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Straightforward Stereoselective Synthesis of Seven-Membered Oxa-Bridged Rings through *In Situ* Generated Cycloheptenol Derivatives

Mengdan Wang,[‖] Liqiang Yin,[‖] Lu Cheng, Yajie Yang, and Yanzhong Li*

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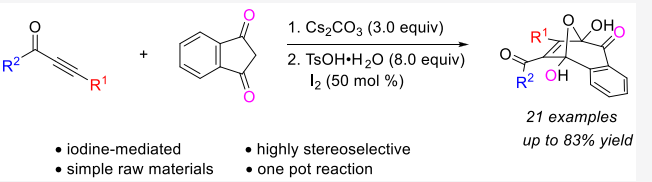
ABSTRACT: An iodine-mediated stereoselective synthesis of seven-membered oxa-bridged rings via *in situ* generated cycloheptenols was reported. This process was realized through the combination of C−C σ-bond cleavage and C−O bond-forming reactions in a one-pot fashion from simple and easily accessible raw materials. The formation of carbon radicals initiated by I_2 was the key to the reaction.



INTRODUCTION

Oxa-bridged heterocyclic scaffolds, especially the seven-membered oxa-bridged rings (OBC), are widely found in many natural products and synthetic molecules with important biological activities (Figure 1).[1] Due to their special biological

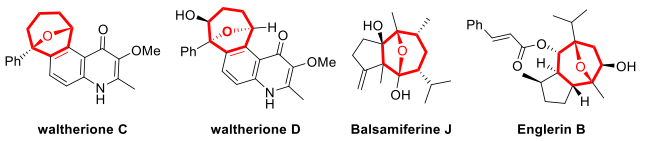
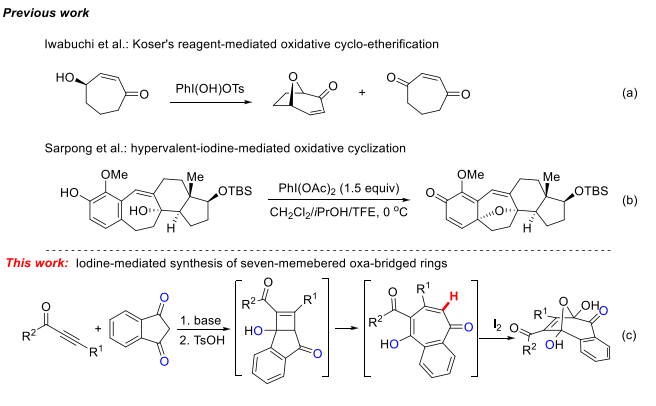


Figure 1. Some natural products with oxa-bridged bicyclic skeletons.

importance, these seven-membered oxa-bridged carbocycles have attracted great attention from synthetic chemists. So far, a large number of methods have been developed to synthesize seven-membered oxa-bridged ring compounds. The reported methods predominantly rely on cycloaddition reaction, such as the [4 + 3] cycloaddition of allyl cations with furans,[2] [4 + 3] cycloaddition between 1,4-dicarbonyls and 1,3-bis(trimethylsilyl)oxy dienes,[3] [5 + 2] annulations between oxidopyrylium and alkenes,[4] etc.[5] These transformations usually require noble metal catalysis. Intramolecular cyclization is also an efficient method, which typically involves multistep reactions in the elaboration of substrates.[6] Another straightforward way to construct seven-membered oxa-bridged rings is the installing of a bridged oxygen atom on cycloheptane or cycloheptene derivatives.[7] However, there are two challenges: (1) The diastereoselective functionalization of a cycloheptene derivative is difficult owing to the inherent conformational uncertainties. (2) The molecular structure of bridge-containing fragments is less flexible compared to their homologous counterparts, and this strategy is rarely reported.

Iwabuchi et al. developed a novel oxidative cyclo-etherification of 4-hydroxycyclohept-2-enone using PhI(OH)OTs (Scheme 1a).[8] A tandem oxidative dearomatization/cyclization

Scheme 1. Synthesis of the Seven-Membered Oxa-Bridged Ring



in the presence of hypervalent iodine $PhI(OAc)_2$ was described by the Sarpong group (Scheme 1b).[9] Nevertheless, these protocols usually relied on cycloheptenols as starting materials, and the range of commercially available cycloheptenol substrates greatly limited its application of this type of transformation. Consequently, there is still an urgent need to develop novel methodologies for the construction of cycloheptenols from simple and easily available reactants; if achieved, it may provide a platform for the direct assembling of seven-membered oxa-bridged rings.

As part of our ongoing interest in C−C σ-bond cleavage chemistry,[10] we have developed efficient base-promoted

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approaches for the preparation of cycloheptenols. It could be nice precursors of oxa-bridged ring compounds via intramolecular C−O bond formation reactions. We envisaged that the construction of such seven-membered oxa-bridged ring compounds might be realized through the combination of C−C σ-bond cleavage and C−O bond-forming reactions in a one-pot fashion by tuning the reaction parameters from simple and easily accessible raw materials. Herein, we report an iodine-mediated stereoselective synthesis of seven-membered oxa-bridged rings (Scheme 1c).

RESULTS AND DISCUSSION

The reaction of 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (**1a**) with 1*H*-indene-1,3(2*H*)-dione (**2a**) was chosen as a template reaction to test our hypothesis and optimize experimental conditions. First, the reaction of **1a** with **2a** was carried out using Cs_2CO_3 (3.0 equiv) as the base and DMSO as the solvent at 110 °C under N_2, as previously reported.[11] Next, we attempted to add iodine into the reaction system at 100 °C for 6 h. Regrettably, no desired C−O bond-forming product could be observed (Table 1, entry 1). Then HCl (6 M) was added to

Table 1. Optimization Studies for the Synthesis of 3a[a]

1a 2a 3a

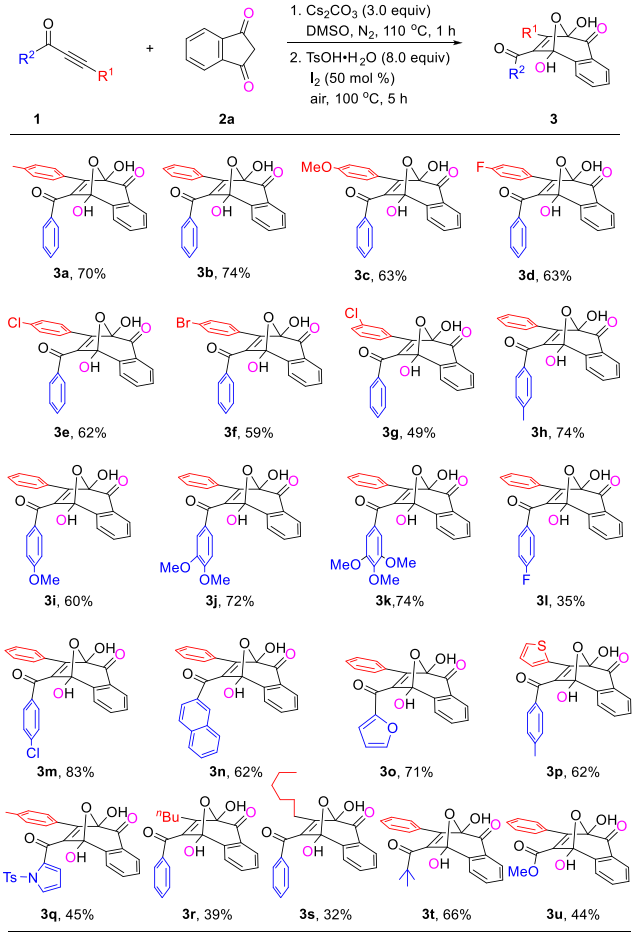
entry	acid (equiv)	catalyst (mol %)	T (°C)[d]	t (h)	yield (%)
1		I_2 (50)	100	6	[c]
2	6 M HCl (6.0)	I_2 (50)	100	2	62
3	CH_3COOH (6.0)	I_2 (50)	100	2	[c]
4	TfOH (6.0)	I_2 (50)	100	6	trace
5	$TsOH·H_2O$ (6.0)	I_2 (50)	100	6	46
6[b]	6 M HCl (6.0)	I_2 (50)	100	2	63
7[b]	6 M HCl (8.0)	I_2 (50)	100	2	55
8[b]	6 M HCl (4.0)	I_2 (50)	100	2	43
9[b]	$TsOH·H_2O$ (8.0)	I_2 (50)	100	6	70
10[b]	$TsOH·H_2O$ (10.0)	I_2 (50)	100	6	69
11[b]	$TsOH·H_2O$ (8.0)	I_2 (25)	100	6	63
12[b]	$TsOH·H_2O$ (8.0)	I_2 (50)	80	6	61
13[b]	$TsOH·H_2O$ (8.0)	I_2 (50)	120	6	60

[a]Isolated yield, **1a** (0.2 mmol), **2a** (0.28 mmol), DMSO (5 mL). [b]2 mL of DMSO. [c]No product. [d]Heating mantle.

neutralize the reaction system, and it was interesting that the desired oxa-bridged product **3a** was obtained in 62% yield (Table 1, entry 2). Considering the importance of acid, different acids were used to increase the yield, but there was no improvement (Table 1, entries 3−5). Reducing the volume of solvent to 2 mL resulted in a slightly higher yield (63%, entry 6). Increasing or decreasing the amount of HCl (6 M) both gave lower yields (entries 7 and 8). We were pleased to find that the yield of **3a** could be increased to 70% by further increasing the amount of $TsOH·H_2O$ to 8.0 equiv (entry 9); 10.0 equiv of $TsOH·H_2O$ gave almost the same result as that of 8.0 equiv (entry 10 vs entry 9). When the amount of iodine was reduced to 25 mol %, the yield of **3a** was decreased to 63% (entry 11). The strategy of raising or lowering the temperature to increase the yield was ineffective (entries 12 and 13). Therefore, the optimized reaction condition is 8.0 equiv of $TsOH·H_2O$ and 50 mol % of I_2 at 100 °C for 6 h (Table 1, entry 9).

After obtaining the optimal reaction conditions, the substrate range was investigated (Scheme 2). Regarding the

Scheme 2. Substrate Scope for the Synthesis of 3[a]



[a]Reaction conditions: 0.3 mmol scale, 3 mL of DMSO, **1**/**2a** = 1:1.4.

R^1 substituent, no matter it has an electron-donating group or an electron-withdrawing group at the para position, the target products were obtained in moderate to good yields (**3a**−**3f**). When the electron-withdrawing group (−Cl) was in the *meta*-position, it provided a lower yield than in the *para*-position (49% vs 62%). For the R^2 substituent, it could tolerate various substituents such as 4-Me, 4-OMe, 3,4-$(OMe)_2$, 4-F, and 4-Cl, and the target products (**3h**−**3m**) were generated in 35−83% yields. It was worth noting that when the −F was in the para position, the yield of **3l** was only 35%. Other aryl substituents were also suitable for this reaction (such as naphthalene ring, 2-furyl) to provide corresponding products with yields of 62% and 71%, respectively. When both R^1 and R^2 were other heteroaryls, such as thiophene-2-yl or *N*-Ts-pyrrole-2-yl, the corresponding products (**3p**−**3q**) were also well afforded. The structure of **3q** was fully confirmed by X-ray crystallography.[12] Interestingly, alkyl-substituted alkynones could also react with **2a** to give **3r**−**3t** in moderate yields. Notably, alkynyl ester could also be employed in the reaction to afford **3u** in a 44% yield.

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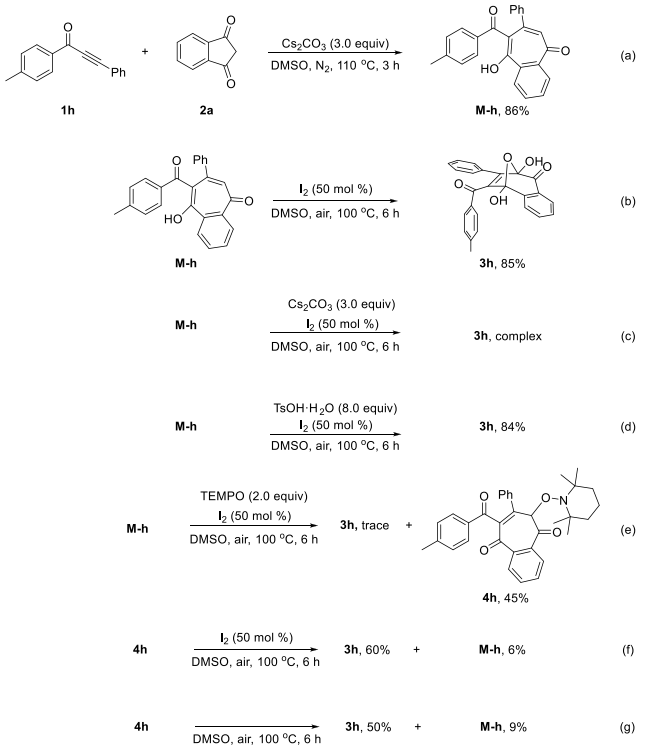
Some control experiments were conducted to explore the reaction mechanism (Scheme 3). The reaction of **1h** with **2a**

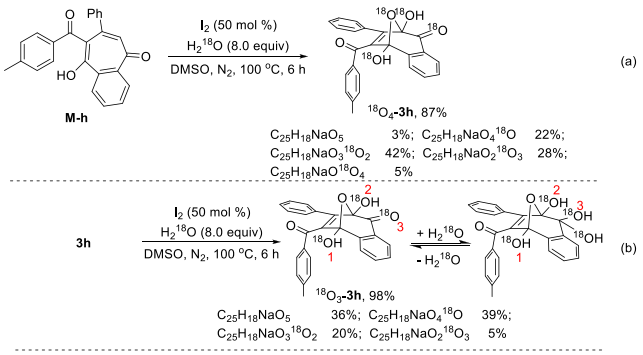
Scheme 3. Control Experiments



was carried out under the optimized reaction conditions for the first step, providing a ring expansion product **M-h** in a yield of 86% (Scheme 3a). When **M-h** was subjected to the general reaction conditions of the second step, the desired product **3h** was obtained 85% yield within 6 h (Scheme 3b). There was no Cs_2CO_3 in the conversion from **M-h** to **3h**, so there was no need to add acid to neutralize the system. This result indicates that **M-h** is an intermediate for the formation of **3h** in the one-pot process. When **M-h** was treated with I_2 in the presence of Cs_2CO_3, a complex reaction mixture was observed (Scheme 3c). Adding TsOH·H_2O to the system under the standard conditions of the second step afforded **3h** in 84% yield (Scheme 3d). These results suggested that the oxa-bridged product could not be formed under basic conditions. When 2,2,6,6-tetramethyl-1-piperinedinyloxy (TEMPO) was added, the radical trapping product **4h** was obtained in 35% yield with a trace amount of **3h** (Scheme 3e), which might suggest a radical process. The radical trapping product **4h** was processed underthe general reaction conditions of the second step to obtain the desired product **3h** in 60% yield (Scheme 3f). When **4h** was treated in the absence of I_2, **3h** was isolated with a yield of 50%. This result indicates that iodine was not required for cyclization reactions.

In order to explore the source of oxygen, ^{18}O isotopic labeling experiments were carried out under the standard reaction conditions. When the seven-membered ring **M-h** was treated with I_2 in the presence of $H_2{}^{18}O$, $^{18}O_4$-**3h** was obtained with a yield of 87%. There are four labeled O atoms in $^{18}O_4$-**3h** (Scheme 4a). These results indicated that two additional oxygen atoms (one from the bridged "O" and the other from the OH group) might come from water. Treatment of **3h**

Scheme 4. ^{18}O-Labeled Experiments[a]

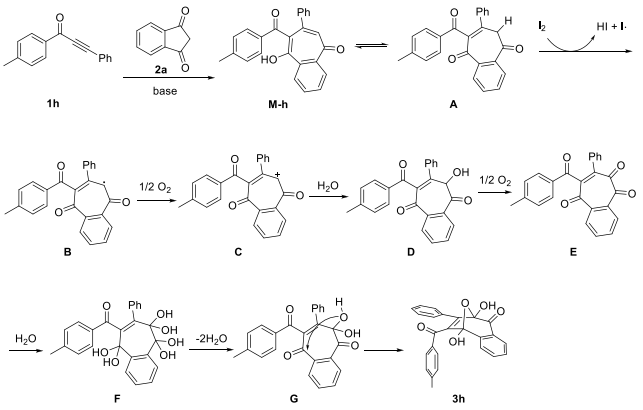


[a]^{18}O determined by ESI-MS.

under the same reaction conditions, it was found that three ^{18}O-labeled atoms were incorporated to give $^{18}O_3$-**3h** (Scheme 4b). This result suggested that O exchange could take place between $H_2{}^{18}O$ and the three O atoms of the bridged compound **3h** (see Scheme 4b, ^1O, ^2O, and ^3O) in the presence of I_2.

Based on the experimental results and previous reports,[10,11,13] a plausible mechanism for the formation of **3h** was proposed in Scheme 5. First, **1h** and **2a** generated **M-h**

Scheme 5. Possible Reaction Mechanism



through C−C bond insertion reaction in the presence of bases. Tautomerization of **M-h** gave **A**. Free radical intermediate **B** was obtained under iodine. Intermediate **B** was oxidized to form **C**, which was hydrolyzed to produce **D**. Then, D was oxidized to form a triketone intermediate **E**. Subsequently, **E** was hydrolyzed to give **F**. Dehydration of **F** gave **G**. Finally, an intramolecular attack of OH to afford product **3h**.

In conclusion, an iodine-mediated protocol for the stereoselective synthesis of seven-membered oxa-bridged rings via *in situ* generated cycloheptenols has been developed. Cascade reactions of Cs_2CO_3-promoted C−C bond cleavage and I_2-mediated C−O bond formation were involved in this process. It is anticipated that the effective combination of C−O bond formation and C−C bond cleavage reactions may be an attractive choice for the construction of complex molecular skeletons from readily available starting materials.

EXPERIMENTAL SECTION

General Information. All reactions under N_2 were performed in flame-dried glassware under an atmosphere of

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dry nitrogen, unless otherwise noted. Column chromatographic purification of products was carried out using silica gel (200−300 mesh). The reagents were used without further purification. ^{1}H NMR spectra were recorded at 400 or 500 MHz, and ^{13}C NMR spectra were recorded at 100 or 125 MHz, in $CDCl_3$ (containing 0.03% TMS) or in DMSO-d_6 solutions. ^{1}H NMR spectra were recorded with tetramethylsilane (δ = 0.00 ppm) as an internal reference. ^{13}C NMR spectra were recorded with $CDCl_3$ (δ = 77.00 ppm) as an internal reference, or ^{13}C NMR spectra were recorded with DMSO-d_6 (δ = 39.50 ppm) as an internal reference. High-resolution mass spectra were performed on a mass spectrometer with a TOF (for EI or ESI) or FT-ICR (for MALDI) analyzer. The crystal preparation and measurement methods of **3q** are as follows: 50 mg of **3q** was placed in a 50 mL round-bottom flask, and **3q** was dissolved in 2 mL of dichloromethane. Then, 6 mL of petroleum ether was added, and the solution was mixed well and left to stand still at room temperature until crystals precipitated out. Single-crystal X-ray diffraction data was collected in Bruker SMARTAPEX diffractiometers with molybdenum cathodes.

Synthesis of 1: Preparation of 1a−1s. To a solution of the alkyne (12 mmol) in anhydrous THF (30 mL), *n*-BuLi (2.5M, 10 mmol, 4 mL) was added at −78 °C. The resulting mixture was stirred at −78 °C for 1 h, then the aldehyde (10 mmol) was added, and the reaction temperature was raised to room temperature until the aldehyde disappeared by TLC analysis. The resulting mixture was quenched with a saturated solution of NH_4Cl and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography with petroleum ether/ethyl acetate = 10:1−5:1 as the eluent afforded the substituted alkynol.

To a solution of substituted alkynol (10 mmol) in DMSO (20 mL) in a round-bottom flask was added IBX (12 mmol, 3.36 g) at room temperature. The reaction was stirred in air until the full conversion of substituted alkynol was monitored by thin-layer chromatography. The resulting mixture was quenched with water (20 mL) and filtered. Then the filtrate was extracted with ethyl acetate (20 mL × 3). The organic layers was combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography with petroleum ether/ethyl acetate = 20:1−10:1 as the eluent afforded the acetyenic ketones.

Preparation of 1t−1u..[18,23] Acetyenic ketones **1** are known compounds, and the spectroscopic data is in agreement with that previously reported: compounds **1a−1c**,[14] **1d**,[15] **1e**,[14] **1f**,[16] **1g**,[17] **1h−1k**,[14] **1l**,[17] **1m**,[14] **1n**,[18] **1o**,[19] **1p**,[20] **1q**,[21] **1r**,[18] **1s**,[22] **1t**,[18] and **1u**.[23]

Compound **2a** was purchased from MACKLIN.

Synthesis of 3. A mixture of 1,3-diphenylprop-2-yn-1-one **1b** (0.30 mmol, 61.9 mg), 1*H*-indene-1,3(2*H*)-dione **2a** (0.42 mmol, 61.4 mg), Cs_2CO_3 (0.9 mmol, 293.2 mg), and DMSO (3.0 mL) in a Schlenk tube was stirred at 110 °C under N_2. After the reaction was completed as monitored by thin-layer chromatography (1 h), the reaction system was cooled to room temperature. The reaction mixture was then quenched by $TsOH·H_2O$ (2.4 mmol, 456.5 mg), then I_2 (0.15 mmol, 38.1 mg) was added, and the reaction temperature was increased to 100 °C for 5 h. The reaction mixture was then quenched by water, and the water layers were extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) afforded desired compound **3b** (light yellow solid, 84.8 mg, 74% yield).

1.0 mmol Scale Reaction for 1b with 2a. A mixture of 1,3-diphenylprop-2-yn-1-one **1b** (1.0 mmol, 206.2 mg), 1*H*-indene-1,3(2*H*)-dione **2a** (1.4 mmol, 204.6 mg), Cs_2CO_3 (3.0 mmol, 977.5 mg), and DMSO (10.0 mL) in a Schlenk tube was stirred at 110 °C under N_2. After the reaction was completed as monitored by thin-layer chromatography (1 h), the reaction system was cooled to room temperature. The reaction mixture was then quenched by $TsOH·H_2O$ (8.0 mmol, 1521.8 mg), then I_2 (0.5 mmol, 126.9 mg) was added, and the reaction temperature was increased to 100 °C for 5 h. The reaction mixture was then quenched by water, and the water layers were extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) afforded desired compound **3b** (light yellow solid, 249.5 mg, 65% yield).

Radical Trapping Experiment. In a Schlenk tube, 9-hydroxy-8-(4-methylbenzoyl)-7-phenyl-5*H*-benzo[7]annulen-5-one **M-h** (0.20 mmol, 73.2 mg), I_2 (0.1 mmol, 25.4 mg), and TEMPO (0.4 mmol, 62.5 mg) were dissolved in DMSO (2.0 mL), and the mixture was stirred at 100 °C for 5 h. The reaction mixture was then quenched by water, and the water layers were extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by chromatography on silica gel (petroleum ether/ethyl acetate = 20:1) afforded the desired compound **4h** (light yellow solid, 47.1 mg, 45%).

*(5R)-6-Benzoyl-5,8-dihydroxy-7-(p-tolyl)-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3a**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 83.3 mg, 70% yield; mp 160−161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (m, 1H), 7.46−7.39 (m, 3H), 7.36−7.31 (m, 3H), 7.10−7.05 (m, 4H), 6.90−6.87 (m, 2H), 5.84 (s, 1H), 5.70 (s, 1H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 195.0, 191.1, 145.9, 145.1, 143.6, 140.1, 134.9, 134.5, 134.5, 129.7, 129.3, 128.7, 128.7, 126.7, 126.1, 123.1, 105.4, 104.0, 21.0; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{25}H_{18}NaO_5$ 421.1046, found 421.1046.

*(5R)-6-Benzoyl-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3b**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 84.8 mg, 74% yield; mp 142−143 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.51 (s, 1H), 7.90−7.88 (m, 1H), 7.60−7.56 (m, 3H), 7.52−7.49 (m, 2H), 7.40−7.38 (m, 1H), 7.35−7.31 (m, 2H), 7.23−7.16 (m, 5H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 194.3, 190.5, 145.5, 144.7, 144.5, 134.6, 134.3, 134.2, 129.5, 129.4, 129.4, 129.4, 128.5, 128.5, 128.4, 128.3, 125.8, 123.0, 105.3, 104.0; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{24}H_{16}O_5Na$ 407.0890, found 407.0889.

*(5R)-6-Benzoyl-5,8-dihydroxy-7-(4-methoxyphenyl)-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3c**):* yellow solid, petroleum ether/ethyl acetate = 2:1, 52.3 mg, 63% yield; mp 163−164 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.56−8.55 (m, 1H), 8.42−8.41 (m, 1H), 7.87−7.85 (m, 1H), 7.62−7.58 (m, 2H), 7.58−7.55 (m, 1H), 7.54−7.46 (m, 2H), 7.40−7.37 (m, 1H), 7.36−7.32 (m, 2H), 7.21−7.18 (m, 2H), 6.76−6.73 (m, 2H), 3.64 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz,

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$CDCl_3$) δ 194.3, 191.0, 160.5, 146.0, 144.9, 141.9, 134.9, 134.4, 134.1, 130.3, 129.4, 129.4, 128.5, 128.5, 125.8, 122.9, 121.9, 113.9, 105.1, 103.7, 55.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{18}O_6Na$ 437.0996, found 437.0996.

*(5R)-6-Benzoyl-7-(4-fluorophenyl)-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3d**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 50.8 mg, 63% yield; mp 144−145 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.54 (s, 1H), 7.90−7.87 (m, 1H), 7.62−7.56 (m, 3H), 7.54−7.49 (m, 2H), 7.43−7.40 (m, 1H), 7.36−7.32 (m, 2H), 7.28−7.23 (m, 2H), 7.07−7.01 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 193.0, 190.3, 163.3, 161.3, 147.0, 146.8, 142.8, 135.5, 134.0, 133.3, 130.7, 130.6, 129.1, 129.0, 128.6, 127.2, 126.8, 126.5, 126.5, 123.4, 115.5, 115.3, 106.2, 103.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}FO_5Na$ 425.0796, found 425.0796.

*(5R)-6-Benzoyl-7-(4-chlorophenyl)-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3e**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 77.5 mg, 62% yield; mp 166−167 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 7.51−7.48 (m, 2H), 7.48−7.44 (m, 1H), 7.41−7.37 (m, 1H), 7.36−7.33 (m, 2H), 7.16−7.07 (m, 6H), 5.52 (brs, 1H), 5.35 (brs, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.6, 190.8, 145.6, 144.7, 143.8, 135.7, 134.7, 134.6, 134.5, 129.8, 129.7, 129.3, 128.7, 128.7, 128.6, 128.0, 125.6, 123.1, 104.9, 103.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$ 441.0500, found 441.0500.

*(5R)-6-Benzoyl-7-(4-bromophenyl)-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3f**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 54.7 mg, 59% yield; mp 166−167 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 7.52−7.48 (m, 2H), 7.48−7.44 (m, 1H), 7.42−7.38 (m, 1H), 7.36−7.33 (m, 2H), 7.27−7.23 (m, 2H), 7.16−7.12 (m, 2H), 7.05−7.01 (m, 2H), 5.51 (brs, 1H), 5.34 (brs, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.7, 190.8, 145.5, 144.8, 143.7, 134.6, 134.6, 134.5, 131.7, 130.0, 129.7, 129.3, 128.7, 128.6, 128.4, 125.6, 124.1, 123.1, 104.9, 103.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}BrO_5Na$ 484.9995, found 484.9995.

*(5R)-6-Benzoyl-7-(3-chlorophenyl)-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3g**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 62.0 mg, 49% yield; mp 162−163 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.62 (s, 1H), 7.92−7.90 (m, 1H), 7.62−7.50 (m, 5H), 7.42−7.33 (m, 4H), 7.30−7.27 (m, 1H), 7.21−7.17 (m, 1H), 7.06−7.03 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 192.8, 190.2, 148.3, 146.8, 142.1, 135.4, 134.1, 133.4, 132.9, 132.0, 130.3, 129.2, 129.0, 128.6, 127.7, 127.3, 126.9, 126.7, 123.4, 106.1, 103.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$ 441.0500, found 441.0500.

*(5R)-5,8-Dihydroxy-6-(4-methylbenzoyl)-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3h**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 87.9 mg, 74% yield; mp 164−165 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.47 (s, 1H), 7.91−7.89 (m, 1H), 7.59−7.55 (m, 1H), 7.52−7.48 (m, 3H), 7.38−7.35 (m, 1H), 7.25−7.21 (m, 2H), 7.21−7.17 (m, 3H), 7.16−7.13 (m, 2H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 192.7, 190.5, 147.1, 147.1, 144.7, 142.6, 133.3, 133.1, 130.2, 129.2, 129.1, 129.0, 128.3, 128.1, 127.2, 126.9, 123.3, 106.3, 103.8, 21.2; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{25}H_{18}O_5Na$ 421.1046, found 421.1046.

*(5R)-5,8-Dihydroxy-6-(4-methoxybenzoyl)-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3i**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 74.2 mg, 60% yield; mp 162−163 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 7.45−7.36 (m, 3H), 7.27−7.24 (m, 2H), 7.22−7.19 (m, 2H), 7.16−7.07 (m, 3H), 6.53−6.50 (m, 2H), 6.26 (brs, 1H), 6.20 (brs, 1H), 3.67 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.7, 190.4, 164.6, 145.3, 144.8, 143.3, 134.1, 132.1, 129.5, 129.4, 129.3, 128.5, 128.4, 128.4, 127.4, 126.0, 122.9, 113.8, 105.4, 104.0, 55.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{19}O_6$ 415.1176, found 415.1176.

*(5R)-6-(3,4-Dimethoxybenzoyl)-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3j**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 95.4 mg, 72% yield; mp 117−118 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09−8.06 (m, 1H), 7.45−7.40 (m, 3H), 7.24−7.21 (m, 2H), 7.17−7.08 (m, 3H), 6.98−6.97 (m, 1H), 6.83−6.80 (m, 1H), 6.42−6.40 (m, 1H), 6.31 (brs, 1H), 6.23 (brs, 1H), 3.74 (s, 3H), 3.57 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 192.7, 190.3, 154.4, 148.7, 145.4, 144.8, 143.3, 134.2, 129.5, 129.4, 129.3, 128.4, 128.3, 127.3, 126.0, 125.4, 123.0, 110.7, 110.0, 105.3, 104.0, 55.9, 55.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{21}O_7$ 445.1282, found 445.1282.

*(5R)-5,8-Dihydroxy-7-phenyl-6-(3,4,5-trimethoxybenzoyl)-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3k**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 81.1 mg, 74% yield; mp 161−162 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.59 (s, 1H), 8.54 (s, 1H), 7.94−7.92 (m, 1H), 7.61−7.56 (m, 1H), 7.53−7.49 (m, 1H), 7.41−7.39 (m, 1H), 7.25−7.21 (m, 5H), 6.79 (s, 2H), 3.64 (s, 3H), 3.56 (s, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 191.4, 190.6, 152.5, 147.1, 146.7, 143.4, 142.4, 133.5, 130.5, 130.4, 129.2, 129.1, 128.4, 128.2, 127.3, 126.9, 123.4, 106.5, 106.1, 103.8, 60.1, 55.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{27}H_{22}O_8Na$ 497.1207, found 497.1207.

*(5R)-6-(4-Fluorobenzoyl)-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3l**):* light yellow solid, petroleum ether/ethyl acetate = 3:1, 28.4 mg, 35% yield; mp 121−122 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.63 (s, 1H), 8.56 (s, 1H), 7.89−7.86 (m, 1H), 7.67−7.63 (m, 2H), 7.63−7.58 (m, 1H), 7.53−7.49 (m, 1H), 7.43−7.40 (m, 1H), 7.23−7.17 (m, 7H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 191.6, 190.3, 166.3, 164.3, 146.9 (d, J = 47.3 Hz), 144.1, 133.4, 132.4 (d, J = 2.5 Hz), 132.1, (d, J = 9.8 Hz), 130.0, 129.2 (d, J = 9.7 Hz), 128.4 (d, J = 2.3 Hz), 127.2, 126.9, 123.4, 115.8 (d, J = 22.3 Hz), 106.3, 103.8, 54.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}FO_5Na$ 425.0797, found 425.0797.

*(5R)-6-(4-Chlorobenzoyl)-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3m**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 104.0 mg, 83% yield; mp 156−157 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.55 (s, 1H), 7.89−7.86 (m, 1H), 7.63−7.56 (m, 3H), 7.53−7.48 (m, 1H), 7.45−7.40 (m, 3H), 7.24−7.16 (m, 5H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO) δ 191.9, 190.2, 147.0, 146.5, 144.5, 138.8, 134.4, 133.4, 130.8, 129.9, 129.3, 129.1, 128.7, 128.4, 128.3, 127.2, 126.8, 123.4, 106.3, 103.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{15}ClO_5Na$ 441.0497, found 441.0499.

*(5R)-6-(2-Naphthoyl)-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3n**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 81.3 mg, 62% yield; mp 165−166 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.59 (s, 1H), 8.01−7.96 (m, 2H), 7.93−7.88 (m, 2H),

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7.78−7.74 (m, 2H), 7.65−7.60 (m, 1H), 7.58−7.51 (m, 3H), 7.42−7.39 (m, 1H), 7.30−7.27 (m, 2H), 7.17−7.09 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 192.9, 190.5, 147.3, 147.1, 143.6, 135.3, 133.4, 132.9, 132.3, 131.6, 130.3, 129.5, 129.2, 129.0, 128.4, 128.3, 128.2, 127.7, 127.3, 127.1, 127.0, 123.4, 123.4, 106.4, 103.9; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{28}H_{18}O_5Na$ 457.1046, found 457.1046.

*(5R)-6-(Furan-2-carbonyl)-5,8-dihydroxy-7-phenyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3o**):* white solid, petroleum ether/ethyl acetate = 1:1, 79.5 mg, 71% yield; mp 159−160 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07−8.04 (m, 1H), 7.52−7.44 (m, 3H), 7.33−7.31 (m, 1H), 7.24−7.16 (m, 5H), 6.34−6.33 (m, 1H), 6.16−6.15 (m, 1H), 5.73 (brs, 1H), 5.57 (brs, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.6, 179.7, 150.9, 148.5, 145.9, 145.5, 143.8, 134.3, 129.7, 129.6, 129.5, 128.5, 128.5, 128.4, 125.7, 123.0, 122.2, 112.7, 105.2, 103.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{14}O_6Na$ 397.0683, found 397.0683.

*(5R)-5,8-Dihydroxy-6-(4-methylbenzoyl)-7-(thiophen-2-yl)-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3p**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 75.4 mg, 62% yield; mp 117−118 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.45 (s, 1H), 7.85−7.83 (m, 1H), 7.72−7.69 (m, 2H), 7.63−7.59 (m, 1H), 7.53−7.47 (m, 2H), 7.43−7.40 (m, 1H), 7.29−7.27 (m, 2H), 7.24−7.22 (m, 1H), 6.94−6.92 (m, 1H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 192.6, 189.7, 147.5, 145.0, 143.5, 136.8, 133.4, 133.2, 130.8, 130.2, 130.1, 129.4, 129.3, 129.0, 127.4, 127.0, 126.8, 123.5, 105.9, 104.2, 21.3; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{17}O_5S$ 405.0792, found 405.0792.

*(5R)-5,8-Dihydroxy-7-(p-tolyl)-6-(1-tosyl-1H-pyrrole-2-carbonyl)-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3q**):* light yellow solid, petroleum ether/ethyl acetate = 2:1, 72.8 mg, 45% yield; mp 187−188 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07−8.04 (m, 1H), 7.87−7.84 (m, 2H), 7.60−7.58 (m, 1H), 7.46−7.39 (m, 2H), 7.37−7.35 (m, 2H), 7.29−7.27 (m, 1H), 7.06−7.04 (m, 2H), 6.96−6.93 (m, 2H), 5.78−5.76 (m, 1H), 5.56−5.54 (m, 1H), 2.47 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.2, 180.0, 145.5, 145.4, 145.3, 143.1, 139.8, 135.0, 134.0, 131.8, 131.7, 129.5, 129.5, 129.1, 128.7, 128.7, 128.5, 127.6, 126.2, 125.9, 122.9, 110.8, 105.2, 103.8, 21.7, 21.3; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{30}H_{23}NO_7SNa$ 497.1207, found 497.1207.

*(5R)-6-Benzoyl-7-butyl-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3r**):* light yellow solid, petroleum ether/ethyl acetate = 4:1, 42.9 mg, 39% yield; mp 168−169 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.21 (s, 1H), 7.83−7.81 (m, 1H), 7.74−7.72 (m, 2H), 7.69−7.65 (m, 1H), 7.63−7.59 (m, 1H), 7.57−7.52 (m, 3H), 7.49−7.44 (m, 1H), 2.16−2.10 (m, 1H), 1.88−1.81 (m, 1H), 1.12−1.03 (m, 1H), 0.99−0.89 (m, 1H), 0.75−0.65 (m, 2H), 0.46 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 193.1, 191.2, 150.4, 148.4, 145.8, 137.8, 134.2, 133.5, 129.4, 129.2, 129.1, 127.6, 127.0, 124.2, 106.5, 104.6, 29.0, 25.6, 21.9, 13.5; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{20}O_5Na$ 387.1203, found 387.1207.

*(5R)-6-Benzoyl-7-hexyl-5,8-dihydroxy-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3s**):* brown solid, petroleum ether/ethyl acetate = 4:1, 37.6 mg, 32% yield; mp 88−89 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.25 (s, 1H), 8.21 (s, 1H), 7.83−7.81 (m, 1H), 7.75−7.72 (m, 2H), 7.69−7.64 (m, 1H), 7.63−7.59 (m, 1H), 7.56−7.52 (m, 3H), 7.48−7.44 (m, 1H), 2.18−2.11 (m, 1H), 1.88−1.81 (m, 1H), 1.13−1.03 (m, 2H), 0.99−0.88 (m, 3H), 0.84−0.79 (m, 2H), 0.69−0.64 (m, 1H), 0.62 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) δ 192.5, 190.7, 150.0, 147.9, 145.4, 137.4, 133.7, 133.0, 128.9, 128.7, 128.6, 127.2, 126.5, 123.8, 106.0, 104.1, 30.3, 27.8, 26.3, 25.3, 21.6, 13.6; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{24}H_{24}O_5Na$ 415.1516, found 415.1520.

*(5R)-5,8-Dihydroxy-7-phenyl-6-pivaloyl-5,8-dihydro-9H-5,8-epoxybenzo[7]annulen-9-one (**3t**):* yellow liquid, petroleum ether/ethyl acetate = 4:1, 71.9 mg, 66%); ^1H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, 1H), 7.40 (s, 1H), 7.86−7.84 (m, 1H), 7.66−7.62 (m, 1H), 7.53−7.49 (m, 1H), 7.42−7.40 (m, 1H), 7.37−7.33 (m, 3H), 7.22−7.18 (m, 2H), 0.80 (s, 9H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) 211.3, 191.1, 150.0, 147.5, 140.1, 133.7, 131.8, 129.6, 129.6, 128.9, 128.6, 127.6, 127.4, 123.7, 106.8, 104.2, 44.4, 26.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{22}H_{20}O_5Na$ 387.1203, found 387.1209.

*Methyl (5R)-5,8-Dihydroxy-9-oxo-7-phenyl-8,9-dihydro-5H-5,8-epoxybenzo[7]annulene-6-carboxylate (**3u**):* light yellow solid, petroleum ether/ethyl acetate = 4:1, 44.5 mg, 44% yield; mp 165−166 °C; ^1H NMR (500 MHz, DMSO-d_6) δ 8.52 (s, 1H), 8.40 (s, 1H), 7.87−7.84 (m, 1H), 7.67−7.62 (m, 1H), 7.59−7.57 (m, 1H), 7.52−7.47 (m, 1H), 7.45−7.41 (m, 2H), 7.39−7.35 (m, 3H), 3.59 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, DMSO-d_6) 190.7, 163.6, 148.7, 146.9, 140.3, 133.4, 130.3, 129.4, 129.0, 128.7, 128.0, 127.0, 126.8, 123.7, 106.0, 102.9, 51.8; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{19}H_{14}O_6Na$ 361.0683, found 361.0681.

*8-(4-Methylbenzoyl)-7-phenyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-5H-benzo[7]annulene-5,9(6H)-dione (**4h**):* light yellow solid, petroleum ether/ethyl acetate = 20:1, 47.1 mg, 45% yield; mp 108−109 °C; ^1H NMR (500 MHz, CDCl3) δ 8.03−8.00 (m, 1H), 7.93−7.91 (m, 1H), 7.74−7.64 (m, 2H), 7.60−7.58 (m, 2H), 7.42−7.40 (m, 2H), 7.24−7.22 (m, 3H), 7.07−7.05 (m, 2H), 5.22 (s, 1H), 2.30 (s, 3H), 1.52−1.49 (m, 1H), 1.39−1.35 (m, 2H), 1.34 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H), 0.56 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CDCl3) δ 194.9, 193.1, 190.9, 146.0, 144.4, 143.8, 137.6, 135.2, 134.0, 133.3, 133.2, 132.5, 129.5, 129.4, 129.4, 129.3, 129.2, 128.6, 128.5, 96.9, 60.6, 60.2, 39.8, 39.7, 33.8, 33.2, 21.6, 21.1, 20.4, 16.8; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{34}H_{36}NO_4$ 522.2639, found 522.2639.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01648.

Experimental procedures, characterization data, and spectra of new compounds (PDF)

Accession Codes

CCDC 2080094 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Yanzhong Li − *School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, China; Key Laboratory of Polar Materials and*

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Devices, Ministry of Education, Shanghai 200241, China; orcid.org/0000-0002-2898-3075; Email: yzli@chem.ecnu.edu.cn

Authors

Mengdan Wang − *School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, China;* orcid.org/0000-0002-9840-5924

Liqiang Yin − *School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, China*

Lu Cheng − *School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, China*

Yajie Yang − *School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200241, China;* orcid.org/0000-0002-3782-1131

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01648

Author Contributions

‖M.W. and L.Y. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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