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Copper-Catalyzed [2 + 2 + 3] Annulation of 1,6-Enynes with α-Bromo-1,3-Dicarbonyl Compounds: Synthesis of Dihydrooxepines

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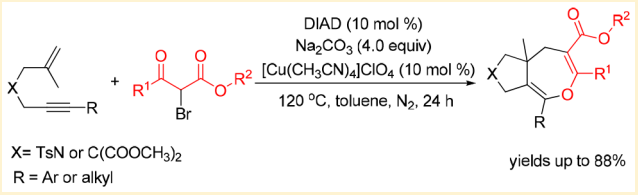
Supporting Information

ABSTRACT: Copper-catalyzed [2 + 2 + 3] annulation of 1,6-enynes with α-bromo-1,3-dicarbonyl compounds is described. This reaction provides facile access to seven-membered dihydrooxepines for epidithiodiketopiperazines with two newly formed C−C bonds and one C−O bond.



The seven-membered dihydrooxepine subunit is found in a wide variety of natural products in which epidithiodiketopiperazines (ETPs) have generally attracted much attention from many research groups for valuable synthetic significance.[1] Classical ETPs, such as (−)-emethallicin A (**1**),[2] acetylapoaranotin (**2**),[3] (−)-acetylaranotin (**3**),[4] (−)-SCH 64874 (**4**),[5] hirsutellomycin (**5**),[6] (+)-MPC 1001 (**6**),[7] and (+)-emestrin (**7**)[8] are recognized as biological properties relevant to the treatment of cancer cell lines and strong antifungal activities (Figure 1). In these reports, the synthesis of dihydrooxepine subunits generally requires several steps from commercially available starting materials. Further interest in new routes for constructing the dihydrooxepine ring system further stimulates studies in this area.

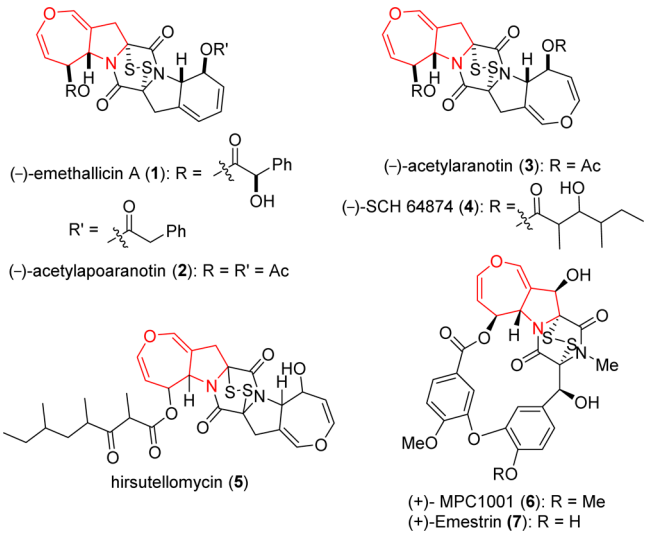


Figure 1. Representative active molecule possessing a dihydrooxepine moiety.

Construction of the C−O bond is one of the most widely used methods for producing alcohols, ethers, and esters for the synthesis of biologically active molecules, materials, and natural products.[9] In recent years, significant progress has been made in C−O bond formation from carbon−halide bonds, which is limited by tedious prefunctionalization of substrates[10] or reductive elimination from Pd(IV) species.[11] The most widely used traditional atom-economical method to prepare oxygen-containing heterocycles is the catalytic hydroalkoxylation of alkenes or alkynes, which remains a challenge due to the relatively high bond enthalpies of most O−H bonds and the modest reactivity of electron-rich olefins with nucleophiles.[12] Additionally, 1,3-dicarbonyl compounds are usually employed to build C−O bonds with alkynes, functional olefins,[13] or cinnamaldehyde[14] for the synthesis of furans or dihydropyranones. Seven-membered lactone was produced through a cascade esterification-alkylation reaction in the presence of a copper(I)-TPMA catalyst system followed by hydrolysis to give various *Z*-olefin compounds.[15] To the best of our knowledge, despite that C−O bond formation has been widely used in natural product syntheses, a convenient route for constructing the C−O bond in seven-membered dihydrooxepines has scarcely been reported.[16] In the present work, an atom-economical approach to the seven-membered dihydrooxepine unit with new C−O bond formation via radical annulation of 1,6-enynes **1** with α-bromo-1,3-dicarbonyl compounds **2** is described. In this reaction, a new type of formation of the C(sp^2)−O bond in the seven-membered dihydrooxepines is presented through enolate coupling with vinylic bromide in the presence of the Cu catalyst.

By taking into consideration the catalytic ability of copper complexes[17] in enyne cyclization, we started to explore the possibility of using a copper catalyst for this enyne radical

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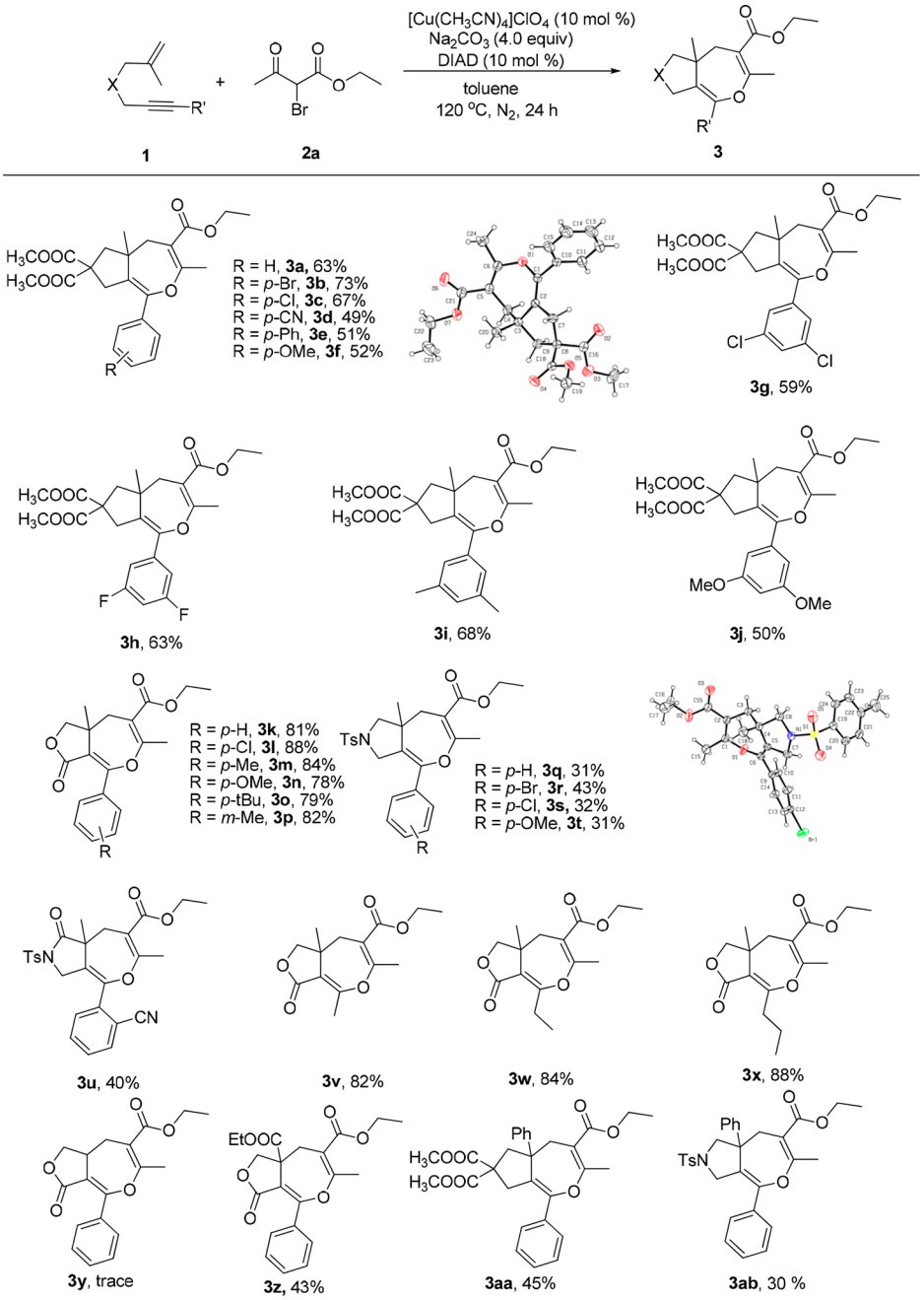
Scheme 1. Reaction of 1,6-Enynes 1 with 2-Bromo-3-oxobutanoate 2a[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.5 mmol), $[Cu(CH_3CN)_4]ClO_4$ (10 mol %), Na_2CO_3 (4.0 equiv), DIAD (10 mol %), toluene (2 mL), 120 °C, 24 h, under N_2.

cyclization to give seven-membered heterocycles. The treatment of 1,6-enynes **1a** with 2-bromo keto esters **2a** in the presence of CuCl (10 mol %) and Na_2CO_3 (2.5 equiv) in DCE at 120 °C under N_2 for 24 h gave desired product **3a** smoothly in 24% yield (Table S1, entry 1). A short survey on solvents showed that toluene was the most efficient (entries 2−5) and that $[Cu(CH_3CN)_4]ClO_4$ performed with a slight advantage over that of other Cu salts (entries 6−15). The base played an important role in this reaction: DBU, CsF, and *t*-BuOLi were totally inactive, whereas NaOAc, $NaHCO_3$, and Na_2CO_3 showed positive effects (entries 17−23). Both Cu and base were necessary for this transformation (entries 16 and 24). When one and a half equivalents of $NaHCO_3$ were added to the reaction system, a yield of 48% was achieved (entry 25). To our delight, the addition of diisopropyl azodicarboxylate (DIAD) or diethyl azodicarboxylate (DEAD) could benefit this reaction as a reagent to promote the regeneration of Cu(I) species[18] (entries 26 and 27). The reaction could not to be carried out at other temperatures as efficiently as at 120 °C (entries 28−31). Increasing Na_2CO_3 or $NaHCO_3$ to 4.0 equiv led to a similar effect compared to that of a mixture of those two bases (entries 32 and 33). Because CO_2 is released from $NaHCO_3$ at 120 °C, Na_2CO_3 was identified as the best chioce.

With the optimal reaction conditions in hand, the scope of 1,6-enyne substrates was then investigated. As shown in Scheme 1, malonate-tethered enynes with several substituents,

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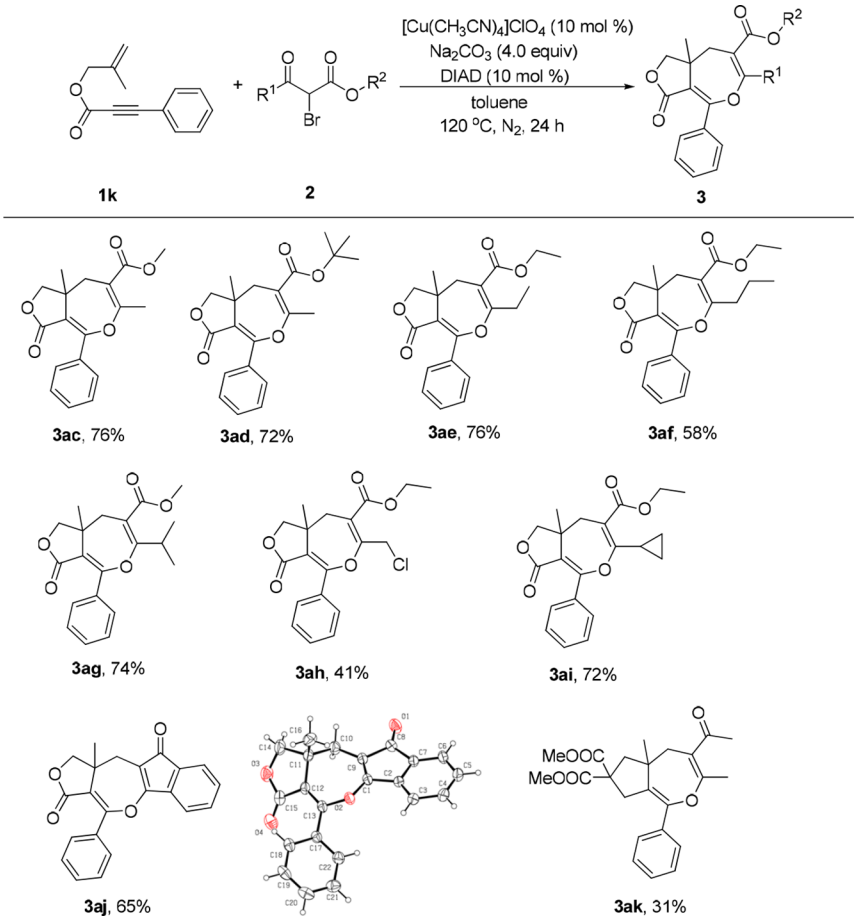
Scheme 2. Reaction of 1a with α-Bromo-1,3-dicarbonyl Compounds 2[a]



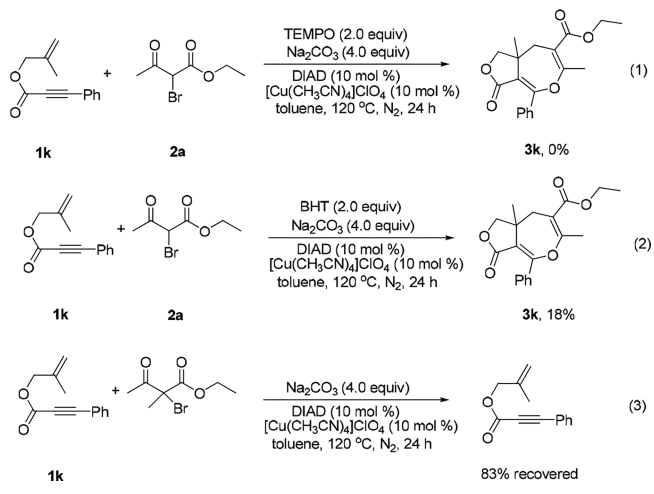
[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.5 mmol), $[Cu(CH_3CN)_4]ClO_4$ (10 mol %), Na_2CO_3 (4.0 equiv), DIAD (10 mol %), toluene (2 mL), 120 °C, 24 h, under N_2.

such as Br, Cl, CN, Ph, and OMe, on the para position of the aromatic ring were well-tolerated and gave desired products **3b**−**3f** in good yields. A key characteristic is that the electron-withdrawing groups showed more compatibilities. Enynes bearing two substituent groups on the aryl proceeded smoothly to afford the corresponding products **3g**−**3j** in this transformation. Moreover, the reaction of ester-tethered 1,6-enynes with 2-bromo-3-oxobutanoate would lead to the respective product under the optimized conditions in excellent yields (**3k**−**3p**). The *N*-tethered 1,6-enynes gave declining yields due to slight decomposition as observed (**3q**−**3u**). Gratifyingly, the aliphatic 1,6-enynes showed compatibility to this transformation and gave the desired products in satisfactory yields (**3v**−**3x**). When no methyl substituent was connected with the vinyl moiety, there was only a trace of desired product **3y**. Ph and CO_2Et substituent enynes had slightly lower yields than that of the methyl substituent one (**3z**−**3ab**). The structures of **3a** and **3r** were confirmed by X-ray crystal structure analysis.[19]

Next, the scope of the α-bromo-1,3-dicarbonyl compounds **2** was examined (Scheme 2). Under standard conditions, alkyl-substituted α-bromo-1,3-dicarbonyl compounds underwent this radical cyclization with ester-tethered enyne **1k** smoothly, providing the cyclic products in good yields (**3ac**−**3ag**). Similarly, chloroethane-substituted keto esters also furnished the reaction in 41% yield (**3ah**). Substituted α-bromo-1,3-dicarbonyl compounds of propylene lowered the efficiency of this transformation, and **3ai** was produced in 72% yield. Product **3aj** could be obtained using α-bromo-1,3-indanedione through annulation in moderate yields, which was confirmed by X-ray crystal structure analysis.[19] A low yield was obtained when enyne was reacted with 3-bromopentane-2,4-dione due to their instability together (**3ak**).

To gain further mechanistic insight into this reaction, some necessary control experiments were carried out (Scheme 3).

Scheme 3. Investigation of the Reaction Mechanism



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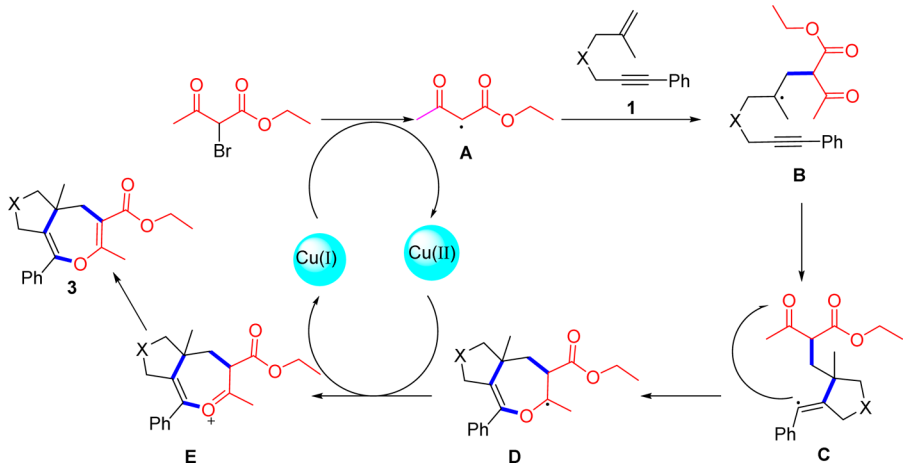
Scheme 4. Plausible Mechanism



The reaction was suppressed absolutely by the radical scavenger of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). When BHT (2,6-di-*tert*-butyl-4-methyl-phenol) was added to the optimal conditions, the desired product was obtained in a very low yield. These results suggested that the reaction may proceed through a free-radical pathway. When ethyl 2-bromo-2-methyl-3-oxobutanoate was employed, the enyne **1k** was recovered in 83% yield, indicated that the proton is necessary in this reaction.

On the basis of the present results, a plausible mechanism for this reaction is proposed in Scheme 4. Initially, radical intermediate **A** is formed via the activation of 2-bromo keto esters in the presence of Cu(I) species. The addition of intermediate **A** to 1,6-enynes **1** generated intermediate **B**, followed by cyclization with a C−C triple bond to afford alkene adduct **C**. Intermediate **C** undergoes 7-*endo*-trig annulation to afford intermediate **D**.[20] Then, **D** is oxidized by the copper catalyst to offord oxonium cation **E** with DIAD as the reducing reagent for the regeneration of Cu(I) species.[18,21] Finally, deprotonation of **E** gave radical cyclization product **3**.[21]

In conclusion, we have accomplished a Cu-catalyzed [2 + 2 + 3] annulation of 1,6-enynes with α-bromo-1,3-dicarbonyl compounds for the synthesis of dihydrooxepines in which two new C−C bonds and one C−O bond were formed through a radical process in one step. The seven-membered dihydrooxepine is identified to be significant scaffold in the epidithiodiketopiperazines and widely exists in a class of important natural products. Further investigation of the mechanistic pathway and synthesis of backbones for some important natural products are underway in our laboratory and will be reported elsewhere.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, reactions were carried out under an argon atmosphere. For column chromatography, a 200−300 mesh silica gel was employed. Analytical TLC was performed with silica gel GF254 plates. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded in $CDCl_3$ using TMS as the internal standard. ^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$. Chemical shifts (ppm) were recorded with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dq (doublet of quartets), q (quartet), or m (multiplet). HR-MS was obtained using a Q-TOF instrument equipped with an ESI source. Data collection for crystal structures was performed at room temperature (293 K) using Mo Kα radiation on a Bruker APEXII diffractometer. All compounds and copies of their ^{1}H and ^{13}C NMR spectra are provided in the Supporting Information.

General Procedure for the Synthesis of Substrate 1. All of the 1,6-enynes were synthesized according to previous literature, and the NMR spectroscopy and GC-MS data were in full accordance with the data reported in the literature.[22]

To a solution of 4-methyl-*N*-(prop-2-ynyl)benzenesulfonamide (1.0 mmol) in CH_2Cl_2 (5 mL) was added iPr_2NEt (1.5 mmol), which was then cooled to 0 °C in the ice−water bath. Methacryloyl chloride (1.2 mmol) was slowly added to the solution at 0 °C, and then the mixture was stirred at room temperature for 1 h. The reaction was quenched by water, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography to afford product **C** as a white solid.

To a dried Schlenk flask was added $Pd(PPh_3)_2Cl_2$ (0.2 mmol), CuI (0.2 mmol), iodobenzene (11.0 mmol), **C** (10.0 mmol), and freshly distilled Et_3N under argon. The resulting mixture was stirred for 16 h at 50 °C. Then, 50 mL of MTBE was added, and the mixture was filtered. After removal of solvent using a rotary evaporator, the residue was purified by flash column chromatography to afford **1**.

General Procedure for the Synthesis of Product 3. In an oven-dried tube, enynes **1** (0.2 mmol), $Cu(CH_3CN)_4ClO_4$ (10 mol %), and Na_2CO_3 (0.8 mmol) were added and charged with nitrogen more than three times. α-Bromo-1,3-dicarbonyl compounds **2** (0.5 mmol) and toluene (2.0 mL) were added, and the DIAD (10 mol %) was subsequent injected into the tube. Afterward, the mixture was allowed to stir at 120 °C for 24 h. When the reaction was considered complete, the solvent was removed under vacuo, and the residue was purified with a chromatography column (PE-EtOAc, 10:1) on silica gel and recrystallized to afford product **3**.

*4-Ethyl 7,7-Dimethyl 3,5a-Dimethyl-1-phenyl-5a,6-dihydro-5H-cyclopenta[c]oxepine-4,7,7(8H)-tricarboxylate (**3a**).* Yellow solid (54.0 mg, 63% yield); mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.26 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.25 (d, J = 1.2 Hz, 3H), 2.39−2.46 (m, 2H), 2.55 (d, J = 15.2 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 3.01 (d, J = 16.4 Hz, 1H), 3.26 (d, J = 16.0 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 4.17−4.22 (m, 2H), 7.28−7.33 (m, 1H), 7.35−7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.3, 172.1, 169.5, 162.3, 145.4, 137.0, 128.2, 128.0, 127.6, 110.0, 60.4, 57.7, 52.9, 52.8, 48.8, 44.0, 39.9, 39.5, 25.5, 22.0, 14.3; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{24}H_{28}O_7Na$ 451.1727, found 451.1733.

*4-Ethyl 7,7-Dimethyl 1-(4-Bromophenyl)-3,5a-dimethyl-5a,6-dihydro-5H-cyclopenta[c]oxepine-4,7,7(8H)-tricarboxylate (**3b**).* Yellow oil (73.8 mg, 73% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.24 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.23 (d, J = 1.2 Hz, 3H), 2.42 (dd, J = 13.6, J = 23.2 Hz, 2H), 2.54 (d, J = 16.0 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H), 3.23 (d, J = 16.4 Hz, 1H),

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3.68 (s, 3H), 3.74 (s, 3H), 4.19 (q, J = 7.2 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.1, 172.0, 169.3, 162.1, 144.3, 135.8, 131.1, 129.8, 128.2, 122.0, 110.2, 60.5, 57.6, 52.9, 52.9, 48.6, 44.1, 39.7, 39.5, 25.4, 21.9, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{27}BrO_7Na$ 529.0832, found 529.0838.

4-Ethyl 7-Methyl 7-Acetoxy-1-(4-chlorophenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta-[c]oxepine-4,7-dicarboxylate (**3c**). Yellow oil (61.9 mg, 67% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.24 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.23 (d, J = 1.2 Hz, 3H), 2.37−2.46 (m, 2H), 2.54 (d, J = 15.2 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 2.96 (d, J = 16.0 Hz, 1H), 3.23 (d, J = 16.0 Hz, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 4.17−4.22 (m, 2H), 7.32 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.2, 172.0, 169.4, 162.1, 144.3, 135.4, 133.8, 129.6, 128.2, 128.0, 110.2, 60.5, 57.6, 53.0, 52.9, 48.7, 44.1, 39.8, 39.5, 25.4, 22.0, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{27}ClO_7Na$ 485.1338, found 485.1345.

4-Ethyl 7-Methyl 7-Acetoxy-1-(4-cyanophenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3d**). Yellow solid (44.4 mg, 49% yield); mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.27 (s, 3H), 1.29−1.32 (m, 3H), 2.25 (s, 3H), 2.44 (dd, J = 13.6 Hz, J = 35.2 Hz, 2H), 2.54 (d, J = 15.6 Hz, 1H), 2.75 (d, J = 15.2 Hz, 1H), 2.98 (d, J = 16.0 Hz, 1H), 3.25 (d, J = 16.0 Hz, 1H), 3.69 (s, 3H), 3.75 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.9, 171.8, 169.1, 161.8, 143.6, 141.2, 131.8, 130.5, 128.7, 118.5, 111.5, 110.6, 60.5, 57.6, 52.9, 52.9, 48.5, 44.4, 39.6, 39.4, 25.3, 21.8, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{25}H_{27}NO_7Na$ 476.1680, found 476.1682.

4-Ethyl 7-Methyl 1-([1,1′-Biphenyl]-4-yl)-7-acetoxy-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3e**). White solid (51.0 mg, 51% yield); mp 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.28 (s, 3H), 1.28−1.32 (m, 3H), 2.28 (s, 3H), 2.44 (dd, J = 13.6 Hz, J = 18.0 Hz, 2H), 2.58 (d, J = 15.2 Hz, 1H), 2.75 (d, J = 15.2 Hz, 1H), 3.07 (d, J = 15.2 Hz, 1H), 3.32 (d, J = 16.4 Hz, 1H), 3.68 (s, 3H), 3.74 (s, 3H), 4.17−4.23 (m, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.44 (dd, J = 8.0 Hz, J = 14.8 Hz, 4H), 7.57−7.61 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.2, 172.1, 169.4, 162.2, 145.1, 140.7, 140.5, 135.9, 128.7, 128.6, 128.0, 127.4, 127.0, 126.6, 110.0, 60.3, 57.7, 52.8, 52.8, 48.8, 44.1, 39.9, 39.6, 25.4, 22.0, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{30}H_{32}O_7Na$ 527.2040, found 527.2045.

4-Ethyl 7-Methyl 7-Acetoxy-1-(4-methoxyphenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3f**). Yellow solid (47.6 mg, 52% yield); mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.25 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.38−2.46 (m, 2H), 2.54 (d, J = 15.2 Hz, 1H), 2.72 (d, J = 15.2 Hz, 1H), 3.00 (d, J = 16.0 Hz, 1H), 3.24 (d, J = 16.0 Hz, 1H), 3.68 (s, 3H), 3.73 (s, 3H), 3.82 (s, 3H), 4.16−4.22 (m, 2H), 6.87 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.3, 172.1, 169.5, 162.3, 159.2, 145.2, 129.6, 129.5, 126.7, 113.3, 109.9, 60.3, 57.7, 55.2, 52.8, 52.8, 48.8, 43.9, 40.0, 39.6, 25.4, 22.0, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{25}H_{30}O_8Na$ 481.1833, found 481.1838.

4-Ethyl 7-Methyl 7-Acetoxy-1-(3,5-dichlorophenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3g**). Yellow solid (58.5 mg, 59% yield); mp 107−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.23 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.23 (d, J = 0.8 Hz, 3H), 2.42 (dd, J = 13.6 Hz, J = 18.0 Hz, 2H), 2.53 (d, J = 14.8 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H), 3.23 (d, J = 16.4 Hz, 1H), 3.71 (s, 3H), 3.75 (s, 3H), 4.17−4.23 (m,2H), 7.26−7.27 (m, 2H), 7.30 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 171.9, 169.1, 162.0, 142.9, 139.7, 134.6, 129.5, 128.1, 126.7, 110.8, 60.5, 57.5, 53.0, 48.6, 44.3, 39.5, 39.4, 30.9, 25.5, 21.8, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{26}Cl_2O_7Na$ 519.0948, found 519.0955.

4-Ethyl 7-Methyl 7-Acetoxy-1-(3,5-difluorophenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3h**). White solid (58.5 mg, 63% yield); mp 111−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.25 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.25 (s, 3H), 2.42 (dd, J = 13.6 Hz, J = 26.0 Hz, 2H), 2.53 (d, J = 15.2 Hz, 1H), 2.73 (d, J = 15.2 Hz, 1H), 3.02 (d, J = 16.4 Hz, 1H), 3.24 (d, J = 16.4 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 4.20 (q, J = 7.2 Hz, 2H), 6.73−6.79 (m, 1H), 6.92−6.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.0, 171.9, 169.2, 162.5 (dd, J = 246.5 Hz, J = 12.9 Hz), 161.8, 143.2 (t, J = 2.8 Hz), 139.9 (t, J = 9.5 Hz), 129.7, 111.2 (d, J = 25.8 Hz), 110.5, 103.4 (t, J = 25.1 Hz), 60.6, 57.7, 53.0, 52.9, 48.6, 44.3, 39.7, 39.5, 25.3, 21.9, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{26}F_2O_7Na$ 487.1539, found 487.1548.

4-Ethyl 7-Methyl 7-Acetoxy-1-(3,5-dimethylphenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3i**). Yellow solid (62.0 mg, 68% yield); mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.24 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.24 (d, J = 1.2 Hz, 3H), 2.32 (s, 6H), 2.42 (d, J = 1.6 Hz, 2H), 2.55 (d, J = 14.8 Hz, 1H), 2.74 (d, J = 15.2 Hz, 1H), 2.95 (d, J = 16.0 Hz, 1H), 3.24 (d, J = 16.0 Hz, 1H), 3.68 (s, 3H), 3.73 (s, 3H), 4.17−4.22 (m, 2H), 6.95 (d, J = 14.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.3, 172.1, 169.4, 162.5, 145.6, 137.4, 136.9, 129.6, 126.9, 126.0, 110.0, 60.3, 57.6, 52.8, 52.7, 48.8, 43.9, 39.8, 39.5, 25.5, 22.0, 21.2, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{32}O_7Na$ 479.2040, found 479.2046.

4-Ethyl 7-Methyl 7-Acetoxy-1-(3,5-dimethoxyphenyl)-3,5a-dimethyl-5a,6,7,8-tetrahydro-5H-cyclopenta[c]oxepine-4,7-dicarboxylate (**3j**). Yellow solid (49.0 mg, 50% yield); mp 106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.22 (s, 3H), 1.29−1.32 (m, 3H), 2.21 (d, J = 1.2 Hz, 3H), 2.41 (s, 2H), 2.61 (d, J = 14.4 Hz, 1H), 2.70 (d, J = 16.4 Hz, 1H), 2.77 (d, J = 14.4 Hz, 1H), 3.08 (d, J = 16.4 Hz, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 3.76 (s, 3H), 3.79 (s, 3H), 4.16−4.24 (m, 2H), 6.84 (s, 2H), 6.85 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.5, 172.3 169.5, 153.3, 151.5, 142.2, 127.8, 126.9, 116.3, 114.9, 112.9, 60.3, 57.0, 56.4, 55.8, 52.8, 52.7, 48.9, 43.8, 39.3, 38.9, 25.6, 21.8, 14.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{32}O_9Na$ 511.1939, found 511.1952.

Ethyl 6,8a-Dimethyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3k**). White solid (53.0 mg, 81% yield); mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.31 (s, 3H), 1.33−1.36 (m, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.72 (d, J = 13.6 Hz, 1H), 2.88 (d, J = 14.4 Hz, 1H), 3.97 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 4.22−4.28 (m, 2H), 7.37−7.45 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.0, 167.9, 162.2, 160.1, 133.4, 130.1, 129.1, 127.7, 113.2, 112.6, 61.0, 45.4, 36.1, 25.1, 21.5, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{20}O_5Na$ 351.1203, found 351.1209.

Ethyl 4-(4-Chlorophenyl)-6,8a-dimethyl-3-oxo-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3l**). Yellow solid (64.0 mg, 88% yield); mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.31−1.35 (m, 3H), 1.37 (s, 3H), 2.35 (d, J = 1.6 Hz, 3H), 2.71 (d, J = 14.4 Hz, 1H), 2.88 (d, J = 14.4 Hz, 1H), 3.97 (d, J = 8.4 Hz, 1H), 4.06 (d, J = 8.4 Hz, 1H), 4.22−4.28 (m, 2H), 7.35−7.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.6, 167.9, 162.0, 158.9, 136.1, 131.8, 130.6, 128.1, 113.7, 112.7, 75.7, 61.1, 45.3, 36.1, 25.2, 21.5, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{19}H_{19}ClO_5Na$ 385.0813, found 385.0820.

Ethyl 6,8a-Dimethyl-3-oxo-4-(p-tolyl)-1,3,8,8a-tetrahydrofuro-[3,4-c]oxepine-7-carboxylate (**3m**). White solid (57.5 mg, 84% yield); mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.33 (t, J = 7.2 Hz, 3H), 1.36 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.38 (s, 3H), 2.70 (d, J = 14.0 Hz, 1H), 2.86 (d, J = 14.0 Hz, 1H), 3.96 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 8.4 Hz, 1H), 4.21−4.29 (m, 2H), 7.19 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.8, 168.0, 162.1, 160.4, 140.4, 130.5, 129.1, 128.5, 112.9, 112.5, 75.7, 61.0, 45.3, 36.1, 25.1, 21.5, 21.4, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}O_5Na$ 365.1359, found 365.1362.

Ethyl 4-(4-Methoxyphenyl)-6,8a-dimethyl-3-oxo-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3n**). Yellow solid (56.0 mg, 78% yield); mp 103−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.33 (t, J = 7.2 Hz, 3H), 1.36 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.70 (d, J = 14.4 Hz, 1H), 2.85 (d, J = 14.4 Hz, 1H), 3.83 (s, 3H), 3.97 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.0 Hz, 1H), 4.22−4.28 (m, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.0, 168.1, 161.9, 161.2, 160.4, 131.0, 125.5, 113.2, 112.5, 112.5, 75.7, 61.0, 55.2, 45.2, 36.3, 25.0, 21.6, 14.2;

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HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}O_6Na$ 381.1309, found 381.1317.

*Ethyl 4-(4-(tert-Butyl)phenyl)-6,8a-dimethyl-3-oxo-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3o**).* White solid (60.0 mg, 79% yield); mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.31−1.34 (m, 12H), 1.36 (s, 3H), 2.37 (d, J = 1.6 Hz, 3H), 2.71 (d, J = 14.4 Hz, 1H), 2.86 (d, J = 14.0 Hz, 1H), 3.97 (d, J = 8.0 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 4.21−4.29 (m, 2H), 7.41 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.8, 168.0, 162.2, 160.4, 153.4, 130.4, 129.0, 124.7, 112.9, 112.6, 75.7, 61.0, 45.4, 36.1, 34.7, 31.1, 25.0, 21.5, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{23}H_{28}O_5Na$ 407.1829, found 407.1836.

*Ethyl 6,8a-Dimethyl-3-oxo-4-(m-tolyl)-1,3,8,8a-tetrahydrofuro-[3,4-c]oxepine-7-carboxylate (**3p**).* White solid (56.0 mg, 82% yield); mp 103−105 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.33 (d, J = 7.2 Hz, 3H), 1.36 (s, 3H), 2.36 (d, J = 1.2 Hz, 3H), 2.37 (s, 3H), 2.71 (d, J = 14.4 Hz, 1H), 2.87 (d, J = 14.4 Hz, 1H), 3.96 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 4.22−4.29 (m, 2H), 7.22−7.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.7, 167.9, 162.2, 160.3, 137.4, 133.4, 130.9, 129.6, 127.7, 126.3, 113.1, 112.6, 75.6, 61.0, 45.4, 36.0, 25.1, 21.5, 21.2, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{22}O_5Na$ 365.1359, found 365.1361.

*Ethyl 6,8a-Dimethyl-4-phenyl-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate (**3q**).* White solid (29.0 mg, 31% yield); mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.21 (s, 3H), 1.28−1.32 (m, 3H), 2.25 (s, 3H), 2.44 (s, 3H), 2.62 (d, J = 14.4 Hz, 1H), 2.73 (d, J = 14.4 Hz, 1H), 3.01 (d, J = 9.2 Hz, 1H), 3.17 (d, J = 9.2 Hz, 1H), 3.83 (d, J = 13.2 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 4.17−4.23 (m, 2H), 7.18−7.21 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.34−7.36 (m, 3H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.7, 163.6, 145.9, 143.7, 135.9, 132.7, 129.7, 128.6, 128.2, 127.7, 127.5, 123.0, 111.1, 60.6, 60.4, 51.3, 44.0, 36.7, 23.7, 21.8, 21.5, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{29}NO_5SNa$ 490.1659, found 490.1664.

*Ethyl 4-(4-Bromophenyl)-6,8a-dimethyl-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate (**3r**).* Yellow solid (47.0 mg, 43% yield); mp 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.20 (s, 3H), 1.28−1.32 (m, 3H), 2.24 (s, 3H), 2.44 (s, 3H), 2.60 (d, J = 14.8 Hz, 1H), 2.73 (d, J = 14.4 Hz, 1H), 2.99 (d, J = 9.2 Hz, 1H), 3.18 (d, J = 8.8 Hz, 1H), 3.76 (d, J = 13.2 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 4.17−4.22 (m, 2H), 7.07 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.6, 163.4, 144.9, 143.8, 134.8, 132.7, 131.4, 129.7, 129.1, 127.7, 123.5, 122.7, 111.4, 60.7, 60.3, 51.2, 44.1, 36.5, 23.8, 21.7, 21.5, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{28}BrNO_5SNa$ 568.0764, found 568.0774.

*Ethyl 4-(4-Chlorophenyl)-6,8a-dimethyl-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate (**3s**).* Yellow solid (32.0 mg, 32% yield); mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.20 (s, 3H), 1.28−1.32 (m, 3H), 2.23 (d, J = 0.8 Hz, 3H), 2.44 (s, 3H), 2.58−2.62 (m, 1H), 2.73 (d, J = 14.8 Hz, 1H), 3.00 (d, J = 9.2 Hz, 1H), 3.18 (d, J = 9.2 Hz, 1H), 3.77 (d, J = 13.2 Hz, 1H), 4.02 (d, J = 13.2 Hz, 1H), 4.17−4.23 (m, 2H), 7.14 (d, J = 8.4 Hz, 2H), 7.31−7.34 (m, 4H), 7.65 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.9, 163.7, 145.2, 144.1, 134.8, 134.7, 133.2, 130.0, 129.2, 128.8, 128.0, 123.8, 111.7, 61.0, 60.6, 51.5, 44.5, 36.9, 24.1, 22.0, 21.8, 14.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{28}ClNO_5SNa$ 524.1269, found 524.1274.

*Ethyl 4-(4-Methoxyphenyl)-6,8a-dimethyl-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate (**3t**).* White solid (31.0 mg, 31% yield); mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.20 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 2.25 (s, 3H), 2.44 (s, 3H), 2.61 (d, J = 14.4 Hz, 1H), 2.72 (d, J = 14.8 Hz, 1H), 3.01 (d, J = 9.2 Hz, 1H), 3.15 (d, J = 8.8 Hz, 1H), 3.82 (d, J = 12.8 Hz, 1H), 3.83 (s, 3H), 4.01 (d, J = 13.2 Hz, 1H), 4.19 (dd, J = 7.2 Hz, J = 14.0 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.8, 163.6, 159.6, 145.8, 143.6, 132.9, 129.7, 128.9, 128.5, 127.7, 122.1, 113.5, 111.1, 60.5, 60.4, 55.3, 51.4, 44.0, 36.8, 23.7, 21.8, 21.5, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{27}H_{31}NO_6SNa$ 520.1764, found 520.1771.

*Ethyl 4-(2-Cyanophenyl)-6,8a-dimethyl-1-oxo-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate (**3u**).* White solid (40.5 mg, 40% yield); mp 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.23 (s, 3H), 1.29 (d, J = 7.2 Hz, 3H), 2.26 (d, J = 1.2 Hz, 3H), 2.45 (s, 3H), 2.57 (d, J = 14.8 Hz, 1H), 3.10 (d, J = 14.8 Hz, 1H), 4.03 (d, J = 13.2 Hz, 1H), 4.17−4.22 (m, 2H), 4.41 (d, J = 13.2 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.55−7.59 (m, 1H), 7.68−7.72 (m, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 174.6, 168.1, 162.4, 145.6, 144.4, 138.1, 134.4, 133.3, 133.1, 129.9, 129.7, 129.4, 128.0, 116.9, 116.5, 112.4, 109.7, 60.8, 48.4, 47.3, 33.7, 22.4, 21.6, 21.2, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{27}H_{26}N_2O_6S$ Na 529.1404, found 529.1414.

*Ethyl 4,6,8a-Trimethyl-3-oxo-1,3,8,8a-tetrahydrofuro[3,4-c]-oxepine-7-carboxylate (**3v**).* White oil (43.6 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.24 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.29 (d, J = 2.0 Hz, 3H), 2.34 (s, 3H), 2.52 (d, J = 14.0 Hz, 1H), 2.78 (d, J = 14.0 Hz, 1H), 3.85 (d, J = 8.4 Hz, 1H), 4.00 (d, J = 8.4 Hz, 1H), 4.20−4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.4, 168.2, 161.8, 160.9, 111.9, 111.8, 75.9, 61.0, 44.4, 36.3, 25.6, 21.6, 18.9, 14.2; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{14}H_{18}O_5Na$ 289.1046, found 289.1054.

*Ethyl 4-Ethyl-6,8a-dimethyl-3-oxo-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3w**).* White oil (47.0 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.13−1.17 (m, 3H), 1.24 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.30 (d, J = 1.6 Hz, 3H), 2.52 (d, J = 14.4 Hz, 1H), 2.63−2.72 (m, 1H), 2.79 (d, J = 14.0 Hz, 1H), 2.83−2.92 (m, 1H), 3.85 (d, J = 8.0 Hz, 1H), 3.99 (d, J = 8.4 Hz, 1H), 4.20−4.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 168.2, 165.9, 162.1, 112.0, 111.2, 75.9, 61.0, 44.3, 36.2, 25.6, 25.1, 21.3, 14.2, 12.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}O_5Na$ 303.1203, found 303.1201.

*Ethyl 6,8a-Dimethyl-3-oxo-4-propyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3x**).* White oil (51.7 mg, 88% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.94−0.98 (m, 3H), 1.25 (s, 3H), 1.30−1.34 (m, 3H), 1.57−1.66 (m, 2H), 2.30 (s, 3H), 2.52 (d, J = 14.0 Hz, 1H), 2.64−2.71 (m, 1H), 2.78−2.86 (m, 2H), 3.85 (d, J = 8.4 Hz, 1H), 3.99 (d, J = 8.4 Hz, 1H), 4.20−4.26 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.0, 168.1, 164.5, 162.1, 112.0, 111.9, 75.8, 60.9, 44.3, 36.2, 33.1, 25.6, 21.3, 20.8, 14.2, 13.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{16}H_{22}O_5Na$ 317.1359, found 317.1356.

*Diethyl 6-Methyl-3-oxo-4-phenyl-1H,3H-furo[3,4-c]oxepine-7,8a-(8H)-dicarboxylate (**3z**).* White oil (33.1 mg, 43% yield); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 1.24 (t, J = 7.2 Hz, 3H), 1.31−1.35 (m, 3H), 2.31 (d, J = 1.6 Hz, 3H), 2.73 (dd, J = 1.6 Hz, J = 14.4 Hz, 1H), 3.40 (d, J = 14.0 Hz, 1H), 4.03 (d, J = 9.2 Hz, 1H), 4.11−4.25 (m, 4H), 4.57 (d, J = 9.2 Hz, 1H), 7.40−7.43 (m, 2H), 7.44−7.51(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.7, 168.6, 167.2, 162.4, 162.1, 133.1, 130.5, 129.2, 127.8, 112.0, 107.3, 71.5, 62.2, 61.1, 55.9, 34.0, 21.4, 14.2, 14.0; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{21}H_{22}O_7Na$ 409.1258, found 409.1261.

*4-Ethyl 7,7-Dimethyl 3-Methyl-1,5a-diphenyl-5a,6-dihydro-5H-cyclopenta[c]oxepine-4,7,7(8H)-tricarboxylate (**3aa**).* Yellow oil (44.0 mg, 45% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.11−1.15 (m, 3H), 2.05 (d, J = 0.8 Hz, 3H), 2.71 (d, J = 13.2 Hz, 1H), 2.84 (dd, J = 1.2 Hz, J = 14.4 Hz, 1H), 2.92−3.00 (m, 2H), 3.30 (s, 3H), 3.39 (d, J = 9.2 Hz, 1H), 3.43 (d, J = 11.2 Hz, 1H), 3.66 (s, 3H), 3.89−3.95 (m, 2H), 7.11−7.16 (m, 1H), 7.23−7.26 (m, 4H), 7.36 (d, J = 7.2 Hz, 1H), 7.41 (t, J = 7.2 Hz, 2H), 7.50−7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.1, 171.1, 168.1, 163.8, 146.7, 144.2, 137.1, 128.4, 128.2, 128.1, 127.8, 127.1, 126.3, 123.0, 110.8, 60.0, 57.4, 53.8, 52.9, 52.4, 48.9, 39.8, 39.5, 21.6, 14.1. HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{29}H_{30}O_7Na$ 513.1884, found 513.1890.

*Ethyl 6-Methyl-4,8a-diphenyl-2-tosyl-2,3,8,8a-tetrahydro-1H-oxepino[3,4-c]pyrrole-7-carboxylate(**3ab**).* Yellow oil (32.0 mg, 30% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.15 (t, J = 7.2 Hz, 3H), 2.06 (d, J = 0.8 Hz, 3H), 2.38 (s, 3H), 2.88−2.92 (m, 1H), 3.33 (d, J = 14.4 Hz, 1H), 3.42 (d, J = 9.6 Hz, 1H), 3.68 (d, J = 9.6 Hz,

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1H), 3.94 (dd, J = 4.8 Hz, J = 7.2 Hz, 2H), 4.01 (d, J = 4.8 Hz, 2H), 7.15 (d, J = 7.6 Hz, 3H), 7.17−7.19(m, 3H), 7.20 (d, J = 9.2 Hz, 1H), 7.30−7.33 (m, 2H), 7.40−7.41 (m, 3H), 7.47 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)167.8, 164.0, 147.8, 143.4, 142.6, 135.9, 132.9, 129.5, 128.9, 128.4, 128.3, 127.7, 127.5, 126.7, 126.7, 120.5, 111.3, 61.1, 60.3, 53.1, 51.9, 36.8, 21.5, 14.1. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{31}H_{31}NO_5SNa$ 552.1815, found 552.1819.

*Methyl 6,8a-Dimethyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro-[3,4-c]oxepine-7-carboxylate (**3ac**).* Yellow oil (47.7 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.36 (s, 3H), 2,37 (d, J = 1.6 Hz, 3H), 2.72 (d, J = 13.6 Hz, 1H), 2.89 (d, J = 14.4 Hz, 1H), 3.79 (s, 3H), 3.97 (d, J = 8.4 Hz, 1H), 4.06 (d, J = 8.0 Hz, 1H), 7.38−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.7, 168.4, 162.6, 160.1, 133.4, 130.2, 129.2, 127.8, 113.3, 112.2, 75.7, 52.1, 45.4, 36.1, 25.2, 21.6; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{18}O_5Na$ 337.1046, found 337.1048.

*tert-Butyl 6,8a-Dimethyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3ad**).* White solid (51.0 mg, 72% yield); mp 111−113 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.37 (s, 3H), 1.53 (s, 9H), 2.31 (d, J = 1.2 Hz, 3H), 2.69 (d, J = 14.0 Hz, 1H), 2.80 (d, J = 14.0 Hz, 1H), 3.97 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 7.37−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.9, 167.4, 160.8, 160.4, 133.6, 130.1, 129.2, 127.8, 114.4, 113.0, 81.6, 75.8, 45.6, 36.3, 28.1, 25.2, 21.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}O_5Na$ 379.1516, found 379.1520.

*Ethyl 6-Ethyl-8a-methyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro-[3,4-c]oxepine-7-carboxylate (**3ae**).* White oil (52.0 mg, 76% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.19−1.23 (m, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.36 (s, 3H), 2.49−2.58 (m, 1H), 2.72−2.78 (m, 1H), 2.80−2.87 (m, 2H), 3.97 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 4.23−4.28 (m, 2H), 7.38−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.8, 168.0, 166.6, 160.5, 133.6, 130.1, 129.1, 127.8, 113.0, 112.2, 75.7, 61.1, 45.5, 36.2, 28.2, 25.2, 14.1, 12.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{22}O_5Na$ 365.1359, found 365.1364.

*Ethyl 8a-Methyl-3-oxo-4-phenyl-6-propyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3af**).* White oil (41.3 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.96−1.00 (m, 3H), 1.33 (t, J = 7.2 Hz, 3H), 1.37 (s, 3H), 1.66 (dd, J = 7.6 Hz, J = 14.8 Hz, 2H), 2.46−2.53 (m, 1H), 2.72−2.79 (m, 1H), 2.81−2.87 (m, 2H), 3.96 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 4.22−4.28 (m, 2H), 7.38−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.9, 167.9, 165.5, 160.3, 133.6, 130.0, 129.0, 127.8, 113.0, 112.9, 75.6, 61.0, 45.6, 36.2, 36.1, 25.2, 21.0, 14.1, 13.8; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{24}O_5Na$ 379.1516, found 379.1525.

*Methyl 6-Isopropyl-8a-methyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3ag**).* White oil (50.6 mg, 74% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.30 (s, 3H), 1.32 (s, 3H), 1.36 (s, 3H), 2.35 (d, J = 1.6 Hz, 3H), 2.71 (d, J = 14.0 Hz, 1H), 2.86 (d, J = 14.0 Hz, 1H), 3.97 (d, J = 8.4 Hz, 1H), 4.05 (d, J = 8.4 Hz, 1H), 5.09−5.15 (m, 1H), 7.37−7.46 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.8, 167.5, 161.9, 160.2, 133.4, 130.1, 129.1, 127.8, 113.1, 113.1, 75.7, 68.6, 45.5, 36.0, 25.1, 21.7, 21.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{20}H_{22}O_5Na$ 365.1359, found 365.1363.

*Ethyl 6-(Chloromethyl)-8a-methyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3ah**).* Yellow oil (30.0 mg, 41% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.37 (t, J = 7.2 Hz, 3H), 1.39 (s, 3H), 2.78 (d, J = 14.4 Hz, 1H), 2.94 (d, J = 14.0 Hz, 1H), 3.99 (d, J = 8.4 Hz, 1H), 4.08 (d, J = 8.0 Hz, 1H), 4.22(d, J = 11.2 Hz, 1H), 4.28−4.34 (m, 2H), 5.00 (d, J = 11.6 Hz, 1H), 7.39−7.46 (m, 3H), 7.53−7.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.4, 166.5, 160.4, 158.7, 132.9, 130.4, 129.3, 127.9, 116.5, 113.4, 75.5, 61.9, 45.2, 42.7, 36.1, 25.2, 14.1; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{19}ClO_5Na$ 385.0813, found 385.0818.

*Ethyl 6-Cyclopropyl-8a-methyl-3-oxo-4-phenyl-1,3,8,8a-tetrahydrofuro[3,4-c]oxepine-7-carboxylate (**3ai**).* Yellow oil (51.0 mg, 72% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 0.72−0.75 (m, 2H), 0.77−0.86 (m, 1 H), 0.93−0.98 (m, 1H), 1.32−1.35 (m, 3H), 1.36 (s, 3H), 2.73 (d, J = 14.0, 1H), 2.82−2.88 (m, 1H), 2.92 (d, J = 14.0 Hz, 1H), 3.94 (d, J = 8.4 Hz, 1H), 4.04 (d, J = 8.0 Hz, 1H), 4.25−4.31 (m, 2H), 7.34−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.6, 168.2, 165.7, 159.9, 133.3, 130.0, 128.7, 127.9, 113.9, 112.2, 75.7, 60.9, 45.5, 36.1, 25.3, 14.2, 13.5, 7.16, 6.26; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{21}H_{22}O_5Na$ 377.1359, found 377.1361.

*11a-Methyl-4-phenyl-11,11a-dihydro-1H-furo[3,4-e]indeno[1,2-b]oxepine-3,10-dione (**3aj**).* Yellow solid (45.0 mg, 65% yield); mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.46 (s, 3H), 2.63 (d, J = 15.6 Hz, 1H), 2.78 (d, J = 16.0 Hz, 1H), 4.20 (dd, J = 8.8 Hz, J = 13.2 Hz, 2H), 7.22 (d, J = 6.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.37−7.40 (m, 1H), 7.45−7.48 (m, 3H), 7.50−7.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.8, 166.5, 162.1, 139.7, 133.1, 132.5, 131.0, 130.6, 129.8, 129.8, 128.0, 122.0, 118.5, 115.8, 111.5, 76.5, 42.6, 33.5, 25.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{16}O_4Na$ 367.0941, found 367.0947.

*Dimethyl 4-Acetyl-3,5a-dimethyl-1-phenyl-5a,6-dihydro-5H-cyclopenta[c]oxepine-7,7(8H)-dicarboxylate (**3ak**).* White oil (24.7 mg, 31% yield); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 1.27 (s, 3H), 2.13 (d, J = 1.2 Hz, 3H), 2.30 (s, 3H), 2.44 (s, 2H), 2.56 (d, J = 14.8 Hz, 1H), 2.65 (d, J = 15.2 Hz, 1H), 3.00 (d, J = 16.0 Hz, 1H), 3.28 (d, J = 16.4 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H), 7.28−7.32 (m, 1H), 7.32−7.41(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 202.3, 172.1, 172.0, 159.3, 145.5, 136.9, 128.2, 128.0, 127.9, 127.2, 118.8, 57.8, 52.9, 52.8, 48.9, 44.2, 40.5, 39.6, 30.2, 25.7, 21.8. HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{26}O_6Na$ 421.1627, found 421.1622.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00879.

Copies of ^{1}H and ^{13}C NMR spectra (PDF)
Crystallographic data for **3r** (CIF)
Crystallographic data for **3aj** (CIF)
Crystallographic data for **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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