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Palladium-Catalyzed Regioselective Domino Cyclization of Cyclohexadienones

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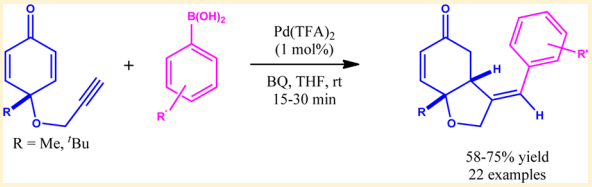
Supporting Information

ABSTRACT: A mild and efficient Pd-catalyzed arylative domino carbocyclization of cyclohexadienone-containing 1,6-enynes is described. The reaction tolerates a variety of functionalized boronic acids to afford a *cis*-fused bicyclic framework containing an α,β-unsaturated ketone with excellent regio- and diastereoselectivity in good yields. The tandem process proceeds with β-arylation of propargylic ether followed by conjugate addition of a vinyl palladium intermediate and subsequent protonolysis of a palladium enolate.



INTRODUCTION

Cyclohexa-2,5-dienones are a versatile class of building blocks for natural product synthesis, which are readily derived from oxidative dearomatization of phenols.[1] Complex natural products such as (+)-rishirilide B,[2] incarviditone,[3] and (−)-cepharatine D[4] have been synthesized from the desymmetrization of suitable cyclohexa-2,5-dienones via new intramolecular C−C bond formation (Figure 1). In this regard,

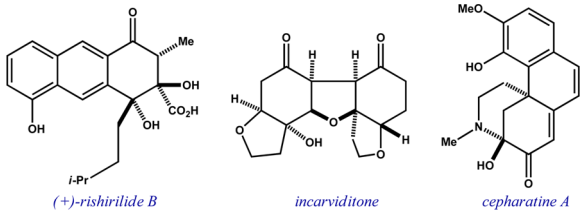


Figure 1. Some natural products which could be derived from oxidative dearomatization of phenols.

the desymmetrization of the prochiral dienones using transition-metal catalysis[5−7] as well as organocatalysis[8] has received great attention since the past decade. From a historical perspective, a variety of transition-metal-catalyzed domino cyclizations are reported in the literature. Among all organometal catalysts, palladium,[5c−e] rhodium,[6] and copper[7e] have had a significant role in the carbocyclization of *meso*-1,6-dienynes to furnish *cis*-hydrobenzofurans.

In 1993, Shibasaki and co-workers were the first to report the enantioselective cyclohexadienone desymmetrization using the palladium-catalyzed intramolecular Heck reaction.[5a] In recent elegant reports, Sasai and co-workers demonstrated a palladium-catalyzed diacetoxylative carbocyclization of alkyne-tethered cyclohexadienones involving an unusual nucleophilic substitution on a palladium enolate.[5f] More recently, the research groups of Lautens[6b] as well as Lin[6c] simultaneously reported rhodium-catalyzed asymmetric arylative domino cyclization of alkynylcyclohexadienones with a variety of boronic acids. They found that the reaction stereoselectivity significantly depends on the choice of ligand, substitution on the substrate, and aryl boronic acid. We report herein a less expensive palladium-mediated regioselective domino cyclization of cyclohexadienones with boronic acids under mild conditions to access *cis*-hydrobenzofurans.

RESULTS AND DISCUSSION

We initiated our investigation by studying the domino cyclization of cyclohexadienone **1a**[6] with boronic acid **2a** using various palladium catalysts and oxidizing agents in THF at room temperature (Table 1). To our delight, the cyclized product **3a** was obtained in the presence of 10 mol % of $Pd(OAc)_2$ and 1.2 equiv of *p*-benzoquinone (BQ) in good yield (69%). The reaction was successful by employing $Pd(PPh_3)_2Cl_2$, $Pd(acac)_2$, and $Pd(C_6H_5CN)_2Cl_2$ as catalysts, albeit in lower yield (Table 1, entries 2−4). The use of $PdCl_2$ gave none of the desired product (Table 1, entry 5). Among all palladium catalysts, $Pd(TFA)_2$ displayed excellent performance, providing bicyclic adduct **3a** in good yield (75%) with high diastereoselectivity (Table 1, entry 6). The reaction was also performed in the presence of bisacetoxyiodobenzene (BAIB) or open air as oxidizing agents, but both cases gave lower yields when compared to that of BQ (Table 1, entries 7 and 8).

Table 2 revealed that the nature of solvent and catalyst loading also had an important role on the yield of the reaction. Various solvents such as CH_3CN, Et_2O, toluene, EtOH, and THF were found to be suitable for the reaction in the presence of 10 mol % of $Pd(TFA)_2$ at room temperature. However, in terms of the product yield, THF was found to give 75%, while

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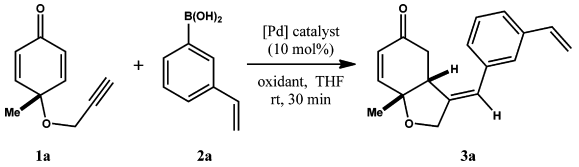
Table 1. Evaluation of Catalyst and Oxidant for Palladium-Catalyzed Regioselective Domino Cyclization of Cyclohexadienones[a]

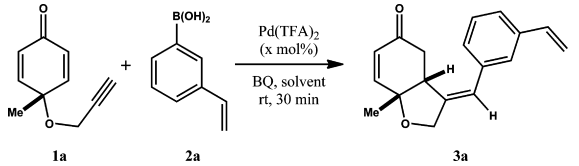


1a 2a 3a

entry	[Pd] catalyst	oxidant	yield (%)[b]
1	$Pd(OAc)_2$	BQ	69
2	$Pd(PPh_3)_2Cl_2$	BQ	31
3	$Pd(acac)_2$	BQ	12
4	$Pd(C_6H_5CN)_2Cl_2$	BQ	>5
5	$PdCl_2$	BQ	
6	**$Pd(TFA)_2$**	**BQ**	**75**
7	$Pd(TFA)_2$	BAIB	42
8	$Pd(TFA)_2$	open air	40

[a]The reaction was carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and oxidant (0.12 mmol) in THF (0.1 M) at room temperature for 30 min. [b]Yield of the isolated product.

Table 2. Evaluation of Solvent Effect and Catalyst Loading for Palladium-Catalyzed Regioselective Domino Cyclization of Cyclohexadienones[a]



1a 2a 3a

entry	solvent	*x* (mol %)	yield (%)[b]
1	CH_3CN	10	60
2	Et_2O	10	58
3	EtOH	10	21
4	toluene	10	45
5	THF	10	75
6	THF	5	74
7	**THF**	**1**	**72**

[a]The reaction was carried out with **1a** (0.1 mmol), **2a** (0.15 mmol), and BQ (0.12 mmol) in THF (0.1 M) at room temperature for 30 min. [b]Yield of the isolated product.

others gave moderate to low yield (Table 2, entries 1−5). Reduction of catalyst loading did not show any significant variation on the reaction yield (Table 2, entries 5−7). Employing 1 mol % of $Pd(TFA)_2$ also gave a similar yield (72%).

With these optimized conditions, we investigated the scope of above reaction with various boronic acids (Scheme 1). Both electron-poor and electron-rich arylboronic acids with a variety of substituents like methyl, vinyl, methoxy, halogen, trifluoromethyl, cyano, and nitro successfully participated in the reaction with cyclohexadienone **1a** to give the corresponding cyclized product **3** under the optimal conditions. In general, boronic acid having an electron-donating group at the 3- or 4-position provided a yield (**3b**−**3e**) slightly higher than that of boronic acid having an electron-withdrawing group (**3f**−**3k**). Furthermore, heteroaromatic boronic acids were also well-suited for this reaction, giving moderate to good yields (**3o**−**3q**). In the case of mesitylboronic acid, formation of the corresponding product **3r** was not observed, which may be due to the steric hindrance with both methyl groups, and the starting material was recovered without any significant loss. Unfortunately, vinyl and aliphatic boronic acids also failed to participate in the cyclization reaction under the present catalyst system and furnished a complex reaction mixture (Scheme 1, **3s** and **3t**). Additionally, *tert*-butyl-substituted cyclohexadienone **1b** was tested for domino cyclization under similar conditions with 9-phenanthrocenylboronic acid and 4-chlorophenylboronic acid to furnish compounds **3u** and **3v**, respectively, albeit in low yield (Scheme 1). An NOE experiment of compound **3n** and X-ray crystal structure of compound **3j** allowed us to confirm the structure of the *cis*-fused bicyclic framework of the product (see the Supporting Information).[9]

A plausible catalytic cycle is proposed on the basis of above experimental outcome (Scheme 2). Initially, transmetalation between the $Pd(TFA)_2$ catalyst and the arylboronic acid gives an active $ArPd(O_2CCF_3)$ species **A**.[10] The following *syn*-arylpalladation with starting material **1** generates the vinyl Pd intermediate **B**,[11] which subsequently undergoes *syn*-migratory carbocyclization across the C−C double bond in cyclohexadienone to furnish palladium enolate **C**.[12] Protonolysis of enolate **C** affords bicylic product **3**, and catalyst is regenerated in the presence of BQ.[13]

In conclusion, we report a mild and convenient Pd-catalyzed arylative domino carbocyclization of cyclohexadienone-containing 1,6-enynes using a variety of functionalized boronic acids to afford a *cis*-fused bicyclic framework containing an *α,β*-unsaturated ketone with excellent regio- and diastereoselectivity. The tandem process proceeds with lower catalyst loading of less expensive $Pd(TFA)_2$ in a short reaction time. Further efforts aimed at synthetic application of this method are in process and will be reported in due course.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were used as received from commercial suppliers. Palladium catalysts and all boronic acids were obtained from Sigma-Aldrich and used without further purification. All reactions were performed under nitrogen atmosphere and in flame-dried or oven-dried glassware with magnetic stirring. THF and Et_2O were dried in the presence of sodium metal using benzophenone as indicator and distilled prior to use. Reactions were monitored using thin-layer chromatography (SiO_2). TLC plates were visualized with UV light (254 nm), iodine treatment, or using *p*-anisaldehyde stain. Column chromatography was carried out using silica gel (60−120 mesh and 100−200 mesh) packed in glass columns. NMR spectra were recorded at 300 and 500 MHz (H) and at 75 and 125 MHz (C). Chemical shifts (δ) are reported in parts per million using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are given in hertz. HRMS were recorded using ESI-TOF techniques.

General Procedure for Palladium-Catalyzed Regioselective Domino Cyclization of Cyclohexadienones. To a solution of enyne **1a** (64.8 mg, 0.4 mmol) in THF (4 mL) were added $Pd(OCOCF_3)_2$ (1.3 mg, 0.004 mmol, 1 mol %), BQ (56.6 mg, 0.48 mmol), and 3-vinyl-$PhB(OH)_2$ (88.8 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated, and the residue was purified by flash column chromatography (hexane/ethyl acetate v/v 90:10) and gave the product **3a** as colorless oil (76.6 mg, 72%).

(3aR,7aR*,E)-7a-Methyl-3-(3-vinylbenzylidene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one (**3a**):* Colorless oil (76.6 mg, 72%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.28 (m, 2H), 7.21 (s, 1H), 7.13−7.05 (m, 1H), 6.74−6.67 (m, 1H), 6.57 (dd, J = 0.8, 10.2 Hz, 1H), 6.43−6.41 (m, 1H), 5.99 (d, J = 10.2 Hz, 1H), 5.74 (d, J = 17.6 Hz, 1H), 5.27 (d, J = 10.9 Hz, 1H), 4.53 (dd, J = 1.4, 13.2 Hz, 1H), 4.43 (ddd, J = 2.3, 2.3, 13.2 Hz, 1H), 3.44−3.39 (m, 1H), 2.65 (dd, J = 5.1,

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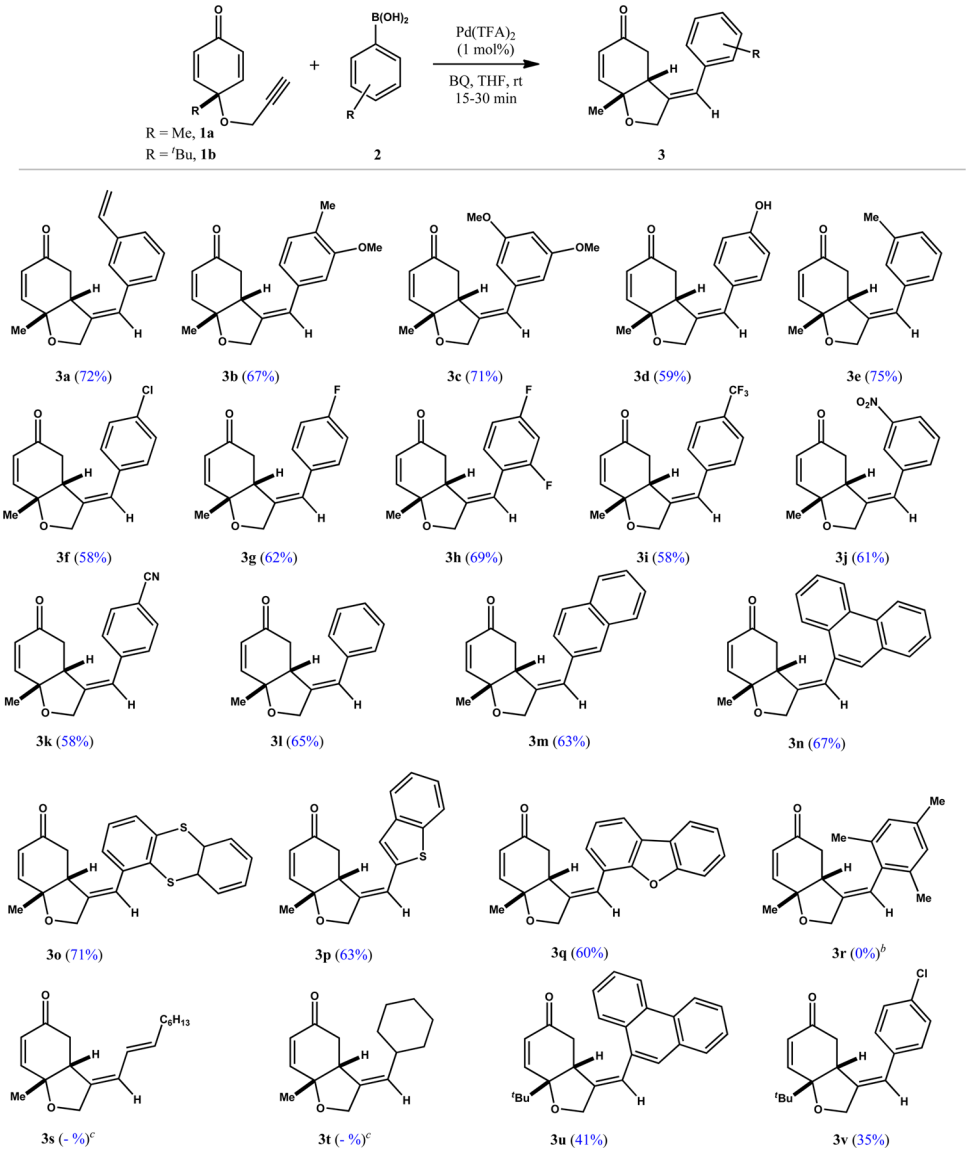
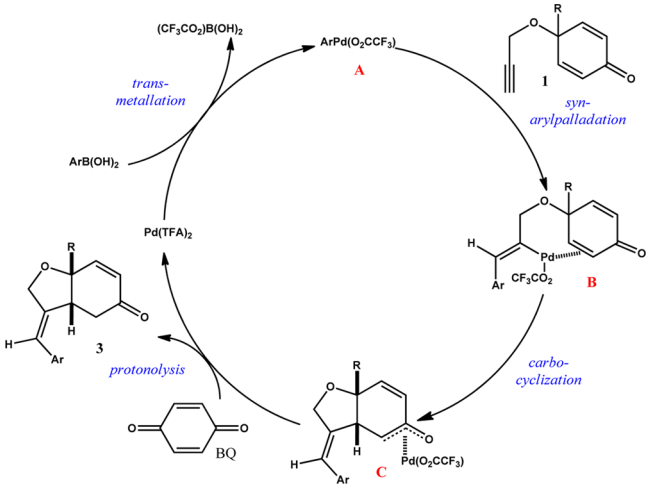
Scheme 1. Evaluation of Boronic Acid Scope[a]



[a]Reaction conditions: $Pd(TFA)_2$ (1 mol %), BQ (1.2 equiv), THF (0.1 M), rt, 15−30 min. [b]Starting material was recovered. [c]Reaction mixture was decomposed.

Scheme 2. Plausible Mechanism for the Domino Cyclization



16.7 Hz, 1H), 2.46 (dd, J = 5.9, 16.7 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 150.0, 142.3, 137.8, 136.6, 136.2, 129.7, 128.7, 127.3, 126.2, 125.0, 122.1, 114.3, 80.4, 71.3, 46.1, 36.2, 24.0; IR (neat) ν 2926, 2854, 1743, 1693, 1596, 1456, 1162, 1044, 909, 795 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}O_2$ $[M + H]^+$ 267.1378; found 267.1380.

(3aR,7aR*,E)-3-(3-Methoxy-4-methylbenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one (**3b**):* Colorless oil (76.1 mg, 67%); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.02−6.97 (m, 2H), 6.79−6.76 (m, 1H), 6.57 (d, J = 10.2 Hz, 1H), 6.35−6.31 (m, 1H), 5.99 (d, J = 10.2 Hz, 1H), 4.51 (dd, J = 0.7, 12.9 Hz, 1H), 4.42 (ddd, J = 2.1, 2.1, 12.9 Hz, 1H), 3.84 (s, 3H), 3.41 (br s, 1H), 2.72 (dd, J = 5.3, 16.7 Hz, 1H), 2.48 (dd, J = 5.9, 16.7 Hz, 1H), 2.20 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.5, 156.9, 150.1, 139.8, 130.6, 129.7, 128.1, 126.6, 122.0, 109.8, 80.3, 71.4, 55.3, 45.9, 36.2, 24.1, 16.3; IR (neat) ν 2926, 2853, 1692, 1607, 1504, 1464, 1254, 1133, 1034, 803 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}O_3$ $[M + H]^+$ 285.1485; found 285.1479.

(3aR,7aR*,E)-3-(3,5-Dimethoxybenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one (**3c**):* Colorless oil (85.2 mg, 71%); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.55 (dd, J = 1.0, 10.2 Hz,

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1H), 6.38−6.33 (m, 4H), 5.99 (d, J = 10.2 Hz, 1H), 4.50 (dd, J = 1.0, 13.2 Hz, 1H), 4.40 (ddd, J = 2.1, 2.1, 13.2 Hz, 1H), 3.79 (s, 6H), 3.41−3.36 (m, 1H), 2.71 (dd, J = 4.8, 16.7 Hz, 1H), 2.46 (dd, J = 5.9, 16.7 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.2, 160.7, 150.2, 142.5, 137.9, 129.8, 122.2, 106.3, 99.0, 80.4, 71.2, 55.3, 46.1, 36.2, 23.9; IR (neat) ν 2928, 2841, 1688, 1683, 1591, 1507, 1456, 1426, 1318, 1205, 1152, 1063 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}O_4$ $[M + H]^+$ 301.1434; found 301.1468.

(3aR,7aR*,E)-3-(4-Hydroxybenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3d**): White solid (60.4 mg, 59%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.59 (d, J = 10.2 Hz, 1H), 6.38−6.33 (m, 1H), 6.00 (d, J = 10.2 Hz, 1H), 5.89 (br s, 1H), 4.52 (d, J = 13.1 Hz, 1H), 4.40 (ddd, J = 2.1, 2.1, 13.1 Hz, 1H), 3.44−3.33 (br, 1H), 2.73 (dd, J = 4.9, 16.6 Hz, 1H), 2.49 (dd, J = 5.8, 16.6 Hz, 1H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.1, 155.2, 150.7, 140.0, 129.6, 129.5, 128.2, 122.0, 115.5, 80.5, 71.3, 46.0, 36.2, 23.9; IR(neat) ν 2972, 2928, 2853, 1674, 1612, 1514, 1231 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{16}NaO_3$ $[M + Na]^+$ 279.0992; found 279.0999; mp 131−133 °C.

(3aR,7aR*,E)-7a-Methyl-3-(3-methylbenzylidene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3e**): White solid (76.2 mg, 75%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32−7.18 (m, 2H), 7.14−6.97 (m, 2H), 6.59 (dd, J = 0.9, 10.2 Hz, 1H), 6.43−6.38 (m, 1H), 6.01 (d, J = 10.2 Hz, 1H), 4.54 (dd, J = 0.9, 13.2 Hz, 1H), 4.44 (ddd, J = 2.2, 2.2, 13.2 Hz, 1H), 3.47−3.40 (m, 1H), 2.68 (dd, J = 5.2, 16.7 Hz, 1H), 2.48 (dd, J = 5.9, 16.7 Hz, 1H), 2.36 (s, 3H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.3, 150.1, 141.7, 138.1, 135.9, 129.7, 128.9, 128.4, 128.0, 125.0, 122.3, 80.3, 71.3, 46.0, 36.2, 24.0, 21.5; IR (neat) ν 2924, 2853, 1690, 1602, 1374, 1162, 1116, 1044, 786 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1379; found 255.1372; mp 75−77 °C.

(3aR,7aR*,E)-3-(4-Chlorobenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3f**): White solid (63.6 mg, 58%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.49 (dd, J = 0.8, 10.2 Hz, 1H), 6.32−6.28 (m, 1H), 5.29 (d, J = 10.2 Hz, 1H), 4.45 (d, J = 13.3 Hz, 1H), 4.33 (ddd, J = 2.2, 2.2, 13.3 Hz, 1H), 3.31 (br s, 1H), 2.52 (dd, J = 4.9, 16.6 Hz, 1H), 2.38 (dd, J = 5.8, 16.6 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9, 150.0, 143.0, 134.4, 133.0, 129.8, 129.4, 128.7, 121.1, 80.5, 71.3, 46.1, 36.2, 23.9; IR (neat) ν 2925, 2855, 1742, 1605, 1492, 1238, 1092, 1013, 882, 817 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}O_2ClNa$ $[M + Na]^+$ 297.0653; found 297.0656; mp 116−118 °C.

(3aR,7aR*,E)-3-(4-Fluorobenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3g**): White solid (64.0 mg, 62%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (dd, J = 5.6, 8.4 Hz, 2H), 6.96 (t, J = 8.7 Hz, 2H), 6.49 (dd, J = 0.7, 10.2 Hz, 1H), 6.33−6.29 (m, 1H), 5.91 (d, J = 10.2 Hz, 1H), 4.45 (d, J = 13.2 Hz, 1H), 4.33 (ddd, J = 2.2, 2.2, 13.2 Hz, 1H), 3.30 (br s, 1H), 2.51 (dd, J = 4.9, 16.6 Hz, 1H), 2.37 (dd, J = 5.8, 16.6 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.0, 161.8 (d, J = 247.0 Hz), 150.1, 142.1, 132.1 (d, J = 3.2 Hz), 129.7, 129.6, 121.2, 115.5 (d, J = 21.5 Hz), 80.5, 71.2, 46.0, 36.2, 23.9; IR (neat) ν 2926, 2854, 1741, 1690, 1602, 1509, 1228, 1160, 829 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}O_2FNa$ $[M + H]^+$ 281.09485; found 281.09483; mp 70−72 °C.

(3aR,7aR*,E)-3-(2,4-Difluorobenzylidene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3h**): Colorless oil (76.2 mg, 69%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16 (dd, J = 8.4, 15.0 Hz, 1H), 6.85 (m, 2H), 6.55 (dd, J = 1.1, 10.2 Hz, 1H), 6.34−6.27 (m, 1H), 5.97 (d, J = 10.2 Hz, 1H), 4.56 (d, J = 13.5 Hz, 1H), 4.39 (ddd, J = 2.2, 2.2, 13.5 Hz, 1H), 3.31−3.23 (m, 1H), 2.54−2.36 (m, 2H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.5, 162.2 (d, J = 250.9 Hz), 160.5 (d, J = 250.6 Hz), 150.3, 144.8, 130.3 (d, J = 5.0 Hz), 130.2 (d, J = 4.8 Hz), 129.6, 114.0, 111.2 (dd, J = 3.0, 21.5 Hz), 104.0 (t, J = 25.8 Hz), 80.7, 71.0, 46.6, 36.0, 23.4; IR (neat) ν 2974, 2927, 2851, 1689, 1615, 1502, 1425, 1274, 1141, 1046, 967, 851, 796 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{13}F_2O_2$ $[M - H]^+$ 275.0878; found 275.0873.

(3aR,7aR*,E)-7a-Methyl-3-(4-(trifluoromethyl)benzylidene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3i**): White solid (71.5 mg, 58%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.57 (dd, J = 1.0, 10.2 Hz, 1H), 6.46−6.42 (m, 1H), 6.00 (d, J = 10.2 Hz, 1H), 4.55 (dd, J = 1.1, 13.5 Hz, 1H), 4.43 (ddd, J = 2.3, 2.3, 13.5 Hz, 1H), 3.42 (br s, 1H), 2.55 (dd, J = 4.9, 16.6 Hz, 1H), 2.46 (dd, J = 5.8, 16.6 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.6, 149.9, 146.6, 139.5, 129.7, 129.1 (q, J = 33 Hz), 128.3, 125.5 (q, J = 3.5 Hz), 124.1 (q, J = 271.7 Hz), 120.9, 80.5, 71.2, 46.2, 36.3, 23.9; IR (neat) ν 2973, 2930, 2855, 1692, 1616, 1325, 1165, 1122, 1067, 1017, 864, 800 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}F_3O_2$ $[M + H]^+$ 309.1097; found 309.1089; mp 133−136 °C.

(3aR,7aR*,E)-7a-Methyl-3-(3-nitrobenzylidene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3j**): Pale yellow crystalline solid (69.6 mg, 61%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.12 (d, J = 7.4 Hz, 1H), 8.06 (s, 1H), 7.57−7.48 (m, 2H), 6.57 (d, J = 10.3 Hz, 1H), 6.49−6.45 (m, 1H), 6.00 (d, J = 10.3 Hz, 1H), 4.57 (dd, J = 0.9, 13.6 Hz, 1H), 4.42 (ddd, J = 2.4, 2.4, 13.6 Hz, 1H), 3.46 (br s, 1H), 2.55−2.45 (m, 2H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.3, 150.2, 148.3, 145.6, 137.6, 134.0, 129.8, 129.6, 122.8, 122.1, 120.0, 80.8, 71.2, 46.2, 36.1, 23.7; IR (neat) ν 2973, 2928, 2852, 1692, 1530, 1352, 1045, 800, 735 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}NO_4Na$ $[M + Na]^+$ 308.0893; found 308.0890; mp 108−110 °C.

4-((E)-((3aR,7aR*)-7a-Methyl-5-oxo-4,5-dihydrobenzofuran-3(2H,3aH,7aH)-ylidene)methyl)benzonitrile* (**3k**): Off-white solid (61.5 mg, 58%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67−7.59 (m, 2H), 7.34−7.25 (m, 2H), 6.57 (d, J = 10.2 Hz, 1H), 6.45−6.40 (m, 1H), 6.00 (d, J = 10.2 Hz, 1H), 4.56 (dd, J = 1.0, 13.7 Hz, 1H), 4.43 (ddd, J = 2.3, 2.3, 13.7 Hz, 1H), 3.45−3.36 (m, 1H), 2.57−2.42 (m, 2H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.6, 150.0, 145.8, 140.6, 132.3, 129.8, 128.7, 120.7, 118.7, 116.1, 111.0, 80.7, 71.3, 46.3, 36.2, 23.7; IR (neat) ν 2972, 2928, 2853, 2226, 1690, 1604, 1374, 1046, 883, 800 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$ 266.1176; found 266.1160; mp 64−65 °C.

(3aR,7aR*,E)-3-Benzylidene-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3l**): White solid (62.4 mg, 65%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.30 (m, 2H), 7.26−7.18 (m, 3H), 6.57 (d, J = 10.2 Hz, 1H), 6.44−6.41 (m, 1H), 5.99 (d, J = 10.2 Hz, 1H), 4.53 (dd, J = 1.8, 13.1 Hz, 1H), 4.44 (ddd, J = 2.1, 2.1, 13.1 Hz, 1H), 3.45−3.39 (m, 1H), 2.62 (dd, J = 5.3, 16.7 Hz, 1H), 2.46 (dd, J = 5.9, 16.7 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.2, 150.0, 142.1, 136.0, 129.7, 128.5, 128.1, 127.3, 122.3, 80.3, 71.3, 46.0, 36.3, 24.1; IR (neat) ν 2925, 2854, 1692, 1448, 1374, 1165, 1043, 880, 697 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1223; found 241.1228; mp 96−98 °C.

(3aR,7aR*,E)-7a-Methyl-3-(naphthalen-2-ylmethylene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3m**): White solid (73.1 mg, 63%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85−7.75 (m, 3H), 7.64 (s, 1H), 7.50−7.43 (m, 2H), 7.34 (dd, J = 1.6, 8.5 Hz, 1H), 6.60−6.56 (m, 2H), 5.99 (dd, J = 0.4, 10.2 Hz, 1H), 4.59 (dd, J = 1.1, 13.2 Hz, 1H), 4.48 (ddd, J = 2.3, 2.3, 13.2 Hz, 1H), 3.55−3.51 (m, 1H), 2.66 (dd, J = 4.9, 16.7 Hz, 1H), 2.49 (dd, J = 5.9, 16.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 150.1, 142.5, 133.5, 133.3, 132.5, 129.8, 128.2, 127.9, 127.7, 127.1, 126.4, 126.1, 126.0, 122.3, 80.5, 71.4, 46.2, 36.3, 24.0; IR (neat) ν 2924, 2852, 1919, 1692, 1463, 1227, 957, 805, 752 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{19}O_2$ $[M + H]^+$ 291.1379; found 291.1374; mp 113−116 °C.

(3aR,7aR*,E)-7a-Methyl-3-(phenanthren-9-ylmethylene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3n**): White solid (91.2 mg, 67%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (d, J = 8.2 Hz, 1H), 8.69 (d, J = 8.0 Hz, 1H), 7.89 (dd, J = 1.0, 8.1 Hz, 1H), 7.86 (dd, J = 1.1, 7.8 Hz, 1H), 7.70−7.64 (m, 2H), 7.63−7.57 (m, 3H), 6.89−6.85 (m, 1H), 6.56 (dd, J = 1.3, 10.2 Hz, 1H), 5.95 (dd, J = 0.7, 10.2 Hz, 1H), 4.72 (dd, J = 1.1, 13.2 Hz, 1H), 4.56 (ddd, J = 2.3, 2.3, 13.2 Hz, 1H), 3.35−3.30 (m, 1H), 2.37 (dd, J = 4.8, 16.7 Hz, 1H), 2.21 (dd, J = 5.8, 16.7 Hz, 1H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.8, 150.3, 144.5, 132.3, 131.4, 130.6, 130.4, 130.2, 129.9, 128.5, 126.9, 126.8, 126.8, 126.8, 126.3, 125.6, 123.1, 122.7, 120.6, 80.5, 70.9, 46.5, 36.4, 23.6; IR (neat) ν 2924, 2853, 2375, 2335, 1688, 1452, 1039, 806, 751 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{21}O_2$ $[M + H]^+$ 341.1536; found 341.1528; mp 101−103 °C.

(3aR,7aR*,E)-7a-Methyl-3-(thianthren-1-ylmethylene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3o**): White solid (107.9 mg, 71%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.33 (m, 3H), 7.21−7.10

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(m, 4H), 7.08−7.04 (m, 1H), 6.56−6.52 (m, 1H), 6.49 (dd, J = 1.2, 10.2 Hz, 1H), 5.90 (d, J = 10.2 Hz, 1H), 4.58 (dd, J = 1.0, 13.4 Hz, 1H), 4.43 (ddd, J = 2.3, 2.3, 13.4 Hz, 1H), 3.24−3.16 (m, 1H), 2.25 (d, J = 5.2 Hz, 2H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.6, 150.2, 144.7, 135.8, 135.2, 129.8, 128.8, 128.6, 128.0, 127.9, 127.7, 127.5, 127.1, 120.1, 80.5, 70.9, 46.6, 36.6, 23.7; IR (neat) ν 2957, 2854, 2926, 1689, 1445, 1399, 1114, 1044, 787 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}O_2S_2$ $[M + H]^+$ 379.0821; found 379.0817; mp 128−130 °C.

(3aR,7aR*,E)-3-(Benzo[b]thiophen-2-ylmethylene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3p**): White solid (74.6 mg, 63%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83−7.78 (m, 1H), 7.62−7.54 (m, 1H), 7.36−7.27 (m, 2H), 7.18−7.15 (m, 1H), 6.52 (dd, J = 1.0, 10.2 Hz, 1H), 6.50−6.48 (m, 1H), 5.92 (dd, J = 0.6, 10.2 Hz, 1H), 4.57 (dd, J = 13.3, 1.1 Hz, 1H), 4.44 (ddd, J = 13.3, 2.3, 2.3 Hz, 1H), 3.26−3.20 (m, 1H), 2.51−2.42 (m, 1H), 2.32 (dd, J = 16.7, 5.9 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.6, 148.7, 143.6, 139.4, 138.9, 129.7, 124.7, 123.8, 123.5, 122.1, 115.9, 79.5, 71.1, 46.4, 37.1, 24.9; IR (neat) ν 2928, 2853, 2322, 1683, 1457, 1374, 1224, 748 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{17}O_2S$ $[M + H]^+$ 297.0944; found 297.0948; mp 147−148 °C.

(3aR,7aR*,E)-3-(Dibenzo[b,d]furan-1-ylmethylene)-7a-methyl-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3q**): White solid (79.2 mg, 60%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.97 (d, J = 7.1 Hz, 1H), 7.88 (dd, J = 1.4, 7.3 Hz, 1H), 7.62−7.55 (m, 1H), 7.51−7.44 (m, 1H), 7.40−7.28 (m, 3H), 6.78−6.74 (m, 1H), 6.59 (dd, J = 1.1, 10.2 Hz, 1H), 5.97 (d, J = 10.2 Hz, 1H), 4.69 (dd, J = 1.2, 13.3 Hz, 1H), 4.55 (ddd, J = 2.4, 2.4, 13.3 Hz, 1H), 3.54 (br s, 1H), 2.45 (dd, J = 4.7, 16.7 Hz, 1H), 2.38 (dd, J = 5.9, 16.7 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9, 153.4, 150.3, 144.8, 129.8, 128.1, 127.3, 126.4, 124.3, 122.9, 120.9, 120.5, 119.9, 115.7, 111.7, 80.6, 71.4, 47.0, 36.2, 23.9; IR (neat) ν 2926, 2855, 1746, 1694, 1451, 1417, 1373, 1189, 1116, 1046, 753 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{19}O_3$ $[M + H]^+$ 331.1329; found 331.1334; mp 165−167 °C.

(3aR,7aR*,E)-7a-tert-Butyl-3-(phenanthren-9-ylmethylene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one* (**3u**): Colorless oil (62.5 mg, 41%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, J = 8.1 Hz, 1H), 8.61 (d, J = 8.1 Hz, 1H), 7.82 (dd, J = 1.1, 3.6 Hz, 1H), 7.80 (dd, J = 1.3, 3.6 Hz, 1H), 7.65−7.50 (m, 5H), 6.76−6.71 (m, 1H), 6.64 (dd, J = 1.3, 10.5 Hz, 1H), 6.05 (d, J = 10.5 Hz, 1H), 4.56 (dd, J = 1.3, 13.0 Hz, 1H), 4.34 (ddd, J = 2.3, 2.3, 13.0 Hz, 1H), 3.66−3.60 (m, 1H), 2.25 (dd, J = 1.9, 17.5 Hz, 1H), 2.21 (dd, J = 6.4, 17.5 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 148.4, 146.2, 132.4, 131.6, 131.5, 130.5, 130.1, 129.6, 128.8, 128.5, 126.9, 126.8, 126.3, 126.0, 125.6, 123.1, 122.6, 119.8, 86.8, 70.5, 40.1, 38.1, 37.6, 25.6; IR (neat) ν 2928, 2849, 2378, 2335, 1692, 1446, 1370, 1039, 806, 751 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{26}NaO_2$ $[M + Na]^+$ 405.1825; found 405.1849.

(3aR,7aR,E)-7a-tert-Butyl-3-(4-chlorobenzylidene)-2,3,3a,4-tetrahydrobenzofuran-5(7aH)-one (**3v**): Colorless oil (44 mg, 35%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.23 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 8.4 Hz, 2H), 6.64 (dd, J = 1.4, 10.6 Hz, 1H), 6.24−6.22 (m, 1H), 6.08 (dd, J = 0.7, 10.6 Hz, 1H), 4.35 (dd, J = 1.6, 13.0 Hz, 1H), 4.17 (ddd, J = 2.5, 2.5, 13.0 Hz, 1H), 3.70−3.66 (m, 1H), 2.56−2.50 (m, 1H), 2.40 (dd, J = 6.8, 17.5 Hz, 1H), 1.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.9, 148.5, 144.6, 134.4, 132.9, 131.5, 129.3, 128.8, 126.4, 120.1, 114.7, 87.0, 70.9, 39.7, 37.5, 31.5, 25.6; IR (neat) ν 2928, 2848, 2379, 2331, 1688, 1452, 1370, 1039, 806, 751 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}ClO_2$ $[M + H]^+$ 317.1303; found 317.1318.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C spectra for all new compounds, NOE spectra of compound **3n**, and X-ray crystallographic data (CIF file) of compound **3j**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00493.

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Notes

The authors declare no competing financial interest.

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(9) CCDC-1044542 (**3j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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