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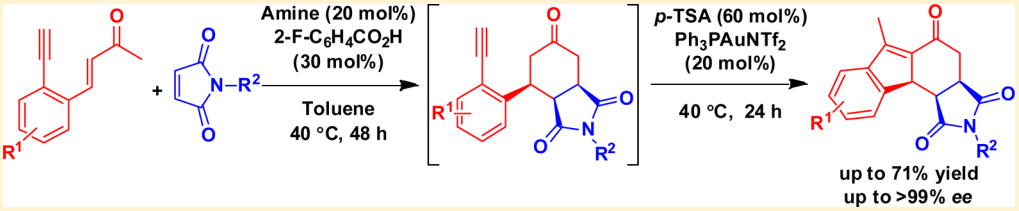
Enantioselective Construction of [6,5,6]-Carbocyclic Systems by Organo/Metal-Catalyzed Sequential Reactions

Xiang Wu,* Ming-Li Li, Dian-Feng Chen, and Shu-Sen Chen

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Supporting Information



ABSTRACT: An efficient strategy for the enantioselective construction of [6,5,6]-carbocyclic compounds has been established via one-pot reaction of (*E*)-4-(2-ethynylphenyl)but-3-en-2-ones with maleimide sequentially catalyzed by cinchona alkaloid-based primary amine and gold complex ($Ph_3PAuNTf_2$). This methodology provided a facile approach to access the [6,5,6]-tricyclic skeleton in fairly good yield and with perfect enantioselectivities (98% to >99% ee).

Nature provides structurally diverse chemical compounds that play important roles in the treatment of life-threatening conditions. In particular, two popular families with intriguing biological activities include the taiwaniaquinoids[1] and gibberellins (GAs)[2] possessing the [6,5,6]-carbotricyclic skeleton that is also found in several other types of natural products (Figure 1). Generally, taiwaniaquinol D and taiwaniaquinone F

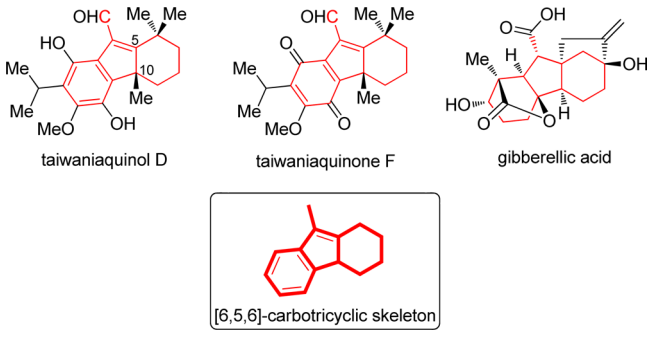


Figure 1. [6,5,6]-Carbotricyclic skeletons in natural products.

exhibit excellent inhibition of human oral epidermoid carcinoma KB cells,[3] while gibberellic acid (GA3) is a potent plant growth-regulating agent used in agriculture.[4] Consequently, their formal and total syntheses have received worldwide research interest.[5,6] However, racemic versions of the natural products were targeted in most of the precedent total synthesis, leading to great demand for the development of efficient approaches to access optically pure [6,5,6]-carbotricyclic skeletons.

A general retrosynthetic analysis of [6,5,6]-carbotricyclic skeletons reveals that the central cyclopentene of the [6,5,6] skeleton **1** can be formed from an annulation reaction of the alkyne-tethered ketone **2** cooperatively catalyzed by transition metal and amine (Scheme 1).[7] Intermediate **2**, in turn, can be accessed by a formal Diels–Alder reaction of alkynylenone **3** with maleimide **4** via asymmetric dienamine catalysis developed by several laboratories.[8]

Previous reports indicated chiral amines were able to smoothly react with enones to generate dienamines, which were very active toward dienophiles to undergo Diels–Alder reactions.[8] Thus, we proposed that the alkynylenone **3** would undergo a condensation reaction with a chiral amine to form an enamine intermediate **I**, which would basically undergo a formal Diels–Alder reaction through dienamine catalysis, leading to the formation of an enamine intermediate **II** (Scheme 2). As reported previously, the intermediate **II** would undergo an intramolecular carboannulation in the presence of π-Lewis acids, such as gold complexes[9] and others,[10−12] to generate an iminium **III**, which could be readily transformed into the desired product **1** after hydrolysis and carbon–carbon double bond migration driven by the more thermodynamic stability of the *endo*-double bond.

The cinchona alkaloids-derived chiral primary amines are excellent organocatalysts, able to promote a large number of enantioselective transformations.[13] In particular, Melchiorre and co-workers described an enantioselective [4 + 2] cycloaddition using the cinchona alkaloid-based primary amine.[8h] Thus, we initially investigated the cyclization of (*E*)-4-(2-ethynylphenyl)but-3-en-2-one **3a** with *N*-benzyl maleimide **4a** in the presence of 20 mol % quinine-derived primary amine **5** and 30 mol % 2-fluorobenzoic acid as a co-catalyst at 40 °C in toluene (Scheme 3). As anticipated, the formal Diels–Alder reaction proceeded smoothly to give **2a** in high yield and with

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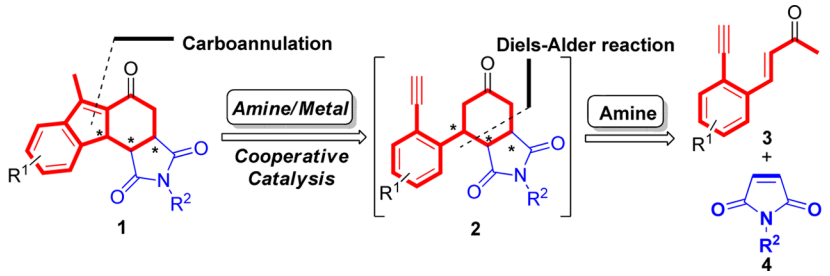
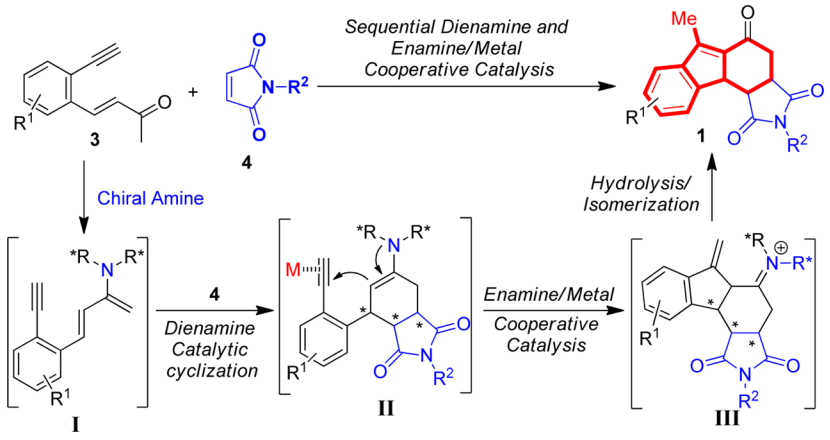
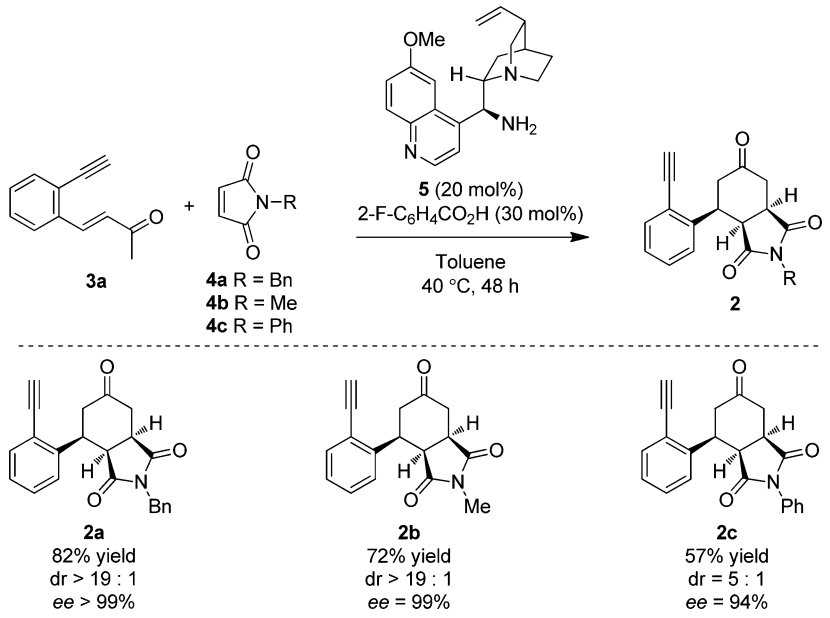
Scheme 1. Retrosynthetic Analysis of the [6,5,6]-Carbotricyclic Skeleton



Scheme 2. Asymmetric Synthesis of the [6,5,6]-Carbotricyclic Skeleton via Sequential Catalysis of Chiral Amine/Metal



Scheme 3. Formal Diels–Alder Reaction via Catalysis of Chiral Amine



excellent diastereo- and enantioselectivity (82% yield, >19:1 dr, >99% ee). The variation of substituent on the nitrogen of maleimide from a benzyl to a methyl provided similar results (72% yield, >19:1 dr, 99% ee). However, when *N*-phenyl maleimide **4c** was applied to the reaction, diminished results were observed (57% yield, 5:1 dr, 94% ee). Other reaction parameters including solvents, the ratios of **3a** to **4a**, the loading of amine **5** and co-catalyst were examined, and it was found that the conditions initially used were optimal for this reaction (see Supporting Information). The absolute configuration of products **2d** was determined by X-ray crystal analysis (see Supporting Information).

Next, we investigated the carboannulation of **2a** by using amine and π-Lewis acid cooperative catalysis. Thus, a variety of Lewis acid complexes previously used to activate alkyne functionality[8−11] were examined for the cyclization (Table 1). Unfortunately, neither $InCl_3$, $Cu(OTf)_2$, $Pd(PPh_3)_4$, nor PPh_3AuNTf_2 was able to collaborate with the chiral amine **5** to render the desired intramolecular cyclization of **2a** (entries 1−4). We envisaged that the presence of basic functionalities in

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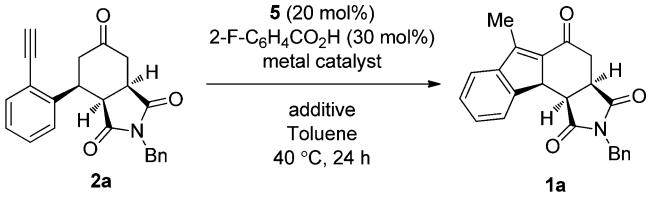
Table 1. Evaluation of Metal Complexes and Optimization of Reaction Conditions[a]



2a 1a

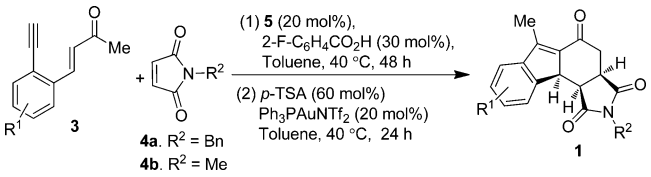
entry	metal catalyst	additive (mol %)	yield (%)	ee (%)[e]
1	$InCl_3$			
2	$Cu(OTf)_2$			
3	$Pd(PPh_3)_4$			
4	PPh_3AuNTf_2			
5	PPh_3AuNTf_2	*p*-TSA (60)	81	99
6	PPh_3AuNTf_2	*p*-TSA (30)		
7	PPh_3AuNTf_2	*p*-TSA (40)		
8	PPh_3AuNTf_2	*p*-TSA (50)	53	99
9	PPh_3AuNTf_2	*p*-TSA (80)	72	99
10		*p*-TSA (60)		
11	PPh_3AuNTf_2[b]	*p*-TSA (60)	80	99
12	PPh_3AuNTf_2[c]	*p*-TSA (60)	72	99
13	PPh_3AuNTf_2[d]	*p*-TSA (60)	34	99
14	$IPrAuSbF_6$	*p*-TSA (60)	12	99
15	PPh_3AuMe	*p*-TSA (60)		
16	PPh_3AuCl	*p*-TSA (60)		
17	$PPh_3AuCl/AgOTf$	*p*-TSA (60)	35	99

[a]Unless stated otherwise, the reaction was carried out with **2a** (0.2 mmol) in the presence of 20 mol % organocatalyst **5**, 30 mol % 2-F-$C_6H_4CO_2H$, 20 mol % metal catalysts, and additives in toluene (0.8 mL). The resulting solution was stirred for 24 h at 40 °C. [b]CH_2Cl_2 was used as solvent. [c]10 mol % PPh_3AuNTf_2 was used. [d]5 mol % PPh_3AuNTf_2 was used. [e]Determined by HPLC.

the chiral amine might be deleterious to the catalytic activity of the π-Lewis acids. Given the addition of strong Brønsted acids to protonate the basic functionalities to reactivate the Lewis acid, the gold complexes would be able to afford the intramolecular cyclization in combination with chiral amine catalyst.[9b] Indeed, the use of 60 mol % *p*-TSA, together with 20 mol % PPh_3AuNTf_2, allowed the amine-catalyzed cyclization reaction to proceed readily to give the product **1a** in 81% yield with maintained diastereo- and enantioselectivities (entry 5). Lowering the amount of *p*-TSA to 30 mol %, 40 mol % or 50 mol % was ineffective to surpass basic functionality to deactivate the gold complex (entries 6−8), while the employment of higher amounts of *p*-TSA also did not provide enhanced results in terms of the yield (entry 9). The result of control experiment showed that in the absence of PPh_3AuNTf_2, only *p*-TSA could not activate alkyne to give desired product (entry 10). Moreover, CH_2Cl_2 was also a suitable reaction media, in which excellent results similar to those in toluene were observed (entry 11). The yield was seemingly highly dependent on the loading of the gold catalyst. As a consequence, the yield gradually dropped with decreased amounts of the gold complex (entries 12 and 13). Some other gold complexes commonly used were also evaluated, and it was found that PPh_3AuNTf_2 was the most suitable catalyst for the reaction (entry 5 vs 14−17).

With the aforementioned results in hand, we next investigated the feasibility of the one-pot sequential reaction by combining dienamine catalysis and enamine/gold cooperative catalysis. After the dienamine-catalyzed Diels−Alder reaction of **3a** with **4a** proceeded completely, the reaction solution was diluted with toluene, and *p*-TSA and PPh_3AuNTf_2 were subsequently added. As such, the one-pot protocol was indeed successful to produce the [6,5,6]-tricyclic product **1a** in 61% yield with maintained levels of stereoselectivity (Table 2, entry 1).

Table 2. Scope of the Sequential Reaction[a]



3 4a. R^2 = Bn 4b. R^2 = Me 1

entry	product	substrates		yield (%)	ee (%)[b]
1	**1a**	**3a**	**4a**	61	98
2	**1b**	**3a**	**4b**	55	99
3	**1c**	**3b** (4-Me)	**4a**	61	99
4	**1d**	**3b** (4-Me)	**4b**	66	>99
5	**1e**	**3c** (4-F)	**4a**	61	>99
6	**1f**	**3d** (5-F)	**4a**	71	>99
7	**1g**	**3d** (5-F)	**4b**	67	98
8	**1h**	**3e** (4-Cl)	**4a**	60	99
9	**1i**	**3f** (5-Cl)	**4a**	64	98
10	**1j**	**3g** (5-MeO)	**4a**	32	>99
11	**1k**	**3h** (4,5-OCH_2O)	**4a**	25	99

[a]The reaction was carried out with **3** (0.2 mmol), **4** (0.4 mmol), **5** (0.04 mmol), and 2-F-$C_6H_4CO_2H$ (0.06 mmol) in 0.2 mL of toluene. The resulting solution was stirred for 48 h at 40 °C. Then, 0.6 mL of toluene, PPh_3AuNTf_2 (0.04 mmol), and *p*-TSA (0.12 mmol) were added to the mixture. The resulting solution was stirred for 24 h at 40 °C. [b]Determined by HPLC.

Under the identical conditions, the sequential reaction of **3a** with *N*-methyl maleimide **4b** gave the desired compound **1b** as a single diastereomer in good yield and excellent enantioselectivity (entry 2). Then, a variety of (*E*)-4-(2-ethynylphenyl)-but-3-en-2-ones **3** were investigated to react with either *N*-benzyl maleimide **4a** or *N*-methyl maleimide **4b** (Table 2). The presence of an alkyl or a halogenated substituent at the benzene ring of **3** was well tolerated, and the reaction gave polycyclic products in fairly good yields ranging from 55% to 71% yield and with excellent levels of stereoselectivity of >20:1 dr and up to >99% ee (entries 3−11). However, the introduction of highly electron-donating substituents to the benzene ring led to an incomplete reaction and thereby gave the desired products in much lower yields, but still with very high levels of enantioselectivity (entries 10 and 11).

The further extension of the one-pot protocol to (*E*)-4-(3-ethynylthiophen-2-yl)but-3-en-2-one **3i**, however, was unable to give the polycyclic product, but the triple bond was hydrolyzed to afford the methyl ketone **6** in 55% yield with 99% ee (Scheme 4, eq 1). In addition, the reaction of nonterminal alkynylenone **3j** and **3k** also did not generate the desired products, and only Diels−Alder adducts **2j** and **2k** were isolated (Scheme 4, eq 2). Moreover, in attempting to construct the core structure of taiwaniaquinoids containing a methyl group at the C10-position, β-methyl-**3a** was prepared but unfortunately did not undergo reaction under standard conditions.

Finally, the hydrogenation of **1d** under the catalysis of Pd/C in EtOAc furnished alcohol **7** in good yield (70%) and with a perfect diastereoselectivity of >99:1 dr (eq 3). The relative stereochemistry of **7** was assigned by the NOE correlation (see Supporting Information).

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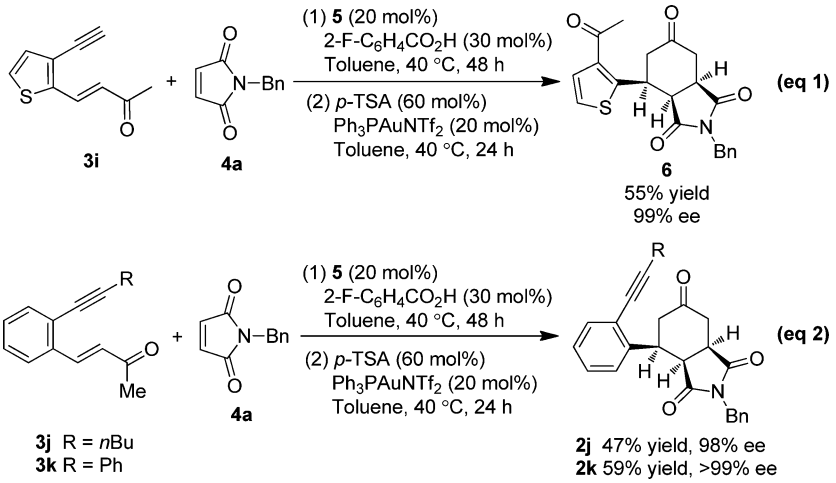
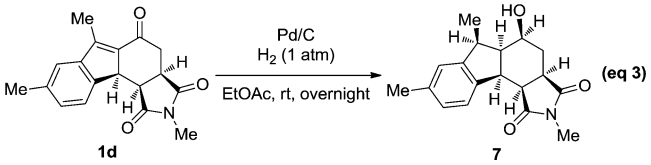
Scheme 4. Substrate Limitations to the Sequential Reaction



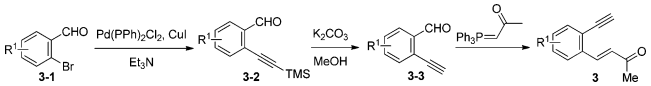


In conclusion, we have developed a highly stereoselective one-pot sequential cyclization reaction of (*E*)-4-(2-ethynylphenyl)-but-3-en-2-ones with maleimides sequentially catalyzed by the cinchona alkaloid-based primary amine and gold complex, providing a facile approach to access the [6,5,6]-tricyclic skeleton in fairly good yield and with perfect enantioselectivities. Importantly, the combination of dienamine catalysis and enamine/gold cooperative catalysis would allow the design of new sequential reactions for efficient construction of structurally complicated polycyclic compounds.

EXPERIMENTAL SECTION

General Methods. NMR spectra were recorded on a 400 MHz spectrometer. Mass spectra were recorded on an Orbitrap ESI-MS spectrometer. Infrared spectra were recorded on a FT-IR spectrometer. The enantiomeric excess of the compounds was determined by chiral HPLC using racemic compounds as references. X-ray crystallography analysis was performed on a CCD diffractionmeter equipped with micro Cu Kα (λ = 1.54184 Å) radiation at room temperature. Melting points were determined on a melting point apparatus with a microscope and were uncorrected. All starting materials, reagents, and solvents were purchased from commercial suppliers and used as supplied unless otherwise stated. Toluene was dried over Na and distilled prior to use.

General Procedure A: Synthesis of ***3****.*



To a suspension of $Pd(PPh_3)_2Cl_2$ (224 mg, 0.32 mmol) and CuI (61 mg, 0.32 mmol) in Et_3N (15 mL) was added a solution of ethynyltrimethylsilane (1.9 g, 19.4 mmol) and substituted 2-bromobenzaldehyde (**3-1**) (16.2 mmol) in Et_3N (30 mL). The mixture was stirred at room temperature for 12 h, diluted with EtOAc (20 mL), filtered off, and evaporated under reduced pressure. The residue was purified through column chromatography (silica gel, petroleum ether) to afford substituted 2-((trimethylsilyl)ethynyl)-benzaldehyde (**3-2**).

A mixture of K_2CO_3 (400 mg, 10 mmol) and **3-2** (12.3 mmol) in MeOH (30 mL) was stirred at room temperature for 1 h. Water (10 mL) was added to quench the reaction, and the mixture was evaporated under reduced pressure to remove MeOH. The residue was diluted with EtOAc (30 mL) and then washed with water (10 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/EtOAc = 15/1 to 8/1) to afford substituted (2-ethynylphenyl)methanol (**3-3**).

To a solution of substituted (2-ethynylphenyl)methanol (**3-3**) (5 mmol) in toluene (25 mL) was added (acetylmethylene)triphenylphosphorane (1.91 g, 6 mmol). The mixture was stirred at reflux for 3 h, cooled to room temperature, and evaporated under reduced pressure. The residue was purified through column chromatography (silica gel, petroleum ether/EtOAc = 15/1 to 10/1) to afford substituted (*E*)-4-(2-ethynylphenyl)but-3-en-2-one (**3**).

General Procedure B: Synthesis of ***1****.* The solution of quinine-derived primary amine **5** (0.04 mmol, 13 mg, 20 mol %) and 2-fluorobenzoic acid (0.06 mmol, 8.4 mg, 30 mol %) in 0.2 mL of toluene was stirred at room temperature for 10 min. Then substituted (*E*)-4-(2-ethynylphenyl)but-3-en-2-one (**3**) (0.4 mmol, 2.0 equiv) and substituted maleimide were added. The reaction mixture was stirred at 40 °C for 48 h. To the mixture were added 0.6 mL of toluene, pTSA (22.8 mg, 0.0012 mmol, 60 mol %), and $Ph_3PAuNTf_2$ (14.8 mg, 0.0004 mmol, 20 mol %). The resulting mixture was stirred for 24 h. The crude mixture was concentrated and was purified through column chromatography (silica gel, petroleum ether/EtOAc = 3/2 to 1/1) to afford **1**.

Determination of Enantiomeric Purity. HPLC traces for compounds **1** were compared to racemic samples prepared by mixing the two product antipodes obtained by performing the reaction with catalyst and quinine-derived primary amine **5** and quinidine-derived primary amine separately.

(*E*)-4-(2-Ethynylphenyl)but-3-en-2-one (3a). 84% overall yield (369.6 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 16.5 Hz, 1H), 7.68−7.63 (m, 1H), 7.59−7.53 (m, 1H), 7.37 (d, J = 7.4, 1.5 Hz, 2H), 6.74 (d, J = 16.4 Hz, 1H), 3.44 (s, 1H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.6, 141.0, 136.5, 133.6, 129.9, 129.2, 129.1, 126.0, 123.1, 83.4, 81.1, 27.2; IR (KBr) ν 708, 756, 907, 987, 1179, 1266, 1322, 1361, 1473, 1609, 1688, 2095, 3242 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{12}H_{10}O$ [(M + H)$^+$] requires m/z 253.1043, found m/z 253.1041; mp (°C) 60−62.

(*E*)-4-(2-Ethynyl-4-methylphenyl)but-3-en-2-one (3b). 80% overall yield (327.5 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 16.4 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 7.38 (s, 1H), 7.19 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 16.4 Hz, 1H), 3.41 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.7, 141.0, 140.4, 134.0, 133.7, 130.3, 128.2, 125.9, 123.0, 82.9, 81.3, 27.1, 21.2; IR (KBr) ν 477, 588, 740, 820, 987, 1179, 1266, 1314, 1361, 1442, 1592, 1616, 1688, 2103, 3227 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{13}H_{12}O$ [(M + H)$^+$] requires m/z 185.0961, found m/z 185.0961; mp (°C) 109−111.

(*E*)-4-(2-ethynyl-4-fluorophenyl)but-3-en-2-one (3c). 82% overall yield (341.9 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 16.4 Hz, 1H), 7.64 (dd, J = 8.8, 5.6 Hz, 1H),

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7.26−7.23 (m, 1H), 7.10 (dt, J = 8.4, 2.7 Hz, 1H), 6.68 (d, J = 16.4 Hz, 1H), 3.49 (s, 1H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.3, 161.8 (d, J_{C-F} = 252.2 Hz), 139.8, 132.9 (d, J_{C-F} = 3.5 Hz), 128.7 (d, J_{C-F} = 2.2 Hz), 128.0 (d, J_{C-F} = 9.0 Hz), 125.0 (d, J_{C-F} = 9.9 Hz), 120.1 (d, J_{C-F} = 23.4 Hz), 117.1 (d, J_{C-F} = 22.1 Hz), 84.4, 79.9 (d, J_{C-F} = 3.1 Hz), 27.2; IR (KBr) ν 541, 661, 716, 820, 867, 987, 1083, 1250, 1497, 1560, 1601, 1673, 2103, 3250 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{12}H_9FO$ [(M + H)$^+$] requires m/z 189.0710, found m/z 189.0710; mp (°C) 66−69.

(*E*)-4-(2-Ethynyl-5-fluorophenyl)but-3-en-2-one (3d). 75% overall yield (302.6 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 16.4, 1.5 Hz, 1H), 7.54 (dd, J = 8.6, 5.7 Hz, 1H), 7.33 (dd, J = 9.6, 2.6 Hz, 1H), 7.06 (dt, J = 8.3, 2.6 Hz, 1H), 6.70 (d, J = 16.4 Hz, 1H), 3.41 (s, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.1, 162.7 (d, J_{C-F} = 251.0 Hz), 139.7 (d, J_{C-F} = 2.6 Hz), 138.9 (d, J_{C-F} = 8.1 Hz), 135.4 (d, J_{C-F} = 8.6 Hz), 129.8, 119.2 (d, J_{C-F} = 3.3 Hz), 117.4 (d, J_{C-F} = 22.5 Hz), 112.7 (d, J_{C-F} = 23.1 Hz), 83.1 (d, J_{C-F} = 1.6 Hz), 80.2, 27.4; IR (KBr) ν 548, 612, 684, 820, 892, 979, 1083, 1154, 1194, 1226, 1274, 1361, 1481, 1569, 1609, 1688, 2103, 3067, 3290 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{12}H_9FO$ [(M + H)$^+$] requires m/z 189.0710, found m/z 189.0710; mp (°C) 105−107.

(*E*)-4-(4-Chloro-2-ethynylphenyl)but-3-en-2-one (3e). 75% overall yield (299.4 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 16.4 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 2.1 Hz, 1H), 7.35 (dd, J = 8.5, 2.0 Hz, 1H), 6.71 (d, J = 16.4 Hz, 1H), 3.49 (s, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): 198.2, 139.6, 135.8, 135.0, 133.2, 129.6, 129.2, 127.2, 124.5, 84.6, 79.8, 27.3; IR (KBr) ν 588, 700, 732, 820, 892, 979, 1106, 1170, 1305, 1361, 1465, 1585, 1609, 1688, 2103, 3227 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{12}H_9ClO$ [(M + H)$^+$] requires m/z 205.0415, found m/z 205.0416; mp (°C) 109−111.

(*E*)-4-(5-Chloro-2-ethynylphenyl)but-3-en-2-one (3f). 84% overall yield (357.6 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 16.4 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.32 (dd, J = 8.3, 2.1 Hz, 1H), 6.73 (d, J = 16.4 Hz, 1H), 3.47 (s, 1H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.0, 139.4, 138.1, 135.4, 134.7, 129.9, 129.8, 126.0, 121.5, 84.3, 80.2, 27.5; IR (KBr) ν 524, 692, 724, 828, 915, 979, 1115, 1170, 1258, 1314, 1361, 1481, 1609, 1688, 2103, 3218 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{12}H_9ClO$ [(M + H)$^+$] requires m/z 205.0415, found m/z 205.0415; mp (°C) 102−103.

(*E*)-4-(2-ethynyl-5-methoxyphenyl)but-3-en-2-one (3g). 55% overall yield (246.3 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 16.4 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.12 (d, J = 2.2 Hz, 1H), 6.90 (dd, J = 8.6, 2.3 Hz, 1H), 6.70 (d, J = 16.4 Hz, 1H), 3.84 (s, 3H), 3.36 (s, 1H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.7, 160.0, 141.1, 137.9, 134.9, 129.2, 116.6, 115.6, 110.5, 81.9, 81.1, 55.5, 27.1; IR (KBr) ν 620, 692, 828, 883, 979, 1035, 1226, 1266, 1442, 1497, 1592, 1648, 1673, 1095, 3259 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{13}H_{12}O_2$ [(M + H)$^+$] requires m/z 201.0910, found m/z 201.0910; mp (°C) 60−61.

(*E*)-4-(6-Ethynylbenzo[*d*][1,3]dioxol-5-yl)but-3-en-2-one (3h). 50% overall yield (212.3 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 16.3 Hz, 1H), 7.08 (s, 1H), 6.96 (s, 1H), 6.56 (d, J = 16.3 Hz, 1H), 6.03 (s, 2H), 3.38 (s, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.5, 149.3, 149.0, 140.8, 131.8, 127.3, 118.0, 112.5, 105.1, 102.1, 82.4, 81.0, 27.1; IR (KBr) ν 541, 597, 676, 836, 867, 915, 971, 1019, 1162, 1266, 1489, 1609, 1641, 1665, 2103, 3290 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{13}H_{10}O_3$ [(M + H)$^+$] requires m/z 215.0703, found m/z 215.0702; mp (°C) 136−138.

(*E*)-4-(3-Ethynylthiophen-2-yl)but-3-en-2-one (3i). 70% overall yield (297.9 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 16.1, 0.7 Hz, 1H), 7.31 (dd, J = 5.2, 0.6 Hz, 1H), 7.11 (d, J = 5.2 Hz, 1H), 6.61 (d, J = 16.1 Hz, 1H), 3.44 (s, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 197.8, 143.0, 133.8, 131.4, 127.4, 127.1, 124.7, 83.6, 27.6; IR (KBr) ν 524, 580, 661, 756, 963, 1170, 1250, 1354, 1417, 1505, 1592, 1688, 2103, 3083, 3242 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{10}H_8OS$ [(M + H)$^+$] requires m/z 177.0369, found m/z 177.0369.

(*E*)-4-(2-(Hex-1-yn-1-yl)phenyl)but-3-en-2-one. 85% overall yield (368.5 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 16.5 Hz, 1H), 7.64−7.59 (m, 1H), 7.48−7.43 (m, 1H), 7.32−7.27 (m, 2H), 6.72 (d, J = 16.5 Hz, 1H), 2.51 (t, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.69−1.60 (m, 2H), 1.58−1.48 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H);$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.8, 142.0, 135.6, 132.9, 129.9, 128.5, 127.9, 125.9, 125.3, 97.2, 78.3, 30.8, 26.9, 22.1, 19.3, 13.6; IR (KBr) ν 756, 971, 1179, 1258, 1354, 1481, 1609, 1673, 1697, 2230, 2868, 2623, 2963 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{16}H_{18}O$ [(M + H)$^+$] requires m/z 227.1430, found m/z 227.1431.

(*E*)-4-(2-(Phenylethynyl)phenyl)but-3-en-2-one (3k). 84% overall yield (342.6 mg), white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 16.5 Hz, 1H), 7.72−7.65 (m, 1H), 7.63−7.53 (m, 3H), 7.43−7.33 (m, 5H), 6.78 (d, J = 16.4 Hz, 1H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 198.7, 141.6, 135.7, 132.9, 131.6, 130.0, 128.8, 128.7, 128.7, 128.6, 126.2, 124.3, 122.8, 95.7, 86.9, 27.1; IR (KBr) ν 766, 973, 1180, 1247, 1355, 1480, 1610, 1673, 1698, 2230, 2868, 2673, 2973 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{18}H_{14}O$ [(M + H)$^+$] requires m/z 247.1118, found m/z 247.1120; mp (°C) 72−73.

(3a*R*,7*S*,7a*S*)-2-Benzyl-7-(2-ethynylphenyl)tetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2a). 81% yield (57.8 mg), yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.4, 1.6 Hz, 1H), 7.36−7.26 (m, 7H), 6.81−6.71 (m, 1H), 4.61 (dd, J = 38.6, 13.8 Hz, 2H), 4.09 (ddd, J = 14.8, 5.8, 3.0 Hz, 1H), 3.81 (ddd, J = 9.3, 5.9, 1.4 Hz, 1H), 3.47−3.39 (m, 1H), 3.37 (s, 1H), 3.09 (dd, J = 17.3, 1.8 Hz, 1H), 2.87 (dd, J = 17.3, 8.0 Hz, 1H), 2.55 (ddd, J = 18.2, 3.0, 1.5 Hz, 1H), 2.29 (dd, J = 18.2, 14.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.5, 177.4, 175.3, 140.3, 135.7, 133.2, 129.0, 128.9, 128.7, 128.3, 127.4, 127.2, 121.2, 82.5, 81.8, 42.7, 42.0, 40.5, 38.2, 37.0, 36.8; IR (KBr) ν 748, 987, 1186, 1337, 1393, 1433, 1740, 1784, 3259 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{19}NO_3$ [(M + H)$^+$] requires m/z 358.1438, found m/z 358.1437; $[\alpha]^{20}_D$ = +143.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-AD, hexane/isopropanol = 70/30, flow rate 0.75 mL/min, T = 30 °C, 254 nm) t_R (minor) =16.85 min, t_R (major) = 26.35 min.

(3a*R*,7*S*,7a*S*)-7-(2-Ethynylphenyl)-2-methyltetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2b). 72% yield (40.5 mg), oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.6, 1.3 Hz, 1H), 7.40 (dt, J = 7.7, 1.4 Hz, 1H), 7.31 (dt, J = 7.5, 1.1 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 4.13 (ddd, J = 14.6, 5.5, 3.2 Hz, 1H), 3.86 (ddd, J = 9.4, 5.6, 1.4 Hz, 1H), 3.50−3.43 (m, 1H), 3.41 (s, 1H), 3.08 (dd, J = 17.2, 1.7 Hz, 1H), 2.96 (s, 3H), 2.91 (dd, J = 17.2, 8.3 Hz, 1H), 2.68 (ddd, J = 18.3, 3.1, 1.6 Hz, 1H), 2.51 (dd, J = 18.4, 14.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.7, 177.8, 175.8, 140.3, 133.3, 129.0, 127.4, 127.2, 121.2, 82.6, 81.8, 42.1, 40.6, 38.1, 37.3, 36.6, 25.1; IR (KBr) ν 627, 666, 774, 1014, 1064, 1229, 1287, 1336, 1381, 1439, 1698, 1720, 1773, 2099, 2884, 2915, 2946 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{17}H_{15}NO_3$ [(M+Na)$^+$] requires m/z 304.0944, found m/z 304.0939; $[\alpha]^{20}_D$ = +73.3 (c 0.3, $CHCl_3$); ee 99%, determined by HPLC (Chiralpak-IC, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 20.57 min, t_R (minor) =25. Twenty-nine min.

(3a*R*,7*S*,7a*S*)-7-(2-Ethynylphenyl)-2-phenyltetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2c). 57% yield (38.7 mg), light yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 7.6, 1.4 Hz, 1H), 7.47−7.40 (m, 2H), 7.40−7.33 (m, 2H), 7.29 (dt, J = 7.6, 1.2 Hz, 1H), 7.20 (dd, J = 5.3, 3.3 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 4.28−4.19 (m, 1H), 4.04 (ddd, J = 9.6, 5.6, 1.4 Hz, 1H), 3.68−3.59 (m, 1H), 3.44 (s, 1H), 3.17 (dd, J = 17.1, 1.9 Hz, 1H), 3.01 (dd, J = 17.1, 8.3 Hz, 1H), 2.77 (ddd, J = 18.3, 4.1, 1.4 Hz, 1H), 2.69 (dd, J = 18.4, 13.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 206.6, 176.8, 174.8, 140.2, 133.3, 131.3, 129.2, 129.1, 128.9, 127.4, 127.3, 126.2, 121.2, 82.7, 81.8, 42.2, 40.7, 38.3, 37.6, 36.9; IR (KBr) ν 693, 754, 1190, 1217, 1383, 1499, 1716, 2853, 2927, 2959 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{22}H_{17}NO_3$ [(M+Na)$^+$] requires m/z 366.1101, found m/z 366.1096; $[\alpha]^{20}_D$ = +4.0 (c 0.3, $CHCl_3$); ee 94%, determined by HPLC (Chiralpak-IA, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) =11.41 min, t_R (major) = 13.82 min.

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(3a*R*,7*S*,7a*S*)-7-(4-Chloro-2-ethynylphenyl)-2-methyltetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2d). 80% yield (50.7 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.2 Hz, 1H), 7.36 (dd, J = 8.5, 2.2 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 4.07 (ddd, J = 14.6, 5.3, 3.3 Hz, 1H), 3.80 (dd, J = 8.5, 5.6 Hz, 1H), 3.50−3.41 (m, 2H), 3.07 (dd, J = 17.1, 1.1 Hz, 1H), 2.96 (s, 3H), 2.89 (dd, J = 17.2, 8.4 Hz, 1H), 2.65 (d, J = 17.2 Hz, 1H), 2.46 (dd, J = 18.3, 14.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.2, 177.7, 175.7, 138.9, 133.2, 132.9, 129.3, 128.6, 122.7, 83.7, 80.5, 42.0, 40.5, 38.0, 37.3, 36.2, 25.1; IR (KBr) ν 497, 577, 603, 678, 740, 824, 864, 880, 1009, 1089, 1218, 1291, 1342, 1382, 1438, 1697, 1725, 2107, 2924, 2952, 3245 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{17}H_{14}ClNO_3$ [(M+Na)$^+$] requires m/z 338.0554, found m/z 338.0547; mp (°C) 121−123; $[\alpha]^{20}_D$ = +58.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiralpak-IC, hexane/isopropanol =80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 29.64 min, t_R (minor) =36.25 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1a). 61% yield (43.6 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 7.4, 0.7 Hz, 1H), 7.54−7.46 (m, 2H), 7.43 (dd, J = 10.9, 4.0 Hz, 1H), 7.23−7.15 (m, 3H), 7.05 (dt, J = 4.7, 3.7 Hz, 2H), 4.42 (s, 2H), 4.18−4.13 (m, 1H), 3.84 (dd, J = 9.0, 7.7 Hz, 1H), 3.54 (ddd, J = 9.3, 5.3, 4.2 Hz, 1H), 3.08−3.01 (m, 2H), 2.40 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.3, 177.2, 174.5, 153.8, 144.2, 143.2, 135.4, 132.8, 129.2, 128.5, 128.2, 127.9, 127.8, 124.7, 122.6, 47.6, 42.3, 40.7, 40.4, 39.5, 12.5; IR (KBr) ν 708, 764, 907, 987, 1179, 1211, 1337, 1393, 1442, 1577, 1609, 1665, 1712, 1776 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{19}NO_3$ [(M + H)$^+$] requires m/z 358.1438, found m/z 358.1437; mp (°C) 90−92. $[\alpha]^{20}_D$ = −72.0 (c 0.1, $CHCl_3$); ee 98%, determined by HPLC (Chiracel-OD, hexane/isopropanol = 70/30, flow rate 0.75 mL/min, T = 30 °C, 254 nm) t_R (minor) = 12.84 min, t_R (major) = 13.89 min.

(3a*R*,10b*S*,10c*S*)-2,6-Dimethyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1b). 55% yield (30.9 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.4 Hz, 1H), 7.52 (dt, J = 7.4, 4.4 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 4.17 (ddd, J = 7.4, 4.9, 2.3 Hz, 1H), 3.87 (dd, J = 9.1, 7.6 Hz, 1H), 3.60−3.50 (m, 1H), 3.08−3.02 (m, 2H), 2.76 (s, 3H), 2.55 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.4, 177.6, 174.9, 153.8, 144.2, 143.3, 132.8, 129.3, 127.9, 124.7, 122.6, 77.4, 77.1, 76.7, 47.5, 40.7, 40.2, 39.6, 25.0, 12.7; IR (KBr) ν 772, 1003, 1282, 1385, 1442, 1569, 1592, 1656, 1704, 1776 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{17}H_{15}NO_3$ [(M + H)$^+$] requires m/z 282.1125, found m/z 282.1126; mp (°C) 130−132; $[\alpha]^{20}_D$ = −58.0 (c 0.1, $CHCl_3$); ee >99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 15.83 min, t_R (minor) = 24.55 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-6,8-dimethyl-3a,4-dihydroindeno-[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1c). 61% yield (45.3 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.7 Hz, 1H), 7.30 (dd, J = 14.4, 4.2 Hz, 2H), 7.22−7.15 (m, 3H), 7.10−7.00 (m, 2H), 4.42 (s, 2H), 4.15−4.06 (m, 1H), 3.81 (dd, J = 8.9, 7.7 Hz, 1H), 3.52 (dt, J = 9.2, 4.8 Hz, 1H), 3.03 (d, J = 4.8 Hz, 2H), 2.44 (s, 3H), 2.39 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.3, 177.2, 174.6, 153.9, 144.4, 140.4, 137.7, 135.4, 133.0, 130.4, 128.5, 128.2, 127.8, 124.4, 123.1, 47.2, 42.3, 40.8, 40.4, 39.5, 21.7, 12.5; IR (KBr) ν 692, 724, 811, 947, 1074, 1170, 1337, 1401, 1433, 1585, 1665, 1712, 1784, 2923 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{24}H_{21}NO_3$ [(M + H)$^+$] requires m/z 372.1594, found m/z 372.1592; mp (°C) 85−87; $[\alpha]^{20}_D$ = −353.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-IA, hexane/isopropanol =85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 20.06 min, t_R (major) = 22.28 min.

(3a*R*,10b*S*,10c*S*)-2,6,8-Trimethyl-3a,4-dihydroindeno[1,2-*e*]-isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1d). 66% yield (43.6 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.2 Hz, 2H), 4.13 (d, J = 5.0 Hz, 1H), 3.84 (t, J = 8.3 Hz, 1H), 3.63−3.42 (m, 1H), 3.12−2.94 (m, 2H), 2.76 (s, 3H), 2.53 (s, 3H), 2.45 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.4, 177.7, 175.0, 153.9, 144.4, 140.5, 137.7, 133.0, 130.4, 124.3, 123.2, 47.2, 40.8, 40.3, 39.5, 25.0, 21.6, 12.7; IR (KBr) ν 820, 995, 1211, 1282, 1378, 1442, 1592, 1665, 1697, 1768, 2915, 2971 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{18}H_{17}NO_3$ [(M + H)$^+$] requires m/z 296.1281, found m/z 296.1281; $[\alpha]^{20}_D$ = −244.0 (c 0.1, $CHCl_3$); ee >99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) =11.82 min, t_R (major) = 12.96 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-8-fluoro-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1e). 61% yield (45.8 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.3, 4.8 Hz, 1H), 7.24−7.15 (m, 4H), 7.12 (dd, J = 8.5, 2.3 Hz, 1H), 7.06 (dt, J = 4.3, 3.6 Hz, 2H), 4.42 (d, J = 1.1 Hz, 2H), 4.18−4.09 (m, 1H), 3.82 (dd, J = 9.0, 7.8 Hz, 1H), 3.54 (ddd, J = 9.2, 6.7, 2.9 Hz, 1H), 3.12−2.96 (m, 2H), 2.34 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.1, 175.9, 173.3, 161.9 (d, J_{C-F} = 245.9 Hz), 151.6 (d, J_{C-F} = 3.4 Hz), 145.2 (d, J_{C-F} = 8.6 Hz), 137.4 (d, J_{C-F} = 2.6 Hz), 134.4, 133.4, 127.5, 127.3, 126.8, 124.8 (d, J_{C-F} = 9.0 Hz), 115.4 (d, J_{C-F} = 23.5 Hz), 108.4 (d, J_{C-F} = 23.0 Hz), 46.1, 41.4, 39.6, 39.2, 38.3, 11.4; IR (KBr) ν 708, 804, 1027, 1098, 1179, 1202, 1266, 1346, 1401, 1577, 1665, 1704, 1776, 2971 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{18}FNO_3$ [(M + H)$^+$] requires m/z 376.1344, found m/z 376.1346; $[\alpha]^{20}_D$ = −139.0 (c 0.1, $CHCl_3$); ee >99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 23.31 min.

(3a*R*,10b*R*,10c*S*)-2-Benzyl-9-fluoro-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1f). 71% yield (53.3 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, J = 8.4, 5.0 Hz, 1H), 7.37−7.29 (m, 2H), 7.21−7.19 (m, 2H), 7.12 (dt, J = 8.8, 2.3 Hz, 1H), 7.06 (dd, J = 6.5, 2.9 Hz, 2H), 4.47−4.38 (m, 2H), 4.18−4.07 (m, 1H), 3.81 (dd, J = 9.0, 7.6 Hz, 1H), 3.54 (ddd, J = 9.3, 6.6, 3.0 Hz, 1H), 3.07−3.00 (m, 2H), 2.37 (d, J = 2.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.8, 177.0, 174.3, 164.0 (d, J_{C-F} = 249.7 Hz), 153.0, 145.7 (d, J_{C-F} = 9.0 Hz), 140.3, 135.4, 132.8 (d, J_{C-F} = 3.9 Hz), 128.9 (d, J_{C-F} = 8.2 Hz), 128.6, 128.2, 127.8, 123.7 (d, J_{C-F} = 9.4 Hz), 115.5 (d, J_{C-F} = 23.4 Hz), 112.5 (d, J_{C-F} = 23.6 Hz), 47.4, 42.4, 40.6, 40.3, 39.5, 12.5; IR (KBr) ν 700, 828, 947, 987, 1074, 1170, 1202, 1337, 1393, 1443, 1577, 1609, 1665, 1704, 1776, 2932 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{18}FNO_3$ [(M + H)$^+$] requires m/z 376.1344, found m/z 376.1346; $[\alpha]^{20}_D$ = −92.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-IA, hexane/isopropanol =85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 8.27 min, t_R (major) = 10.75 min.

(3a*R*,10b*S*,10c*S*)-9-Fluoro-2,6-dimethyl-3a,4-dihydroindeno-[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1g). 67% yield (40.1 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.4, 4.9 Hz, 1H), 7.42−7.30 (m, 1H), 7.15 (dd, J = 12.0, 5.5 Hz, 1H), 4.20−4.03 (m, 1H), 3.90−3.76 (m, 1H), 3.64−3.44 (m, 1H), 3.04 (d, J = 4.4 Hz, 2H), 2.78 (s, 3H), 2.53 (d, J = 2.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.9, 177.4, 174.7, 164.0 (d, J_{C-F} = 250.0 Hz), 145.8 (d, J_{C-F} = 9.2 Hz), 136.5 (d, J_{C-F} = 767.5 Hz), 123.9 (d, J_{C-F} = 9.4 Hz), 115.5 (d, J_{C-F} = 23.5 Hz), 112.4 (d, J_{C-F} = 23.6 Hz), 47.4, 40.5, 40.2, 39.6, 25.0, 12.8; IR (KBr) ν 820, 1003, 1211, 1282, 1385, 1425, 1569, 1601, 1704, 1768, 2963 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{17}H_{14}FNO_3$ [(M + H)$^+$] requires m/z 300.1031, found m/z 300.1032; mp (°C) 159−162. $[\alpha]^{20}_D$ = −41.8 (c 0.1, $CHCl_3$); ee 98%, determined by HPLC (Chiracel-AD, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) =13.72 min, t_R (major) = 20.72 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-8-chloro-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1h). 60% yield (46.9 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.0, 1.9 Hz, 1H), 7.41 (d, J = 1.7 Hz, 1H), 7.23−7.15 (m, 3H), 7.06 (dd, J = 6.4, 3.0 Hz, 2H), 4.42 (s, 2H), 4.19−4.08 (m, 1H), 3.82 (dd, J = 8.9, 7.9 Hz, 1H), 3.54 (ddd, J = 9.2, 7.0, 2.5 Hz, 1H), 3.12−2.95 (m, 2H), 2.34 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.2, 176.9, 174.3, 152.4, 145.9, 141.2, 135.3, 134.1, 134.0, 129.2, 128.9, 128.3, 127.9, 125.8, 122.7, 47.3, 42.4, 40.6, 40.2, 39.4, 12.4; IR (KBr) ν 695, 722, 821, 950, 982, 1079, 1189, 1344, 1395, 1482, 1563, 1595, 1673, 1705, 1770, 2926

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cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{18}ClNO_3$ [(M + H)$^+$] requires m/z 392.1048, found m/z 392.1048; mp (°C) 126−128; $[\alpha]^{20}_D$ = −145.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 18.50 min, t_R (major) =21.06 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-9-chloro-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1i). 64% yield (50.0 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 0.7 Hz, 1H), 7.39 (d, J = 1.9 Hz, 2H), 7.23−7.14 (m, 3H), 7.08−7.01 (m, 2H), 4.47−4.36 (m, 2H), 4.18−4.07 (m, 1H), 3.80 (dd, J = 9.0, 7.6 Hz, 1H), 3.54 (ddd, J = 9.3, 6.6, 3.0 Hz, 1H), 3.10−2.96 (m, 2H), 2.36 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 193.0, 177.0, 174.2, 152.8, 144.8, 142.8, 135.6, 135.4, 133.0, 128.6, 128.4, 128.2, 127.8, 125.2, 123.3, 47.4, 42.4, 40.5, 40.2, 39.6, 12.4; IR (KBr) ν 692, 724, 828, 979, 1074, 1186, 1337, 1393, 1425, 1560, 1592, 1665, 1074, 1776, 2940 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{23}H_{18}ClNO_3$ [(M + H)$^+$] requires m/z 392.1048, found m/z 392.1046; mp (°C) 102−104; $[\alpha]^{20}_D$ = +198.0 (c 0.1, $CHCl_3$); ee 98%, determined by HPLC (Chiracel-OD, hexane/isopropanol =80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 15.25 min, t_R (minor) =20.75 min.

(3a*R*,10b*S*,10c*S*)-2-Benzyl-9-methoxy-6-methyl-3a,4-dihydroindeno[1,2-*e*]isoindole-1,3,5(2*H*,10b*H*,10c*H*)-trione (1j). 32% yield (24.8 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.5 Hz, 1H), 7.23−7.15 (m, 4H), 7.09−7.02 (m, 2H), 6.95 (dd, J = 8.5, 2.3 Hz, 1H), 4.43 (s, 2H), 4.14−4.05 (m, 1H), 3.89 (s, 3H), 3.81−3.75 (m, 1H), 3.53 (dt, J = 9.3, 4.8 Hz, 1H), 3.01 (d, J = 4.8 Hz, 2H), 2.38 (d, J = 2.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.7, 177.3, 174.4, 161.5, 154.2, 145.7, 137.4, 135.4, 131.2, 128.5, 128.2, 127.8, 123.5, 113.9, 110.7, 55.6, 47.3, 42.3, 40.8, 40.5, 39.5, 12.6; IR (KBr) ν 700, 828, 1067, 1186, 1337, 1433, 1553, 1665, 1704, 1776, 2932 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{24}H_{21}NO_4$ [(M + H)$^+$] requires m/z 388.1543, found m/z 388.1544; $[\alpha]^{20}_D$ = −154.0 (c 0.1, $CHCl_3$); ee > 99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 14.26 min, t_R (minor) =17.08 min.

(3a*R*,11b*S*,11c*S*)-2-Benzyl-6-methyl-3a,4-dihydro[1,3]-dioxolo[4′,5′:5,6]indeno[1,2-*e*]isoindole-1,3,5(2*H*,11b*H*,11c*H*)-trione (1k). 25% yield (20.1 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J = 6.6, 3.7 Hz, 3H), 7.12−7.01 (m, 3H), 6.89 (s, 1H), 6.06 (s, 2H), 4.45 (s, 2H), 4.05 (ddd, J = 7.4, 5.0, 2.4 Hz, 1H), 3.76 (dd, J = 9.0, 7.6 Hz, 1H), 3.52 (ddd, J = 9.2, 6.0, 3.5 Hz, 1H), 3.07−2.94 (m, 2H), 2.34 (d, J = 2.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.2, 177.2, 174.5, 154.0, 149.9, 148.2, 138.8, 138.5, 135.4, 132.1, 128.6, 128.2, 127.8, 105.5, 102.5, 101.8, 47.2, 42.4, 40.9, 40.4, 39.3, 12.7; IR (KBr) ν 548, 692, 724, 939, 1035, 1211, 1465, 1569, 1648, 1704, 1776, 2923 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{24}H_{19}NO_5$ [(M + H)$^+$] requires m/z 402.1341, found m/z 402.1340; $[\alpha]^{20}_D$ = −61.5 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 14.98 min, t_R (major) = 21.33 min.

(3a*R*,7*S*,7a*R*)-7-(3-Acetylthiophen-2-yl)-2-benzyltetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (6). 55% yield (41.9 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 5.4 Hz, 1H), 7.33−7.26 (m, 5H), 7.26(d, J = 5.4 Hz, 1H) 4.67 (ddd, J = 14.8, 5.8, 3.3 Hz, 1H), 4.60 (q, J = 13.9 Hz, 2H), 3.95 (ddd, J = 9.4, 5.8, 1.4 Hz, 1H), 3.52−3.44 (m, 1H), 3.04 (dd, J = 17.0, 1.8 Hz, 1H), 2.88 (dd, J = 17.0, 8.1 Hz, 1H), 2.77−2.68 (m, 1H), 2.57 (s, 3H), 2.30 (dd, J = 18.2, 14.9 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 205.5, 194.6, 177.4, 175.6, 152.3, 135.6, 135.5, 129.4, 128.8, 128.7, 128.2, 123.5, 42.7, 42.1 (d, J = 2.2 Hz), 38.2, 37.2, 34.7, 30.1; IR (KBr) ν 653, 705, 739, 879, 943, 975, 1079, 1150, 1221, 1260, 1350, 1395, 1434, 1518, 1660, 1712, 1776, 2932, 3042 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{21}H_{19}NO_4S$[(M + H)$^+$] requires m/z 382.1108, found m/z 382.1107; mp (°C) 128−130; $[\alpha]^{20}_D$ = +14.0 (c 0.1, $CHCl_3$); ee 99%, determined by HPLC (Chiracel-OD, hexane/isopropanol =85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (major) = 17.92 min, t_R (minor) =26.50 min.

(3a*R*,7*S*,7a*S*)-2-Benzyl-7-(2-(hex-1-yn-1-yl)phenyl)-tetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2j). 47% yield (38.8 mg), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.42 (m, 1H), 7.36−7.27 (m, 5H), 7.25−7.21 (m, 2H), 6.78−6.69 (m, 1H), 4.60 (dd, J = 35.5, 13.8 Hz, 2H), 4.13−4.01 (m, 1H), 3.81 (ddd, J = 9.2, 5.9, 1.3 Hz, 1H), 3.42−3.32 (m, 1H), 3.08 (dd, J = 17.2, 1.7 Hz, 1H), 2.82 (dd, J = 17.2, 8.1 Hz, 1H), 2.55 (ddd, J = 18.2, 2.8, 1.4 Hz, 1H), 2.50−2.42 (m, 2H), 2.30 (dt, J = 18.3, 9.8 Hz, 1H), 1.59 (ddd, J = 14.0, 10.9, 6.9 Hz, 2H), 1.54−1.43 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.8, 177.4, 175.3, 139.3, 135.7, 132.5, 129.0, 128.7, 128.2, 127.6, 127.2, 126.9, 123.1, 95.8, 78.7, 42.7, 41.9, 40.6, 38.2, 37.1, 36.9, 30.9, 22.1, 19.3, 13.6; IR (KBr) ν 485, 629, 700, 756, 939, 979, 1067, 1179, 1218, 1346, 1401, 1433, 1489, 1712, 1776, 2222, 2868, 2923, 2955, 3035, 3067 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{27}H_{27}NO_3$ [(M + H)$^+$] requires m/z 414.2064, found m/z 414.2064; $[\alpha]^{20}_D$ = +24.0 (c 0.3, $CHCl_3$); ee 98%, determined by HPLC (Chiracel-OD, hexane/isopropanol =85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 9.29 min, t_R (minor) =10.87 min.

(3a*R*,7*S*,7a*S*)-2-Benzyl-7-(2-(phenylethynyl)phenyl)-tetrahydro-1*H*-isoindole-1,3,5(2*H*,6*H*)-trione (2k). 59% yield (49.4 mg), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61−7.55 (m, 1H), 7.45 (ddd, J = 6.9, 4.9, 3.5 Hz, 2H), 7.41−7.34 (m, 3H), 7.34−7.26 (m, 7H), 6.87−6.74 (m, 1H), 4.59 (dd, J = 36.6, 13.8 Hz, 2H), 4.17 (ddd, J = 14.8, 5.7, 3.1 Hz, 1H), 3.90 (ddd, J = 9.2, 5.8, 1.3 Hz, 1H), 3.41 (dd, J = 12.6, 4.7 Hz, 1H), 3.07 (dd, J = 17.2, 1.7 Hz, 1H), 2.86 (dd, J = 17.2, 8.1 Hz, 1H), 2.59 (dd, J = 18.2, 1.3 Hz, 1H), 2.33 (dd, J = 18.3, 14.8 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 206.7, 177.4, 175.4, 139.7, 135.7, 132.5, 131.3, 129.0, 128.9, 128.7, 128.7, 128.5, 128.3, 127.4, 127.1, 122.7, 122.3, 94.8, 87.2, 42.7, 42.1, 40.5, 38.1, 37.2, 37.0; IR (KBr) ν 700, 786, 966, 989, 1070, 1188, 1218, 1345, 1411, 1443, 1500, 1722, 1780, 2225, 2878, 2933, 2957, 3035 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{29}H_{23}NO_3$ [(M + H)$^+$] requires m/z 434.1751, found m/z 434.1750; mp (°C) 101−102. $[\alpha]^{20}_D$ = +17.2 (c 0.1, $CHCl_3$); ee >99%, determined by HPLC (Chiralpak-IC, hexane/isopropanol =67/33, flow rate 1.0 mL/min, T = 30 °C, 254 nm) t_R (minor) = 24.86 min, t_R (minor) =30.42 min.

(3a*R*,5*S*,5a*R*,6*S*,10b*S*,10c*S*)-5-Hydroxy-2,6,8-trimethyl-4,5,5a,6,10b,10c-hexahydroindeno[1,2-*e*]isoindole-1,3-(2*H*,3a*H*)-dione (7). To a solution of **1d** (29.5 mg, 0.1 mmol) in EtOAc (10 mL) was added 10% palladium on carbon (5.0 mg). The mixture was stirred at room temperature overnight under 1 atm of H_2. The resulting mixture was filtered through Celite, washed with EtOAc, and the combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent, petroleum ether/ethyl acetate =2:1) to afford 7 as a white solid (20.9 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 7.8 Hz, 1H), 7.04−6.86 (m, 2H), 4.30 (brs, 1H), 3.77 (t, J = 8.7 Hz, 1H), 3.50 (t, J = 9.2 Hz, 1H), 3.28 (p, J = 7.3 Hz, 1H), 3.00−2.88 (m, 4H), 2.55 (ddd, J = 14.5, 4.6, 1.7 Hz, 1H), 2.46 (dt, J = 7.7, 3.0 Hz, 1H), 2.31 (s, 3H), 1.75 (ddd, J = 14.5, 7.9, 1.8 Hz, 1H), 1.60 (brs, 1H), 1.43 (d, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 179.9, 178.7, 147.2, 139.2, 136.7, 127.5, 123.4, 122.7, 66.0, 47.3, 40.1, 39.7, 39.3, 37.4, 29.2, 24.6, 21.3, 14.7; IR (KBr) ν 841, 1014, 1055, 1128, 1151, 1274, 1382, 1432, 1691, 1770, 2845, 2874, 2924, 2964 cm^{-1}; HRMS (ESI) exact mass calcd for $C_{18}H_{21}NO_3$ [(M + H)$^+$] requires m/z 300.1594, found m/z 300.1589; mp (°C) 211−213; $[\alpha]^{20}_D$ = +8.5 (c 0.04, $CHCl_3$).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectral data for all new compounds, crystallographic data, and CIF information for **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wxnk@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

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