, aryl carboxylic acids with electron-donating substituents, such as the *o*-methoxy group, gave higher yields than those bearing electron-withdrawing substituents, such as the *o*-nitro group (products **17** and **18**). In addition, electron-rich heteroaryl carboxylic acids, such as thiophene-2- and furan-3-carboxylic acids, also performed well in the reaction to afford the targeted products **23** and **24** in 81% and 65% yields, respectively. In contrast, carboxylic acids containing an electron-poor heterocyclic moiety, such as thiazole-4- and pyrazine-2-carboxylic acids, led to products **25** and **26** in lower yields, respectively.

Encouraged by the broad generality of carboxylic acids, the scope and limitations of the Tan-IIA substrates were investigated (Scheme 3). Cryptotanshinone,[2] a Tan-IIA analogue possessing a saturated D-ring isolated from the same herb, was utilized as the substrate to react with propionic acid under the optimal conditions. The expected propionyloxy product **27** was obtained as a pair of diastereomers with a ratio of approximately 1:1 in 65% yield. These two diastereomers possess identical NMR spectra and could be separated only by chiral HPLC, not by TLC or a silica gel column. A small class of Tan-IIA derivatives containing diverse substituents at C-15 of the furan ring also proceeded smoothly in the reaction, providing the corresponding products **28**−**32** in moderate to good yields. Analogues with a hydroxy or chloro functional group at C-17 were tolerant to the reaction conditions but afforded the targeted products **33** and **34** in lower yields (47%). Note that substrates produced by either breaking the *o*-quinone into a diester or masking the *o*-diketo moiety with diacetate did not react with propionic acid under the optimal conditions (**35** and **36**), suggesting that the *o*-diketo moiety is essential for the acyloxylation reaction.

Scheme 3. Reactions of Various Tan-IIA-Derived Substrates with Propionic Acid[a]



[a]Reaction conditions: Tan-IIA analogues (0.1 mmol), propionic acid (0.2 mmol), TEMPO (0.12 mmol), PhCl (1 mL), 120 °C, 24 h.

TEMPO is widely used as a radical-trapping agent, and no TEMPO-trapped radical intermediate was observed in this acyloxylation reaction. Therefore, a radical process could be excluded for the current acyloxylation pathway. To confirm whether a hydroxy intermediate was formed first and then reacted with carboxylic acids to give the ester product, treatment of the 1-hydroxy derivative **37**[7a] with HOAc under the optimized reaction conditions failed to give the target acetate **5** (Scheme 4, a). To gain further insight into the reaction mechanism, HOAc was replaced with KOAc as the acyloxylating reagent to react with Tan-IIA, which failed to generate the acetate **5** (Scheme 4, a), suggesting that the carboxylic acid proton was probably essential to initiate the reaction. To investigate the exact role of the acidic proton,

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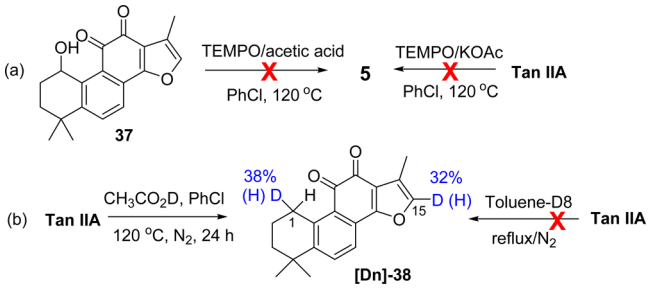
Scheme 4. Preliminary Reaction Mechanism Studies



deuterated acetic acid (AcOD) was used to react with Tan-IIA in the absence of TEMPO for 24 h under a N_2 atmosphere. As expected, no acetate **5** was found, and NMR analysis of the recovered Tan-IIA displayed that protons at C-1 and C-15 were partially exchanged with deuterium, as in the structure of [**D*n***]-**38** (*n* = 0, 1, 2) (Scheme 4, b), indicating that the C-1 C−H bond was activated under the acidic condition. For D-labeling at C-15, we speculated that an aromatic electrophilic substitution by D^+ occurred due to the high electron density of the furan ring. It should be noted that [**D*n***]-**38** is a mixture of several inseparable compounds, most likely including Tan-IIA, the C-1-deuterated Tan-IIA derivative, the C-15-deuterated Tan-IIA derivative, and/or both the C-1- and C-15-deuterated Tan-IIA derivative. The deuteration experiment was also performed by heating Tan-IIA in toluene-d_8, but NMR analysis showed that no deuterated product was produced (Scheme 4, b).

Based on the results above, a plausible mechanism for the C-1 acyloxylation was tentatively proposed. As shown in Figure 1,

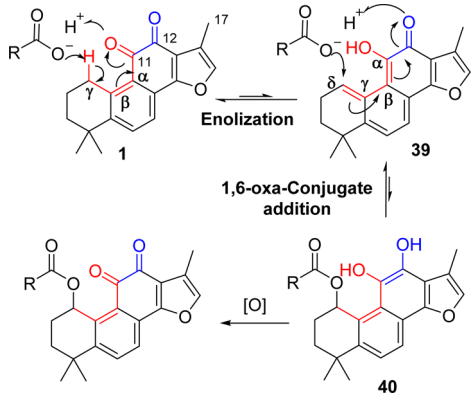


Figure 1. Proposed Reaction Mechanism.

in the presence of a carboxylic acid at 120 °C, the *γ*-methylene-*α*,*β*-unsaturated C-11 oxo structural unit of Tan-IIA undergoes an enolization, leading to the dienol quinonemethide **39**, which was also proposed as a key intermediate by Kusumi and co-workers in a photoinduced oxidation of Tan-IIA.[7a] The resulting dienol structural unit along with the neighboring C-12 carbonyl group form another reactive *α*,*β*,*γ*,*δ*-unsaturated dienone. The further addition of the 1,6-oxa-conjugate of the carboxylate ion to this dienone system, with its extended conjugation, affords the C-1 acetoxylated dihydroquinone **40**, which is prone to oxidation to furnish the final product. It should be noted that the enolization/oxa-conjugate addition process is reversible, and the equilibrium heavily favored the formation of the *o*-quinone Tan-IIA at room temperature. However, further oxidation could drive this equilibrium toward the formation of the acyloxylation product, as suggested by the fact that no reaction occurred without oxidant. On the other hand, the C-17 methyl group on the furan ring is not involved in the formation of the *γ*-methylene-*α*,*β*-unsaturated C-12 oxo structural unit, which might account for the regioselectivity favoring C-1.

In conclusion, a novel catalyst-free sp^3 C−H acyloxylation approach was developed that allows the direct introduction of a wide range of acyloxy groups regioselectively at C-1 of various Tan-IIA substrates under simple and mild conditions. Compared with the literature procedures using palladium or *n*-Bu_4NI as the catalyst, our protocol demonstrated atom-economy, lower cost, higher efficiency, and robust functional-group tolerance. Preliminary mechanistic studies suggest that this approach is initiated by a unique acid-induced reversible enolization/oxa-conjugate addition process, followed by oxidation to exclusively give the C-1 acetoxylated products. These findings provide an economical and efficient chemical method to modify the A-ring of the pharmacologically valuable Tan-IIA. Further application of this approach as well as the biological evaluation of the resulting acyloxylated derivatives will be reported in the future.

EXPERIMENTAL SECTION

General Experimental Procedures. All the reactions were performed in a sealed tube containing a Teflon-coated stir bar and monitored by TLC (0.2 mm silica-gel-coated HSGF 254 plates) under UV light at 254 nm. ^{1}H NMR spectra were recorded on a Bruker 500 MHz NMR spectrometer ($CDCl_3$ solvent). The chemical shifts were reported in parts per million (ppm), downfield from $SiMe_4$ (δ 0.0) and relative to the signal of $CDCl_3$ (δ 7.26, singlet) or DMSO-d_6 (δ 2.54, singlet). Multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), or m (multiplet). The number of protons for a given resonance is indicated by *n*H. Coupling constants are reported as *J* values in Hz. ^{13}C NMR data are reported in ppm using $CDCl_3$. Low- and high-resolution mass spectra were obtained using EI or ESI-TOF.

General Experimental Procedure for the Catalyst-Free Acyloxylation Reaction. A 10 mL sealed tube was charged with **1** (0.1 mmol), propionic acid (0.2 mmol), and TEMPO (0.12 mmol). PhCl (1 mL) was added, and the resulting mixture was stirred at 120 °C. The reaction was monitored by TLC until the starting material disappeared. The solvent was removed *in vacuo*, and the residue was purified using a silica gel column with CH_2Cl_2 as the eluent to give the acyloxylated products in 45−95% yields.

1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**4**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.24 (s, 1H), 6.48−6.39 (m, 1H), 2.35−2.12 (m, 6H), 2.05−1.81 (m, 2H), 1.60−1.50 (m, 1H), 1.39 (s, 2H), 1.27 (s, 2H), 1.13 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 175.3, 173.5, 161.2, 150.8, 141.7, 138.2, 134.2, 128.5, 127.1, 123.0, 121.4, 120.3, 67.3, 34.9, 32.4, 31.6, 31.2, 27.7, 24.8, 9.4, 8.9; ESIMS *m*/*z* 389 [M + Na]$^+$; HRESIMS *m*/*z* 389.1367 [M + Na]$^+$ (calcd for $C_{22}H_{22}O_5Na$ 389.1365).

1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl acetate (**5**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.3 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.19 (s, 1H), 6.39−6.32 (m, 1H), 2.19 (s, 3H), 2.17−2.09 (m, 1H), 1.98 (s, 3H), 1.98−1.78 (m, 2H), 1.56−1.45 (m, 1H), 1.36 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 174.9, 169.9, 161.0, 150.7, 141.7, 137.9, 134.2, 128.3, 126.8, 123.0, 121.2, 120.2, 67.4, 34.8, 32.2, 31.5, 31.0, 24.6, 21.03, 8.8; ESIMS *m*/*z* 375 [M + Na]$^+$; HRESIMS *m*/*z* 375.1208 [M + Na]$^+$ (calcd for $C_{21}H_{20}O_5Na$ 375.1214).

1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl butyrate (**6**): ^{1}H NMR (300 MHz,

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$CDCl_3$) δ 7.70 (s, 2H), 7.23 (s, 1H), 6.47−6.41(m, 1H), 2.33−2.11 (m, 6H), 2.05−1.81 (m, 2H), 1.73−1.47 (m, 3H), 1.39 (s, 8H), 1.27 (s, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 175.2, 172.6, 161.1, 150.7, 141.7, 138.1, 134.1, 128.4, 127.0, 123.0, 121.3, 120.2, 67.1, 36.3, 34.8, 32.3, 31.6, 31.2, 24.7, 18.6, 13.8, 8.9; ESIMS m/z 403 $[M + Na]^+$; HRESIMS m/z 403.1527 $[M + Na]^+$ (calcd for $C_{23}H_{24}O_5Na$ 403.1521).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl hexanoate (**7**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.23 (d, J = 1.6 Hz, 1H), 6.48−6.38 (m, 1H), 2.33−2.10 (m, 4H), 2.06−1.81 (m, 2H), 1.72−1.49 (m, 3H), 1.39 (s, 3H), 1.27 (s, 3H), 0.92 (t, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 175.2, 172.6, 161.2, 150.7, 141.7, 138.2, 134.2, 128.4, 127.1, 123.0, 121.4, 120.3, 67.2, 36.4, 34.9, 32.4, 31.6, 31.2, 24.7, 18.6, 13.9, 8.9; ESIMS m/z 431 $[M + Na]^+$; HRESIMS m/z 431.1837 $[M + Na]^+$ (calcd for $C_{25}H_{28}O_5Na$ 431.1834).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl cyclopropanecarboxylate (**8**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 1.4 Hz, 2H), 7.25−7.19 (m, 1H), 6.45 (t, J = 3.1 Hz, 1H), 2.25 (s, 3H), 2.24−2.09 (m, 1H), 2.04−1.85 (m, 2H), 1.58−1.44 (m, 2H), 1.40 (s, 3H), 1.27 (s, 3H), 1.17−1.05 (m, 1H), 0.98−0.88 (m, 1H), 0.85−0.71 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 175.3, 173.7, 161.2, 150.8, 141.7, 138.1, 134.1, 128.4, 127.1, 123.0, 121.4, 120.3, 67.2, 34.9, 32.4, 31.7, 31.2, 24.7, 13.1, 8.9, 8.6, 8.3; ESIMS m/z 401 $[M + Na]^+$; HRESIMS m/z 401.1364 $[M + Na]^+$ (calcd for $C_{23}H_{22}O_5Na$ 401.1365).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl cyclohexanecarboxylate (**9**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.23 (d, J = 1.5 Hz, 1H), 6.48−6.40 (m, 1H), 2.29−2.10 (m, 5H), 2.03−1.79 (m, 4H), 1.76−1.63 (m, 2H), 1.62−1.40 (m, 4H), 1.39 (s, 3H), 1.27−1.12 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 175.3, 174.8, 161.2, 150.7, 141.7, 138.2, 134.1, 128.4, 127.0, 123.0, 121.4, 120.3, 66.8, 43.4, 34.9, 32.3, 31.7, 31.2, 29.2, 29.1, 25.9, 25.6, 25.6, 24.7, 8.9; ESIMS m/z 421 $[M + H]^+$; HRESIMS m/z 421.2019 $[M + H]^+$ (calcd for $C_{26}H_{29}O_5$ 421.2015).

*(3r,5r,7r)-1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl adamantane-1-carboxylate (**10**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.23 (s, 1H), 6.42 (s, 1H), 2.36−2.05 (m, 4H), 2.04−1.73 (m, 10H), 1.73−1.46 (m, 7H), 1.46−1.10 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 176.1, 175.4, 161.2, 150.7, 141.6, 138.4, 134.0, 128.3, 127.1, 122.9, 121.4, 120.3, 66.5, 40.8, 38.9 (3), 36.6 (3), 34.9, 32.4, 31.8, 31.20, 28.1 (3), 24.7, 8.9; ESIMS m/z 473 $[M + H]^+$; HRESIMS m/z 473.2331 $[M + H]^+$ (calcd for $C_{30}H_{33}O_5$ 473.2328)

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-((tert-butoxycarbonyl)amino)-acetate (**11**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.23 (d, J = 1.3 Hz, 1H), 6.46−6.39 (m, 1H), 5.19−5.06 (m, 1H), 3.98 (dd, J = 18.2, 7.0 Hz, 1H), 3.70 (dd, J = 18.2, 3.9 Hz, 1H), 2.22 (s, 3H), 2.21−2.15 (m, 1H), 2.06−1.79 (m, 2H), 1.64−1.45 (m, 1H), 1.41 (s, 9H), 1.38 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 174.9, 169.5, 161.1, 155.8, 150.8, 141.8, 137.3, 134.4, 128.5, 127.0, 123.3, 121.4, 120.3, 79.8, 68.5, 42.4, 34.8, 32.2, 31.6, 31.1, 28.4, 24.8, 8.8; ESIMS m/z 490 $[M + Na]^+$; HRESIMS m/z 490.1849 $[M + Na]^+$ (calcd for $C_{26}H_{29}O_7NNa$ 490.1842).

*(2R)-1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-((tert-butoxycarbonyl)-amino)propanoate (**12**).* One isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.24 (s, 1H), 6.48 (t, J = 3.6 Hz, 1H), 5.13 (d, J = 7.3 Hz, 1H), 4.24 (t, J = 7.3 Hz, 1H), 2.24 (s, 3H), 2.21−2.09 (m, 2H), 2.07−1.77 (m, 2H), 1.63−1.49 (m, 2H), 1.47−1.32 (m, 15H), 1.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.2, 175.3, 171.8, 161.1, 155.1, 150.8, 141.8, 137.4, 134.3, 128.5, 127.1, 123.3, 121.4, 120.4, 79.5, 68.2, 49.6, 34.9, 32.35, 31.7, 31.1, 28.41, 24.6, 18.98, 8.9; ESIMS m/z 482 $[M + H]^+$; HRESIMS m/z 482.2166 $[M + H]^+$ (calcd for $C_{27}H_{32}O_7N$ 482.2179). Another isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73 (s, 2H), 7.24 (s, 1H), 6.52−6.46 (m, 1H), 5.20 (d, J = 8.3 Hz, 1H), 4.31−4.15 (m, 1H), 2.25 (s, 3H), 2.22−2.14 (m, 1H), 2.05−1.81 (m, 2H), 1.61−1.49 (m, 1H), 1.43 (s, 9H), 1.40 (s, 3H), 1.27 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 175.2, 172.3, 161.2, 155.3, 150.9, 141.8, 137.4, 134.3, 128.6, 127.0, 123.3, 121.5, 120.4, 79.7, 68.3, 49.4, 34.9, 32.2, 31.6, 31.2, 28.5, 24.7, 19.12, 8.9; ESIMS m/z 482 $[M + H]^+$; HRESIMS m/z 482.2166 $[M + H]^+$ (calcd for $C_{27}H_{32}O_7N$ 482.2179).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-hydroxyacetate (**13**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (d, J = 1.2 Hz, 1H), 7.25 (0H), 6.53 (t, J = 3.5 Hz, 1H), 4.17−4.01 (m, 2H), 2.66−2.53 (m, 1H), 2.31−2.16 (m, 4H), 2.10−1.79 (m, 2H), 1.62−1.51 (m, 1H), 1.40 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 174.9, 172.7, 161.1, 150.8, 141.9, 137.0, 134.5, 128.6, 126.9, 123.4, 121.5, 120.4, 68.8, 60.6, 34.9, 32.2, 31.6, 31.1, 24.9, 8.9; ESIMS m/z 391 $[M + Na]^+$; HRESIMS m/z 391.1159 $[M + Na]^+$ (calcd for $C_{21}H_{20}O_6Na$ 391.1158).

*Ethyl (1,6,6-trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl) fumarate (**14**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.26 (s, 1H), 6.80 (s, 2H), 6.57 (s, 1H), 4.21 (q, J = 7.2 Hz, 2H), 2.37−2.16 (m, 4H), 2.10−1.81 (m, 2H), 1.68−1.49 (m, 1H), 1.42 (s, 3H), 1.36−1.17 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 174.7, 165.2, 164.0, 161.0, 150.8, 141.8, 137.2, 134.4, 134.0, 133.7, 128.6, 126.9, 123.4, 121.5, 120.4, 68.3, 61.3, 34.9, 32.2, 31.7, 31.1, 24.7, 14.2, 8.9; ESIMS m/z 459 $[M + Na]^+$; HRESIMS m/z 459.1421 $[M + Na]^+$ (calcd for $C_{25}H_{24}O_7Na$ 459.1420).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl cinnamate (**15**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 2H), 7.69 (d, J = 16.1 Hz, 1H), 7.51−7.42 (m, 2H), 7.39−7.27 (m, 3H), 7.23 (s, 1H), 6.66−6.59 (m, 1H), 6.36 (d, J = 16.0 Hz, 1H), 2.38−2.26 (m, 1H), 2.23 (s, 3H), 2.11−1.90 (m, 2H), 1.67−1.49 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.6, 174.9, 166.0, 161.1, 150.9, 144.8, 141.7, 138.0, 134.8, 134.3, 130.1, 128.95, 128.5, 128.1, 127.0, 123.2, 121.5, 120.4, 118.5, 67.3, 34.9, 32.4, 31.8, 31.2, 24.8, 8.9; ESIMS m/z 463 $[M + Na]^+$; HRESIMS m/z 463.1519 $[M + Na]^+$ (calcd for $C_{28}H_{24}O_5Na$ 463.1521).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl benzoate (**16**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99−7.88 (m, 2H), 7.76 (d, J = 1.3 Hz, 4H), 7.51−7.42 (m, 1H), 7.38−7.29 (m, 2H), 7.24−7.18 (m, 1H), 6.76−6.69 (m, 1H), 2.44−2.30 (m, 1H), 2.21 (s, 3H), 2.10−1.93 (m, 2H), 1.64−1.52 (m, 1H), 1.44 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.8, 165.6, 161.1, 150.9, 141.7, 137.9, 134.3, 132.7, 130.8, 129.8, 128.5, 128.2, 127.0, 123.2, 121.4, 120.4, 67.7, 35.0, 32.4, 31.9, 31.2, 24.8, 8.9; ESIMS m/z 437 $[M + Na]^+$; HRESIMS m/z 437.1358 $[M + Na]^+$ (calcd for $C_{26}H_{22}O_5Na$ 437.1365).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-methoxybenzoate (**17**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 2H), 7.67 (dd, J = 7.9, 1.6 Hz, 1H), 7.37 (td, J = 8.2, 1.7 Hz, 1H), 7.24−7.17 (m, 1H), 6.95−6.82 (m, 2H), 6.75−6.68 (m, 1H), 3.81 (s, 3H), 2.49−2.31 (m, 1H), 2.22 (s, 3H), 2.13−1.96 (m, 2H), 1.65−1.55 (m, 1H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 175.0, 165.4, 161.1, 158.8, 150.8, 141.6, 138.0, 134.0, 132.8, 131.5, 128.2, 127.1, 122.9, 121.3, 121.1, 120.2, 120.1, 111.9, 67.7, 55.9, 34.8, 32.3, 31.7, 31.2, 24.7, 8.8; ESIMS m/z 445 $[M + H]^+$; HRESIMS m/z 445.1657 $[M + H]^+$ (calcd for $C_{27}H_{25}O_6$ 445.1651).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-nitrobenzoate (**18**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1, 1H), 7.83 (d, J = 7.7, 1H), 7.72 (s, 2H), 7.69−7.60 (m, 1H), 7.58−7.48 (m, 1H), 7.23 (d, J = 1.5 Hz, 1H), 6.75−6.66 (m, 1H), 2.61−2.45 (m, 1H), 2.24 (s, 3H), 2.18−2.02 (m, 1H), 2.01−1.87 (m, 2H), 1.71−1.58 (m, 2H), 1.38 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.3, 175.3, 165.0, 161.2, 151.1, 146.6, 141.8, 136.8, 134.4, 133.8, 130.9, 130.2, 129.4, 128.5, 127.1, 123.8, 123.4, 121.4, 120.3, 69.5, 34.8, 32.3, 31.6, 31.1, 24.1, 8.9. 31.1, 24.8, 8.9; ESIMS m/z 482 $[M + Na]^+$; HRESIMS m/z 482.1222 $[M + Na]^+$ (calcd for $C_{26}H_{21}O_7NNa$ 482.1216).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 3-methylbenzoate (**19**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85−7.71 (m, 4H), 7.37−7.21 (m, 3H), 6.79−6.72 (m, 1H), 2.46−2.30 (s, 4H), 2.25 (s, 3H), 2.14−1.96 (m,

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2H), 1.66−1.56 (s, 1H), 1.48 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.9, 165.8, 161.1, 150.9, 141.7, 138.0, 134.3, 133.4, 130.7, 130.3, 128.5, 128.1, 127.0, 126.9, 123.2, 121.5, 120.4, 67.6, 35.0, 32.4, 31.9, 31.2, 24.8, 21.4, 8.9; ESIMS m/z 451 $[M + Na]^+$; HRESIMS m/z 451.1528 $[M + Na]^+$ (calcd for $C_{27}H_{24}O_5Na$ 451.1521).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 4-nitrobenzoate (**20**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (d, J = 8.9 Hz, 2H), 8.11 (d, J = 8.9 Hz, 2H), 7.79 (s, 2H), 7.25−7.22 (m, 1H), 6.73−6.67 (m, 1H), 2.45−2.31 (m, 1H), 2.22 (s, 3H), 2.16−1.90 (m, 2H), 1.69−1.55 (m, 1H), 1.46 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 174.7, 163.8, 161.0, 150.9, 150.4, 141.9, 137.1, 136.2, 134.6, 130.9, 128.7, 127.0, 123.5, 123.5, 121.5, 120.4, 69.0, 35.0, 32.4, 31.9, 31.1, 24.8, 8.9; ESIMS m/z 460 $[M + H]^+$; HRESIMS m/z 460.1403 $[M + H]^+$ (calcd for $C_{26}H_{22}O_7N$ 460.1396).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 4-methylbenzoate (**21**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, J = 8.2 Hz, 2H), 7.78−7.70 (m, 2H), 7.21 (d, J = 1.6 Hz, 1H), 7.13 (d, J = 8.2 Hz, 2H), 6.72 (t, J = 3.2 Hz, 1H), 2.41−2.30 (m, 4H), 2.20 (s, 3H), 2.12−1.92 (m, 2H), 1.64−1.52 (m, 1H), 1.44 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.8, 165.6, 161.1, 150.9, 143.1, 141.7, 138.0, 134.2, 129.8, 128.9, 128.4, 128.0, 127.0, 123.1, 121.4, 120.3, 67.4, 34.9, 32.4, 31.9, 31.2, 24.8, 21.7, 8.9; ESIMS m/z 429 $[M + H]^+$; HRESIMS m/z 429.1705 $[M + H]^+$ (calcd for $C_{27}H_{25}O_5$ 429.1702).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl 2-naphthoate (**22**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.97 (d, J = 1.5 Hz, 1H), 7.88−7.68 (m, 5H), 7.55−7.40 (m, 2H), 7.20 (d, J = 1.2 Hz, 1H), 6.79 (t, J = 2.9 Hz, 1H), 2.52−2.34 (m, 1H), 2.18 (s, 3H), 2.15−1.98 (m, 2H), 1.69−1.56 (m, 1H), 1.47 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.7, 165.7, 161.0, 150.9, 141.6, 137.8, 135.4, 134.3, 132.5, 131.0, 129.3, 128.5, 128.0, 128.0, 127.9, 127.8, 127.0, 126.4, 125.6, 123.2, 121.4, 120.3, 67.8, 35.0, 32.4, 31.9, 31.1, 24.9, 8.8; ESIMS m/z 465 $[M + H]^+$; HRESIMS m/z 465.1699 $[M + H]^+$ (calcd for $C_{30}H_{25}O_5$ 465.1702).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl thiophene-2-carboxylate (**23**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80−7.65 (m, 3H), 7.44 (d, J = 5.0 Hz, 1H), 7.22 (s, 1H), 7.01 (t, J = 4.3 Hz, 1H), 6.68 (t, J = 3.2 Hz, 1H), 2.42−2.29 (m, 1H), 2.21 (s, 3H), 2.13−1.91 (m, 2H), 1.67−1.50 (m, 1H), 1.43 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.8, 161.2, 161.0, 150.8, 141.7, 137.6, 134.2, 134.2, 133.4, 131.9, 128.4, 127.6, 126.9, 123.2, 121.4, 120.3, 67.9, 34.9, 32.3, 31.8, 31.1, 24.9, 8.9; ESIMS m/z 443 $[M + Na]^+$; HRESIMS m/z 443.0928 $[M + Na]^+$ (calcd for $C_{24}H_{20}O_5NaS$ 443.0929).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl furan-3-carboxylate (**24**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91−7.84 (m, 1H), 7.75 (d, J = 1.1 Hz, 2H), 7.34 (t, J = 1.7 Hz, 1H), 7.23 (d, J = 1.5 Hz, 1H), 6.73−6.62 (m, 2H), 2.37−2.27 (m, 1H), 2.23 (s, 3H), 2.10−1.89 (m, 2H), 1.61−1.51 (m, 1H), 1.42 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 174.9, 162.2, 161.1, 150.9, 147.6, 143.5, 141.7, 137.9, 134.3, 128.5, 127.0, 123.2, 121.5, 120.4, 119.7, 110.2, 67.3, 35.0, 32.4, 31.82, 31.2, 24.9, 8.9; ESIMS m/z 427 $[M + Na]^+$; HRESIMS m/z 427.1159 $[M + Na]^+$ (calcd for $C_{24}H_{20}O_6Na$ 427.1158).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl thiazole-4-carboxylate (**25**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.22 (s, 1H), 7.73 (s, 2H), 7.22 (s, 1H), 6.74 (t, J = 3.4 Hz, 1H), 2.43−2.31 (m, 1H), 2.20 (s, 3H), 2.18−1.89 (m, 2H), 1.68−1.51 (m, 1H), 1.42 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 174.7, 161.1, 160.6, 153.2, 151.0, 148.3, 141.7, 137.4, 134.2, 128.6, 127.6, 127.1, 123.2, 121.3, 120.2, 68.6, 34.9, 32.3, 31.5, 31.1, 24.85, 8.8; ESIMS m/z 422 $[M + H]^+$; HRESIMS m/z 422.1058 $[M + H]^+$ (calcd for $C_{23}H_{20}O_5NS$ 422.1062).

*1,6,6-Trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl pyrazine-2-carboxylate (**26**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.66 (d, J = 12.4 Hz, 2H), 7.75 (s, 2H), 7.23 (s, 1H), 6.80−6.71 (m, 1H), 2.46−2.30 (m, 1H), 2.20 (s, 3H), 2.20−1.90 (m, 2H), 1.69−1.54 (m, 1H), 1.43 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.7, 174.7, 163.3, 161.1, 151.0, 147.4, 146.7, 144.3, 143.8, 141.8, 137.1, 134.5, 128.8, 127.1, 123.5, 121.4, 120.3, 69.6, 35.0, 32.4, 31.6, 31.1, 24.8, 8.9; ESIMS m/z 439 $[M + Na]^+$; HRESIMS m/z 439.1276 $[M + Na]^+$ (calcd for $C_{24}H_{20}O_5N_2Na$ 439.1270).

*(1R)-1,6,6-Trimethyl-10,11-dioxo-1,2,6,7,8,9,10,11-octahydrophenanthro[1,2-b]furan-9-yl propionate (**27**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 6.48−6.41 (m, 1H), 4.89 (t, J = 9.5 Hz, 1H), 4.36 (dd, J = 9.4, 6.1 Hz, 1H), 3.58 (dt, J = 10.5, 6.8 Hz, 1H), 2.34−2.14 (m, 3H), 2.03−1.79 (m, 2H), 1.60−1.49 (m, 1H), 1.41−1.31 (m, 6H), 1.26 (s, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 175.2, 173.3, 170.4, 152.9, 137.5, 133.4, 129.2, 127.3, 125.2, 118.7, 81.7, 67.1, 35.1, 34.8, 32.3, 31.8, 31.3, 27.6, 24.7, 18.9, 9.3; ESIMS m/z 369 $[M + H]^+$; HRESIMS m/z 369.1707 $[M + H]^+$ (calcd for $C_{22}H_{25}O_5$ 369.1702).

*1,6,6-Trimethyl-10,11-dioxo-2-(thiophen-3-yl)-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**28**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.58 (s, 1H), 7.46 (s, 2H), 6.48−6.40 (m, 1H), 2.47 (s, 3H), 2.35−2.13 (m, 3H), 2.06−1.83 (m, 2H), 1.62−1.47 (m, 2H), 1.41 (s, 3H), 1.29 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 175.4, 173.4, 158.9, 150.6, 149.0, 138.3, 134.1, 130.8, 128.3, 127.1, 126.7, 125.3, 122.9, 122.0, 121.7, 115.6, 6.34, 34.9, 32.4, 31.6, 31.2, 27.6, 24.7, 9.8, 9.3; ESIMS m/z 471 $[M + Na]^+$; HRESIMS m/z 471.1233 $[M + Na]^+$ (calcd for $C_{26}H_{24}O_5NaS$ 471.1242).

*1,6,6-Trimethyl-10,11-dioxo-2-phenyl-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**29**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86−7.62 (m, 4H), 7.54−7.33 (m, 3H), 6.51−6.36 (m, 1H), 2.50 (s, 3H), 2.36−2.11 (m, 3H), 2.06−1.81 (m, 2H), 1.61−1.51 (m, 1H), 1.41 (s, 3H), 1.29 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 175.4, 173.4, 159.4, 151.6, 150.7, 138.2, 134.1, 129.8, 128.9 (3), 128.5, 128.3, 127.2, 126.1 (3), 123.0, 122.0, 116.8, 67.3, 34.9, 32.4, 31.6, 31.2, 27.6, 24.7, 10.23, 9.3; ESIMS m/z 465 $[M + Na]^+$; HRESIMS m/z 465.1673 $[M + Na]^+$ (calcd for $C_{28}H_{26}O_5Na$ 465.1678).

*1,6,6-Trimethyl-10,11-dioxo-2-vinyl-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**30**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 6.55 (dd, J = 17.4, 11.4 Hz, 1H), 6.43 (t, J = 3.6 Hz, 1H), 5.81 (d, J = 17.4 Hz, 1H), 5.36 (d, J = 11.5 Hz, 1H), 2.35−2.10 (m, 6H), 2.07−1.82 (m, 2H), 1.69−1.49 (m, 1H), 1.40 (s, 3H), 1.28 (s, 3H), 1.13 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.8, 175.2, 173.4, 159.6, 151.2, 150.9, 138.3, 134.1, 128.2, 127.3, 123.1, 121.9, 121.5, 118.1, 114.5, 67.3, 34.9, 32.4, 31.6, 31.2, 27.6, 24.7, 9.3, 8.9; ESIMS m/z 415 $[M + Na]^+$; HRESIMS m/z 415.1516 $[M + Na]^+$ (calcd for $C_{24}H_{24}O_5Na$ 415.1521).

*2-Ethyl-1,6,6-trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**31**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (s, 2H), 6.42 (t, J = 3.6 Hz, 1H), 2.65 (q, J = 7.5 Hz, 2H), 2.26 (qd, J = 7.6, 3.2 Hz, 2H), 2.21−2.12 (m, 4H), 2.04−1.78 (m, 2H), 1.59−1.48 (m, 1H), 1.38 (s, 3H), 1.30−1.17 (m, 3H), 1.18−1.04 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.2, 175.3, 173.4, 159.2, 156.2, 150.0, 138.0, 134.0, 128.7, 126.8, 122.7, 121.1, 114.4, 67.3, 34.8, 32.4, 31.6, 31.1, 27.6, 24.7, 19.23, 12.7, 9.34, 8.7; ESIMS m/z 395 $[M + H]^+$; HRESIMS m/z 395.1852 $[M + H]^+$ (calcd for $C_{24}H_{27}O_5$ 395.1858).

*2-Bromo-1,6,6-trimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**32**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79−7.61 (m, 2H), 6.43−6.36 (m, 1H), 2.35−2.10 (m, 6H), 2.05−1.81 (m, 2H), 1.63−1.45 (m, 1H), 1.39 (s, 3H), 1.27 (s, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 174.1, 173.3, 161.2, 151.2, 138.5, 134.3, 127.6, 126.9, 125.2, 122.9, 121.1, 120.7, 67.2, 34.9, 32.3, 31.6, 31.1, 27.6, 24.7, 9.56, 9.3; ESIMS m/z 467 $[M + Na]^+$; HRESIMS m/z 467.0452 $[M + Na]^+$ (calcd for $C_{22}H_{21}O_5BrNa$ 467.0470).

*1-(Chloromethyl)-6,6-dimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**33**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 2H), 7.57 (s, 1H), 6.46 (s, 1H), 4.72 (s,

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2H), 2.19−2.36 (m, 3H), 1.87−2.06 (m, 2H), 1.55−1.65 (d, 1H), 1.43 (s, 3H), 1.30 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.52, 174.80, 173.85, 162.31, 151.97, 143.82, 139.06, 134.73, 128.28, 127.64, 123.76, 123.62, 118.80, 67.65, 35.73, 35.38, 32.74, 32.02, 31.61, 28.03, 25.13, 9.73; EIMS m/z 400 [M^+] (6), 343 (100), 292 (26), 277 (47), 263 (46); HREIMS m/z 400.1080 (calcd for $C_{22}H_{21}ClO_5$ 400.1078).

*1-(Hydroxymethyl)-6,6-dimethyl-10,11-dioxo-6,7,8,9,10,11-hexahydrophenanthro[1,2-b]furan-9-yl propionate (**34**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (s, 2H), 7.42 (s, 1H), 6.44 (t, J = 3.0 Hz, 1H), 4.68 (d, J = 3.0, 2H), 3.49 (brs, 1H), 2.18−2.32 (m, 3H), 2.07−1.86 (m, 2H), 1.41 (s, 3H), 1.29 (s, 3H), 1.14 (t, J = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.88, 175.18, 173.18, 162.45, 151.45, 140.70, 138.44, 134.18, 127.61, 126.81, 125.80, 123.05, 119.56, 66.97, 55.01, 34.73, 32.04, 31.34, 30.93, 27.37, 24.45, 9.08; EIMS m/z 382 [M^+] (4), 308 (100), 292 (52), 263 (49); HREIMS m/z 382.1424 (calcd for $C_{22}H_{22}O_6$ 382.1416).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00370.

^{1}H and ^{13}C NMR spectra for compounds **4**−**34** and chiral HPLC spectra of compound **27** (PDF)

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Notes

The authors declare no competing financial interest.

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