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ONE-POT, DIVERSITY-ORIENTED SYNTHESIS OF ARYL-SUBSTITUTED BENZOXACYCLES INCLUDING BENZOFURAN, COUMARIN, AND BENZOXAZEPINE

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Abstract – A one-pot method for the synthesis of benzoxacycles including benzofuran, coumarin, benzoxazepine, and benzoxazocine from a common synthetic intermediate was established. Benzoxacycles are privileged structures in medicinal chemistry and have featured in several clinically used drugs. The synthesis of a benzofuran containing an aryl substituent was accomplished using potassium carbonate and sodium hydride. The one-pot synthesis of coumarin was also carried out using *trans*-decalin as the solvent. The optimized conditions for the one-pot synthesis of benzoxazepine can also be applied to the synthesis of benzoxazocine.

Benzoxacycles, including benzofuran, coumarin, and benzoxazepine, have garnered significant attention owing to their biological activities and useful function as drugs.[1] These compounds play an important role

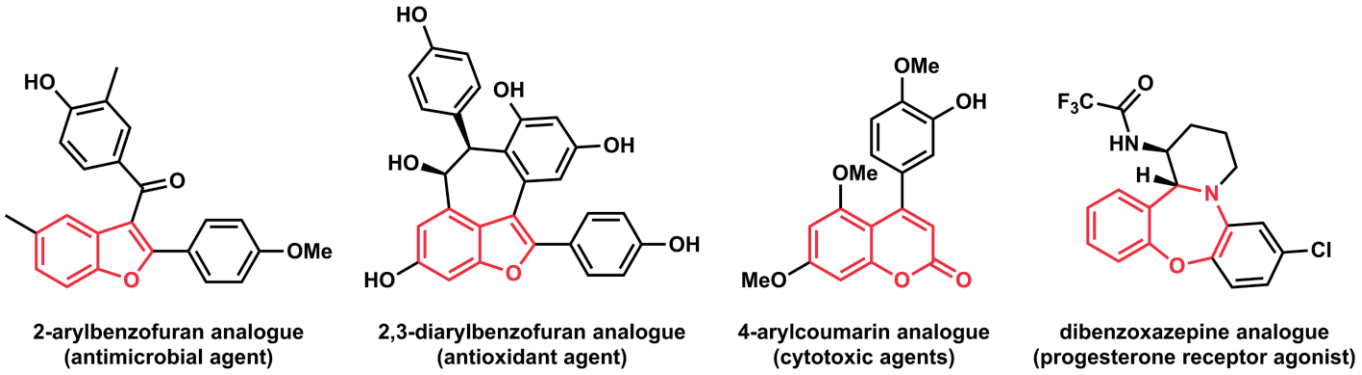


Figure 1. Structures of benzoxacycles

in the design and discovery of new physiological/pharmacologically active molecules. In particular, benzoxacycles with aryl substituents are present in various bioactive compounds such as antimicrobial agents,[2] antioxidant agents,[3] cytotoxic agents,[4] and progesterone receptor agonists.[5] These are privileged structures[6] in medicinal chemistry and may be suitable scaffolds for binding to proteins.

Various synthetic routes towards aryl-substituted benzofurans, coumarins, and benzoxazepines have been reported. The primary synthetic strategies for aryl-substituted benzofurans are as follows: 1) intramolecular electrophilic substitution of α-phenoxyketones,[7] 2) dehydration of *o*-hydroxybenzyl ketones,[8] and 3) aldol reaction of *o*-acylphenoxyacetic acids.[9] The concise synthesis of 4-arylcoumarins (neoflavones) involves the cross-coupling of coumarin[10] and hydroarylation of phenyl alkynoate.[11] Benzoxazepines have been synthesized via the Bischler-Napieralski reaction[12] of the corresponding amides.[5,13] These methods are very useful for the synthesis of benzoxacyclic compounds because of their high yields. However, the conventional methods require the preparation of certain substrates such as α-phenoxyketones, phenyl alkynoate, and *N*-(2-aryloxyethyl)arylamide for each benzoxacycle. Since benzoxacycles such as benzofuran, coumarin, and benzoxazepine possess similar skeletons except for the ring fused to the benzene ring, they can all be synthesized from a common intermediate. A highly efficient synthesis of benzoxacycles from a common intermediate remains an important goal.

One-pot reactions are powerful synthetic methodologies for the rapid synthesis of complex molecules from simple reactants.[14] Such protocols require neither purification nor work-up of the reaction intermediates, so they exhibit excellent synthetic efficiencies. We have developed a one-pot, multi-component coupling approach for the synthesis of useful compounds.[15] For the efficient synthesis of benzoxacycles, it is important to develop a one-pot method for the construction of a benzoxacyclic ring from a common intermediate. Herein, we report the one-pot, diversity-oriented synthesis of benzoxacycles including benzofuran, coumarin, and benzoxazepine.

The developed synthetic strategy is shown in Figure 2. Aryl-substituted benzoxacycles can be synthesized

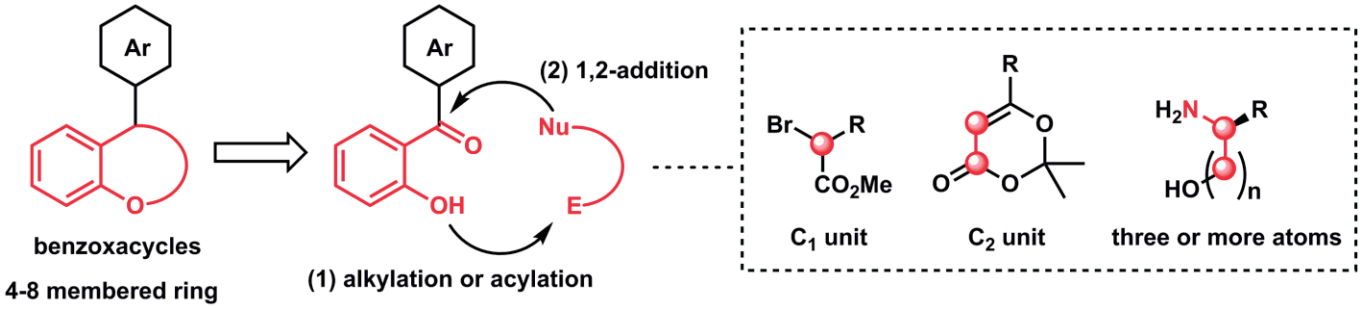
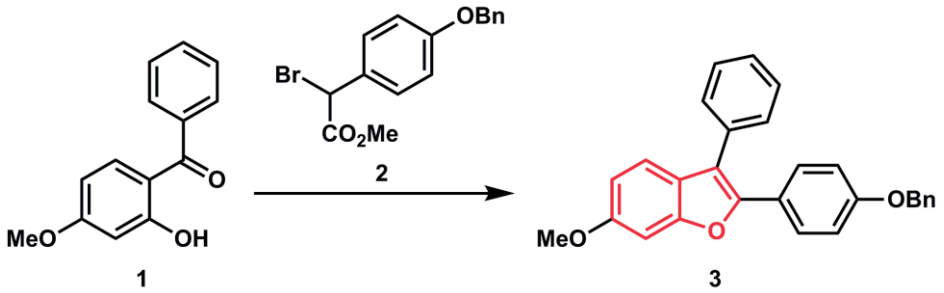


Figure 2. Synthetic strategy towards benzoxacycles

from *o*-aryloyl-phenols via the alkylation or acylation of phenol, followed by intramolecular nucleophilic addition to the ketone. The highly effective and concise synthesis of benzoxacycles can be achieved by performing the alkylation and intramolecular nucleophilic addition in one-pot. Various benzoxacycles can be systematically synthesized using the appropriate units. For example, benzofuran analogs can be synthesized using an α-halo ester as the C_1 unit, as they contain electrophilic and nucleophilic moieties. Coumarin and benzoxazepine analogs can be achieved using two- and three-atom units, respectively.

Initially, the one-pot synthesis of benzofuran analogs was examined using 2-hydroxy-4-methoxybenzophenone (**1**) and α-halo ester **2** (Table 1). A five-membered ring was constructed via the alkylation of phenol with an α-halo ester, followed by aldol condensation. In this reaction, the aromatization can be occurred with Krapcho decarboxylation[16] type reaction by the attack of bromide anion generated in the alkylation. When the alkylation was carried out using potassium carbonate as the base, the aldol reaction did not proceed efficiently because of steric hindrance. Therefore, sodium hydride was added after the alkylation with potassium carbonate to give benzofuran analog **3** in 53% yield (Table 1, entry 1). When only sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were used, the desired compound **3** was obtained in 24% and 5% yield, respectively (Table 1, entries 4 and 5).

Table 1. Optimization of construction of benzofuran **3**[a]



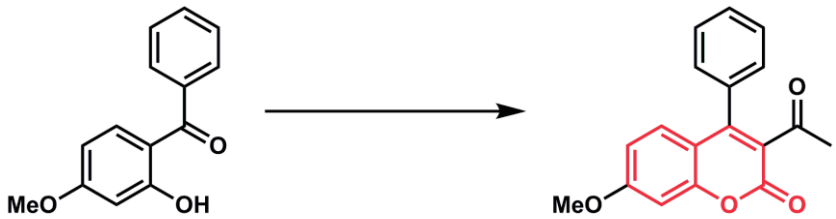
Entry	Conditions	Yield (%)[b]
1	K_2CO_3, DMF, rt, 1 h, then NaH, rt, 3 h	53
2	K_2CO_3, DMF, rt, 1 h, then DBU, rt, 17 h	33
3	K_2CO_3, DMF, rt, 25 h	3
4	NaH, DMF, rt, 30 min	24
5	DBU, DMF, rt, 14 h	5

[a] DMF = *N*,*N*-dimethylformamide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

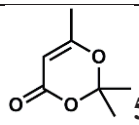
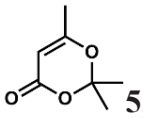
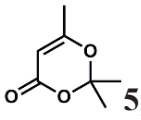
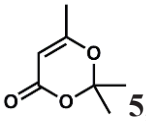
[b] Isolated yield

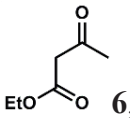
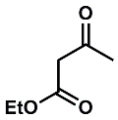
Next, the one-pot synthesis of coumarin analogs was examined (Table 2). The coumarin ring can be constructed by the condensation of phenol with acetoacetic acid, followed by aldol condensation. Methods for the condensation with acetoacetic acid using acylketene[17,18] or acetoacetate[19] have been reported. First, 2,2,6-trimethyl-1,3-dioxin-4-one (**5**) was employed as a precursor of acylketene,[17] and the solvent was optimized. A high temperature was necessary for conversion of 2,2,6-trimethyl-1,3-dioxin-4-one (**5**) into acylketene.[17] Therefore, the boiling point of the solvent significantly affected the reaction (Table 2, entries 1-4). The best result was obtained using *trans*-decalin (boiling point 185 °C) as a solvent (Table 2, entry 1). The basicity of the solvent did not affect the yield of the reaction (Table 2, entry 2). When *m*-xylene (boiling point 139 °C) or diglyme (boiling point 162 °C) were employed as solvents, the desired compound **4** was obtained in 44% and 39% yields, respectively (Table 2, entries 3 and 4). The reaction did not proceed when ethyl acetoacetate **6** was used (Table 2, entries 5 and 6). Although manganese carbonate is reported to be a good reagent for the alkolysis of acetoacetate,[19] the reaction likely did not proceed in this case because of steric hindrance (Table 2, entry 6).

Table 2. Optimization of construction of coumarin analog **4**[a]



1 **4**

Entry	Conditions	Yield (%)[b]
1	 **5**, *trans*-decalin, reflux, 12 h	100
2	 **5**, 2,6-lutidine, reflux, 12 h	61
3	 **5**, *m*-xylene, reflux, 19 h	44
4	 **5**, diglyme, reflux, 22 h	39

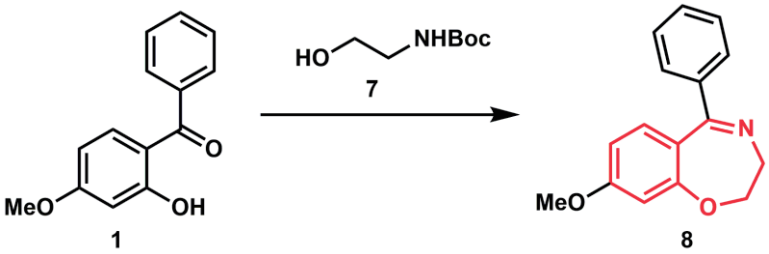
5	 **6**, piperidine, MeCN, 60 °C, 17 h	no reaction
6	 **6**, $MnCO_3$, toluene, reflux, 36 h	no reaction

[a] diglyme = diethylene glycol dimethyl ether

[b] Isolated yield

Next, the one-pot synthesis of benzoxazepine was examined (Table 3). The benzoxazepine ring can be constructed by alkylation of phenol with an aliphatic alcohol containing a protected amino group, followed by deprotection and imination. The best result was obtained via a Mitsunobu reaction[20] using bis(2-methoxyethyl) azodicarboxylate (DMEAD)[21] and triphenylphosphine, followed by Boc deprotection and imination using trifluoroacetic acid (TFA) as an acid (Table3, entry 1). Target compound **8** was not obtained using diethyl azodicarboxylate (DEAD) in the Mitsunobu reaction because of the formation of impurities derived from DEAD (Table 3, entry 3).

Table 3. Optimization of construction of benzoxazepine analogs **7**[a]



Entry	Conditions	Yield (%)[b]
1	DMEAD, PPh_3, THF, rt, then TFA, 60 °C, 90 h	88
2	DMEAD, PPh_3, THF, rt, then 4 M HCl in 1,4-dioxane, 60 °C, 90 h	trace
3	DEAD, PPh_3, THF, rt, then TFA, 60 °C, 90 h	complex mixture

[a] Boc = *tert*-butoxycarbonyl; DMEAD = bis(2-methoxyethyl) azodicarboxylate; TFA = trifluoroacetic acid; DEAD = diethyl azodicarboxylate

[b] Isolated yield

Finally, the diversity-oriented synthesis of benzoxacycles from a common intermediate, *o*-aryloyl-phenol, was demonstrated (Figure 3) using the optimized conditions. The syntheses of 2-carbonyl benzofuran **10** and 3-indole benzofuran **12** were achieved in 40% yield and 57% yield, respectively. The one-pot

synthesis of coumarin **14** and benzoxazepine **16** with long alkyl chain was also achieved under the optimized conditions. Our developed method can be used for the construction of a benzoxacycle containing an 8-membered ring, benzoxazocine **18**, which can be applied to a sympathetic β-receptor blocking agents.[22]

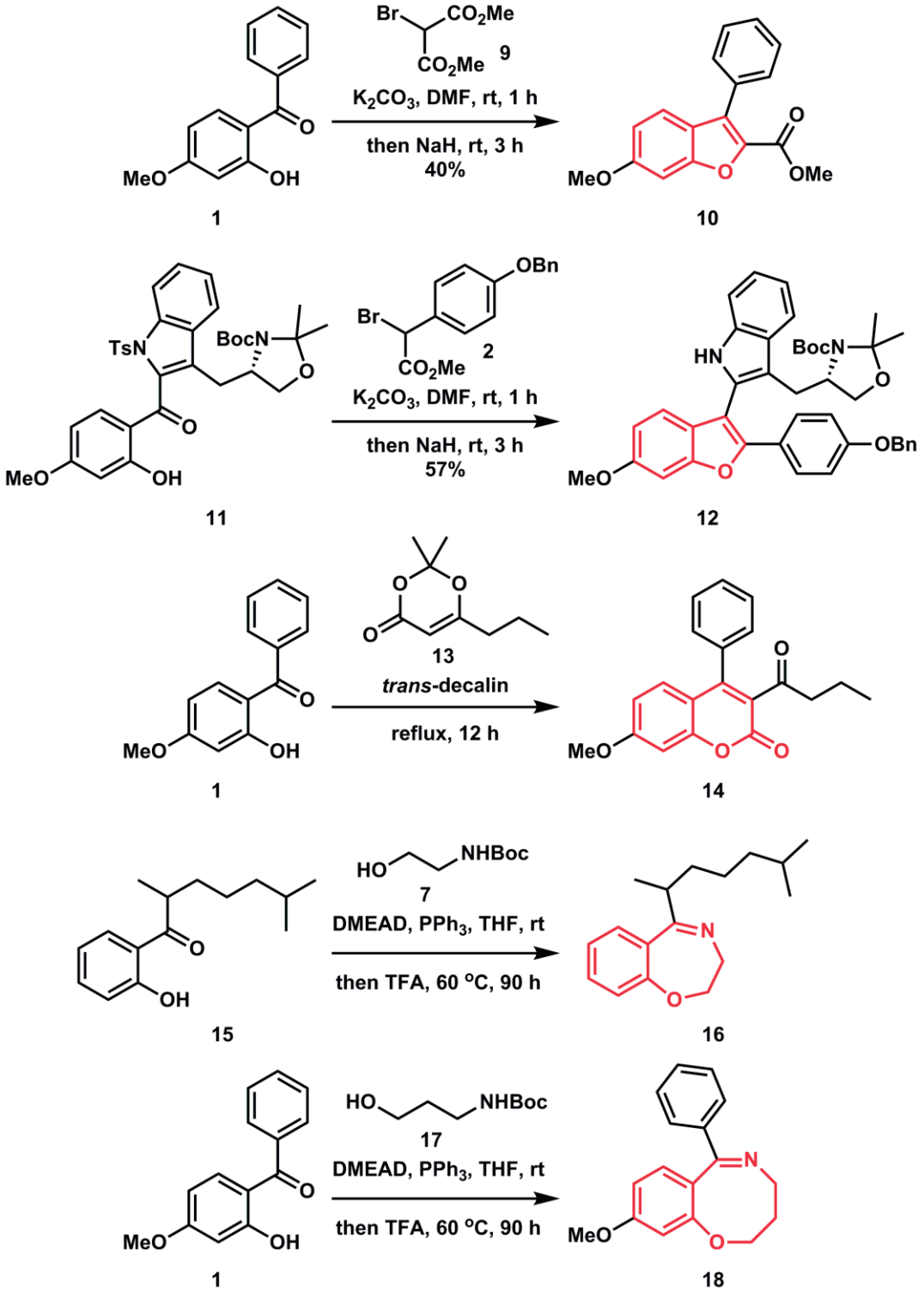


Figure 3. Synthesis of benzoxacyclic compounds

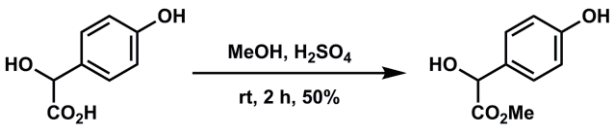
In conclusion, we established a one-pot method for the synthesis of benzoxacycles including benzofuran, coumarin, benzoxazepine, and benzoxazocine from a common synthetic intermediate. The synthesis of benzofuran was accomplished using potassium carbonate and sodium hydride. The one-pot synthesis of coumarin was also carried out using *trans*-decalin as the solvent. The optimized conditions for the one-pot synthesis of benzoxazepine could be applied in the synthesis of benzoxazocine. Our developed method will be useful for the concise synthesis of various pharmaceutical compounds containing benzoxacycle.

EXPERIMENTAL

General

NMR spectra were recorded on a JEOL Model ECA-500 instrument. Chemical shifts are reported in parts per million (ppm) relative to the signal for the internal standard tetramethylsilane (0.0 ppm) or the solvent $CDCl_3$ (7.26 ppm, ^{1}H NMR; or 77.1 ppm, ^{13}C NMR) peaks. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ^{13}C NMR spectrum data are reported as follows: chemical shift (δ ppm), and where applicable, multiplicity and coupling constants. Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; sp, septet; m, multiplet; br, broad; and J, coupling constants in hertz. Only the strongest and/or structurally relevant IR peaks are reported (cm^{-1}). All reactions were monitored by thin-layer chromatography performed using 0.2 mm E. Merck silica gel plate (60F-254). The reactants and products were visualized using UV light (254 nm), or by heating after treatment with *p*-anisaldehyde solution, ceric sulfate solution, or 10% ethanolic phosphomolybdic acid. Column chromatography separations were performed using silica gel (Merck). ESI-TOF Mass spectra were acquired on a Waters LCT PremierTM XE. HRMS (ESI-TOF) were calibrated using a standard curve obtained using leu-enkephalin.

Methyl 4-hydroxymandelate (19)[23]

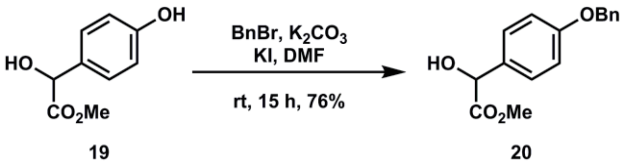


19

To a solution of 4-hydroxymandelic acid (3.00 g, 17.9 mmol, 1.00 equiv.) in MeOH (35.8 mL) was added conc. H_2SO_4 (286 μL, 5.39 mmol, 0.300 equiv.) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with two portions of EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from EtOAc to give methyl 4-hydroxymandelate (1.64 g, 8.95 mmol, 50%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 5.82 (s, 1H), 4.96 (s, 1H), 3.59 (s, 3H).

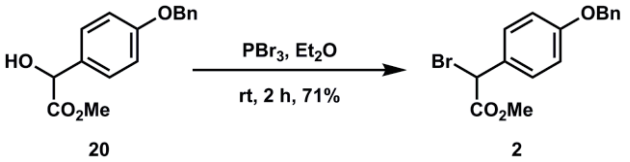
Methyl 4-benzyloxymandelate (20)[24]



To a solution of methyl 4-hydroxymandelate (1.50 g, 8.19 mmol, 1.00 equiv.) in DMF (24.6 mL) was added potassium carbonate (3.40 g, 24.6 mmol, 3.00 equiv.), potassium iodide (680 mg, 4.10 mmol, 0.500 equiv.), and benzyl bromide (1.46 mL, 12.3 mmol, 1.50 equiv.) at room temperature. After being stirred at the same temperature for 15 h, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2:1) to give methyl 4-benzyloxymandelate (2.08 g, 6.54 mmol, 76%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.3 Hz, 1H), 7.34-7.32 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 5.13 (d, *J* = 5.7 Hz, 1H), 5.06 (s, 2H), 3.75 (s, 3H).

Methyl 2-bromo-2-[4-(benzyloxy)phenyl]acetate (2)

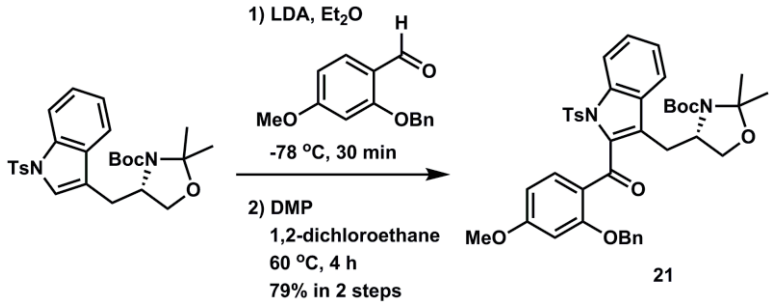


To a solution of 4-benzyloxymandelate (1.00 g, 3.67 mmol, 1.00 equiv.) in Et_2O (4.59 mL) was added phosphorus tribromide (174 μL, 1.84 mmol, 0.500 equiv.) at room temperature. After being stirred at the same temperature for 2 h, the reaction mixture was poured into MeOH and the aqueous layer was extracted with two portions of EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 9:1) to give methyl 2-bromo-2-[4-(benzyloxy)phenyl]acetate (879 mg, 2.62 mmol, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.43-7.38 (m, 4H), 7.34 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 5.34 (s, 1H), 5.06 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 159.5, 136.6, 130.2, 128.7, 128.1, 127.9, 127.5, 115.1, 70.1, 53.3, 46.5; IR (solid): 3034, 2950, 1752, 1606, 1582, 1509, 1454, 1386, 1246, 1218, 1176, 1144, 1080, 1012, 866, 834, 738, 695; HRMS (ESI-TOF) calcd for $C_{16}H_{16}O_3Br$ $[M + H]^+$ 335.0283, found 335.0283.

***tert*-Butyl (*S*)-4-((2-(2-(benzyloxy)-4-methoxybenzoyl)-1-tosyl-1*H*-indol-3-yl)methyl)-2,2-dimethyl-**

oxazolidine-3-carboxylate (21)

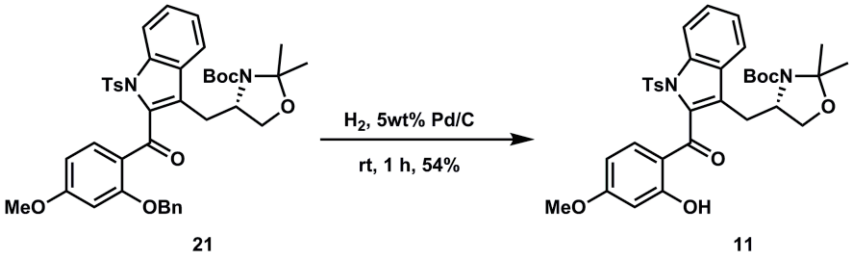


To a solution of diisopropylamine (954 µL, 6.81 mmol, 3.30 equiv.) in Et_2O (6.20 mL) was added *n*-butyl-lithium (3.87 mL, 6.19 mmol, 3.00 equiv.) at -78 °C. After being stirred at the same temperature for 1 h, the reaction mixture was added *tert*-butyl (*S*)-2,2-dimethyl-4-((1-tosyl-1*H*-indol-3-yl)methyl)-oxazolidine-3-carboxylate[25] (1.00 g, 2.06 mmol, 1.00 equiv.) at the same tempareture. After being stirred at the same temperature for 30 min, the reaction mixture was added was 2-(benzyloxy)-4-methoxybenzaldehyde (1.00 g, 4.13 mmol, 2.00 equiv.). After being stirred at the same temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl and the organic layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of residue (1.50 g, 2.06 mmol, 1.00 equiv.) in 1,2-dichloroethane (18.6 mL) was added Dess-Martin periodinane (1.31 g, 3.10 mmol, 1.50 equiv.) at room temperature. After being stirred at 60 °C for 4 h, the reaction mixture was quenched with 10% aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (5% EtOAc in toluene) to give *tert*-butyl (*S*)-4-((2-(2-(benzyloxy)-4-methoxybenzoyl)-1-tosyl-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylat e (1.18 g, 1.62 mmol, 79% in 2 steps) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38-7.90 (m, 4H), 7.85-7.60 (m, 2H), 7.45-7.20 (m, 10H), 6.68-6.45 (m, 2H), 6.40-6.20 (m, 2H), 5.00 (m, 3H), 4.40 (m, 2H), 4.30-4.12 (m, 6H), 3.82-3.60 (m, 4H), 2.08 (s, 3H), 1.58-1.23 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ186.7, 165.0, 160.1, 152.3, 144.8, 138.4, 136.5, 135.5, 134.0, 133.8, 131.0, 130.0, 129.5, 128.9, 128.7, 128.5, 128.3, 127.9, 127.7, 127.5, 127.4, 127.3, 126.9, 126.4, 126.1, 124.4, 122.7, 121.7, 120.6, 115.5, 106.0, 105.8, 99.5, 80.1, 70.8, 65.7, 55.6, 28.8, 27.0, 21.6; IR (solid): 2929, 1687, 1636, 1597, 1501, 1444, 1365, 1258, 1154, 1104, 1064, 1019, 959, 812, 751, 697, 665, 574, 542; HRMS (ESI-TOF) calcd for $C_{41}H_{45}N_2O_8S$ $[M + H]^+$ 725.2897, found 725.2846.

***tert*-Butyl (*S*)-4-((2-(2-hydroxy-4-methoxybenzoyl)-1-tosyl-1*H*-indol-3-yl)methyl)-2,2-dimethyl-oxazolidine-3-carboxylate (11)**



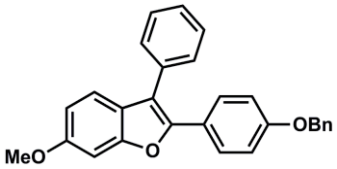
To a solution of *tert*-butyl (*S*)-4-((2-(2-(benzyloxy)-4-methoxybenzoyl)-1-tosyl-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (304 mg, 0.414 mmol, 1.00 equiv.) in MeOH (3.70 mL) was added 5 wt% Pd/C (973 mg, 0.455 mmol, 1.10 equiv.) at room temperature. After being stirred under an atmosphere of H_2 (balloon pressure) at the same temperature for 1 h, the reaction mixture was filtered, through a short plug of Celite and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (20% EtOAc in toluene) to give *tert*-butyl (*S*)-4-((2-(2-hydroxy-4-methoxybenzoyl)-1-tosyl-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (143 mg, 0.225 mmol, 54%) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-8.00 (m, 1H), 7.72-7.60 (m, 4H), 7.48-7.36 (m, 3H), 7.28-7.22 (m, 1H), 7.03 (s, 1H), 6.28-6.23 (m,1H), 4.13-4.08 (m, 1H), 3.85 (s, 3H), 3.62-3.39 (m, 1H), 3.52-2.46 (m, 2H), 2.08 (s, 3H), 1.58-1.23 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 165.3, 164.9, 155.8, 142.5, 138.0, 137.0, 135.6, 134.0, 133.3, 130.6, 130.5, 130.0, 128.9, 128.7, 128.3, 128.0, 127.4, 127.1, 126.7, 124.8, 122.5, 121.6, 120.5, 115.8, 106.0, 105.8, 99.4, 79.2, 70.8, 65.7, 55.6, 28.5, 26.3, 21.1; IR (solid): 3425, 2935, 2159, 2023, 1972, 1702, 1595, 1500, 1443, 1366, 1254, 1154, 1124, 1048, 1019, 958, 831, 751, 696, 667, 575; HRMS (ESI-TOF) calcd for $C_{34}H_{39}O_8S$ $[M + H]^+$ 635.2427, found 635.2437.

General procedure for one-pot synthesis of benzofuran analogs

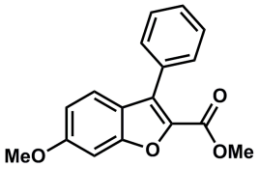
To a solution of 2-aryloyl-phenol (1.00 equiv.) and methyl 2-bromocarboxylate (1.00 equiv) in DMF was added K_2CO_3 (3.00 equiv.) at room temperature. After being stirred at the same temperature for 1 h, to the reaction mixture was added NaH (3.00 equiv.) at room temperature. After being stirred at the same temperature, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give benzofuran analog.

2-[4-(Benzyloxy)phenyl]-6-methoxy-3-phenylbenzofuran (3)



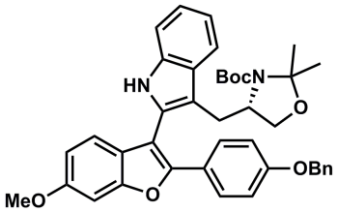
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.9 Hz, 2H), 7.51-7.33 (m, 11H), 7.09 (s, 1H), 6.92 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 1H), 5.07 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.7, 155.4, 150.4, 137.3, 133.7, 130.3, 129.5, 128.7, 128.6, 128.1, 128.0, 124.4, 120.5, 116.6, 115.4, 112.3, 96.3, 70.6, 56.4, 30.3; IR (neat): 3035, 2937, 2835, 1739, 1608, 1591, 1511, 1492, 1454, 1439, 1417, 1380, 1344, 1300, 1271, 1246, 1195, 1175, 1152, 1492, 1454, 1439, 1417, 1380, 1344, 1300, 1271, 1246, 1195, 1175, 1152, 1130, 1111, 1064, 1026, 967, 943, 832, 770, 744, 701, 633, 586, 534 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{28}H_{23}O_3$ $[M + H]^+$ 407.1647, found 407.1642.

Methyl 6-methoxy-3-phenylbenzofuran-2-carboxylate (10)



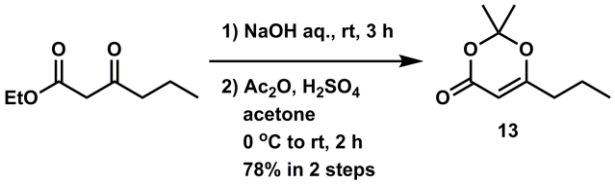
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2H), 7.51-7.42 (m, 4H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.94 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 160.3, 155.9, 139.0, 130.7, 130.1, 130.0, 128.5, 128.3, 122.6, 121.6, 114.1, 95.6, 55.8, 52.1; IR (neat): 3001, 2849, 1690, 1578, 1534, 1487, 1444, 1414, 1315, 1276, 1240, 1203, 1180, 1068, 1015, 906, 791; HRMS (ESI-TOF) calcd for $C_{17}H_{15}O_4$ $[M + H]^+$ 283.0970, found 283.0983.

***tert*-Butyl (*S*)-4-((2-(2-(4-(benzyloxy)phenyl)-6-methoxybenzofuran-3-yl)-1*H*-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (12)**



^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16-7.70 (m, 2H), 7.56-7.30 (m, 4H), 7.25-6.87 (m, 9H), 6.67-6.56 (m, 3H), 5.00 (s, 2H), 4.36-4.10 (m, 1H), 3.94 (s, 3H), 3.51-3.27 (m, 3H), 1.72-1.43 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 158.0, 135.7, 132.1, 130.1, 129.6, 129.3, 129.0, 128.6, 128.5, 128.4, 128.1, 127.0, 126.8, 122.3, 122.0, 121.0, 111.9, 106.0, 79.2, 70.7, 62.8, 55.8, 28.6, 26.5; IR (solid): 2919, 2851, 2500, 2160, 2030, 1977, 1713, 1602, 1504, 1464, 1366, 1259, 1166, 1075, 958, 831, 749, 696; HRMS (ESI-TOF) calcd for $C_{17}H_{15}O_4$ $[M + H]^+$ 659.3116, found 659.3186.

2,2-Dimethyl-6-propyl-4*H*-1,3-dioxin-4-one (13)[26]



To aqueous NaOH (1.00 M solution, 31.3 mL, 1.00 equiv.) was added ethyl 3-oxohexanoate (5.00 mL, 31.3 mmol, 1.00 equiv.) at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

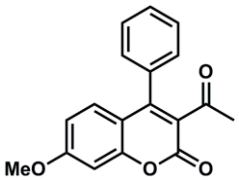
To a solution of residue (4.07 g, 31.3 mmol, 1.00 equiv.) in acetone (31.3 mL) were added acetic anhydride (31.3 mL) and sulfuric acid (3.13 mL) at 0 ^{o}C. After being stirred at room temperature for 2 h, the reaction mixture was poured into water and the aqueous layer was extracted with two portions of EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4:1) to give 2,2-dimethyl-6-propyl-4*H*-1,3-dioxin-4-one (4.18 g, 24.5 mmol, 78%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.15 (s, 1H), 2.12 (t, *J* = 7.5 Hz, 2H), 1.61 (s, 6H), 1.53-1.47 (m, 2H), 0.89 (t, *J* = 7.5 Hz, 3H).

General procedure for one-pot synthesis of coumarin analogs

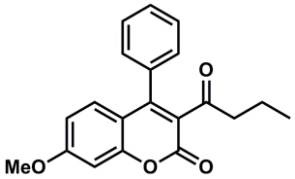
To a solution of 2-aryloyl-phenol (1.00 equiv.) in *trans*-decalin (1.00 mL) was added 2,2,6-trimethyl-1,3-dioxin-4-one (10.0 equiv) at room temperature. After being stirred at the reflux temperature for 12 h, the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give coumarin analog.

3-Acetyl-7-methoxy-4-phenylcoumarin (4)



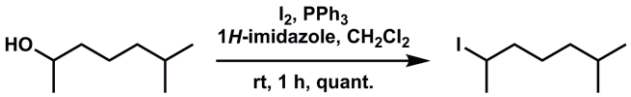
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51-7.48 (m, 3H), 7.29-7.26 (m, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.87 (s, 1H), 6.76 (d, *J* = 8.8 Hz), 3.89 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 163.7, 155.5, 152.9, 129.6, 129.5, 128.9, 128.5, 113.1, 113.0, 100.8, 56.0, 31.5; IR (neat): 2941, 2844, 1715, 1614, 1550, 1509, 1492, 1463, 1444, 1372, 1295, 1285, 1263, 1204, 1166, 1135, 1117, 1077, 1044, 1025, 996, 964, 839, 776, 753, 703, 655, 622, 566, 540, 482 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{18}H_{15}O_4$ $[M + H]^+$ 295.0970, found 295.0971.

3-Butyryl-7-methoxy-4-phenylcoumarin (14)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49-7.46 (m, 3H), 7.30-7.26 (m, 2H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.77 (dd, *J* = 2.0 Hz, 9.0 Hz, 1H), 3.89 (s, 3H), 2.46 (t, *J* = 7.0 Hz, 2H), 1.49-1.43 (m, 2H), 0.71 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 163.5, 159.1, 155.4, 152.2, 133.1, 129.6, 129.2, 128.8, 128.7, 124.8, 113.0, 100.8, 56.0, 45.7, 29.8, 16.8, 13.5; IR (neat): 2961, 2930, 1713, 1658, 1602, 1593, 1550, 1462, 1443, 1370, 1293, 1282, 1261, 1196, 1160, 1115, 1029, 995, 838, 701 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{20}H_{19}O_4$ $[M + H]^+$ 323.1283, found 323.1307.

2-Iodo-6-methylheptane (22)

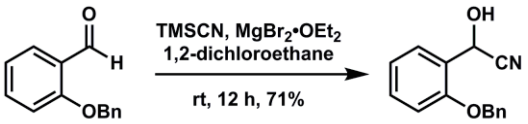


22

To a solution of 6-methyl-2-heptanol (7.91 mL, 50.0 mmol, 1.00 equiv.) in CH_2Cl_2 (150 mL) were added iodine (15.2 g, 60.0 mmol, 1.20 equiv.), PPh_3 (13.1 g, 50.0 mmol, 1.00 equiv.), and 1*H*-imidazole (3.40 mL, 50.0 mmol, 1.00 equiv.) at room temperature. After being stirred at the same temperature for 1 h, the reaction mixture was poured into aqueous $Na_2S_2O_3$ and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane) to give 2-iodo-6-methylheptane (11.4 g, 53.7 mmol, quant.) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21-4.17 (m, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.87-1.79 (m, 1H), 1.62-1.44 (m, 3H), 1.41-1.33 (m, 1H), 1.24-1.12 (m, 2H), 0.88 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.2, 38.1, 31.0, 29.0, 27.9, 27.6, 22.7, 22.6; IR (neat): 2954, 2928, 2868, 1466, 1377, 1367, 1277, 1245, 1314, 1172, 1139, 1075, 992, 961, 895, 833, 806, 736, 857, 487 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_8H_{17}I$ $[M + H]^+$ 241.0453, found 241.0450.

2-(2-Benzyloxyphenyl)-2-hydroxyacetonitrile (23)[27]

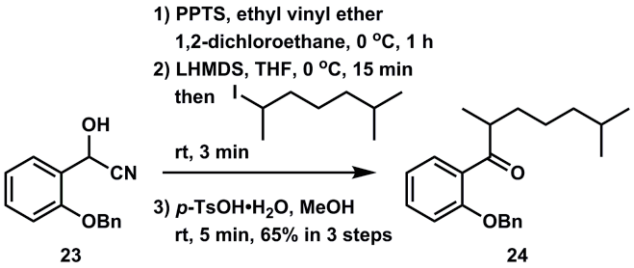


23

To a solution of 2-(benzyloxy)benzaldehyde (6.34 g, 30.0 mmol, 1.00 equiv.) in 1,2-dichloroethane (90.0 mL) were added trimethylsilyl cyanide (7.44 mL, 60.0 mmol, 2.00 equiv.), and magnesium bromide ethyl etherate (2.23 g, 9.00 mmol, 0.300 equiv.) at room temperature. After being stirred at the same temperature for 12 h, the reaction mixture was poured into 1 M HCl and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 4:1) to give 2-(2-benzyloxyphenyl)-2-hydroxyacetonitrile (7.18 mg, 21.3 mmol, 71%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.0 Hz, 2H), 7.42-7.35 (m, 5H), 7.05-7.02 (m, 2H) 5.57 (d, *J* = 9.0 Hz, 1H), 5.21 (dd, *J* = 3.9 Hz, 2H), 3.47 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 156.2, 131.3, 129.6, 128.4, 127.8, 124.2, 121.5, 114.3, 112.6, 70.7, 61.3, 55.4; IR (neat): 3416, 3065, 1706, 1602, 1490, 1453, 1382, 1288, 1264, 1243, 1191, 1180, 1164, 1114, 1047, 1023, 917, 857, 822, 732, 697, 649, 623, 487, 456 (cm^{-1}).

1-(2-Benzyloxyphenyl)-2,6-dimethylheptan-1-one (24)



To a solution of 2-(2-(benzyloxy)phenyl)-2-hydroxyacetonitrile (3.59 g, 15.0 mmol, 1.00 equiv.) in 1,2-dichloroethane (90.0 mL) was added pyridinium *p*-toluenesulfonate (377 mg, 60.0 mmol, 2.00 equiv.) and ethyl vinyl ether (2.16 mL, 22.5 mmol, 1.50 equiv.) at 0 °C. After being stirred at the same temperature for 1 h, the reaction mixture was poured into $NaHCO_3$ and the aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

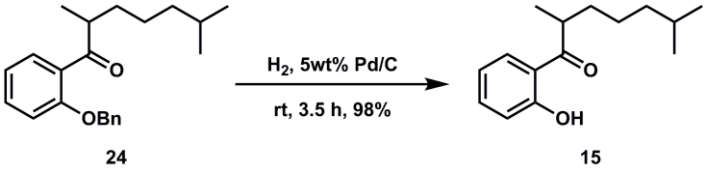
To a solution of the residue (2.59 g, 8.33 mmol, 1.00 equiv.) in THF (25.0 mL) was added LHMDS in THF (1.0 M, 25.0 mL, 25.0 mmol, 3.00 equiv.) at 0 °C. After being stirred at the same temperature for 15 min, to the reaction mixture was added 2-iodo-6-methylheptane (3.00 g, 12.5 mmol, 1.50 equiv.) at 0 °C. After being stirred at the same temperature for 3 min, the reaction mixture was poured into aqueous NH_4Cl and the aqueous layer was extracted with two portions of EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification.

To a solution of the residue (2.59 g, 8.33 mmol, 1.00 equiv.) in MeOH (6.81 mL) was added *p*-toluenesulfonic acid monohydrate (432 mg, 2.27 mmol, 1.00 equiv.) at the room temperature. After being stirred at the same temperature for 5 min, the reaction mixture was poured into 10% NaOH and the aqueous layer was extracted with two portions of Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 9:1) to give 1-(2-benzyloxyphenyl)-2,6-dimethylheptan-1-one (514 mg, 2.27 mmol, 65% in 3 steps) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.33-7.42 (m, 6H), 7.01-6.98 (m, 2H), 5.12 (s,

2H), 1.71-1.64 (m, 1H), 1.46-1.39 (m, 1H), 1.32-0.985 (m, 9H), 0.871 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 132.5, 130.1, 128.7, 128.3, 127.7, 121.1, 112.7, 70.7, 45.4, 39.1, 33.5, 27.9, 25.1, 22.7, 22.6, 16.5; IR (neat): 3067, 3034, 2952, 2931, 2869, 1674, 1596, 1498, 1482, 1447, 1382, 1285, 1234, 1162, 1111, 1080, 1050, 1006, 969, 916, 857, 817, 751, 696, 645, 622, 522, 493 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{22}H_{29}O_2$ $[M + H]^+$ 325.2168, found 325.2188.

1-(2-Hydroxyphenyl)-2,6-dimethylheptan-1-one (15)



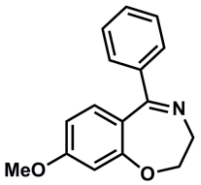
To a solution of 1-(2-benzyloxyphenyl)-2,6-dimethylheptan-1-one (474 mg, 1.46 mmol, 1.00 equiv.) in THF (4.00 ml) was added 5 wt% Pd/C (311 mg, 0.146 mmol, 0.100 equiv.) at room temperature. After being stirred under an atmosphere of H_2 (balloon pressure) at the same temperature for 3.5 h, the reaction mixture was filtered through a short plug of Celite. The filtrate was collected and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 50:1) to give 1-(2-hydroxyphenyl)-2,6-dimethylheptan-1-one (344 mg, 1.47 mmol, 98%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.00 (d, J = 8.5 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 3.55-3.48 (m, 1H), 1.84-1.77 (m, 1H), 1.56-1.40 (m, 2H), 1.39-1.10 (m, 7H), 0.85 (d, J = 6.4 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0, 163.3, 136.3, 129.9, 118.9, 118.8, 118.7, 40.2, 39.0, 34.1, 27.9, 25.3, 22.7, 17.6; IR (neat): 2953, 2932, 2869, 1635, 1612, 1582, 1487, 1446, 1383, 1367, 1349, 1289, 1241, 1209, 1161, 1148, 1125, 1099, 1035, 976, 860, 810, 752, 700, 656, 561, 529 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{15}H_{23}O_2$ $[M + H]^+$ 235.1698, found 235.1691.

General procedure for one-pot synthesis of benzoxazepine analogs

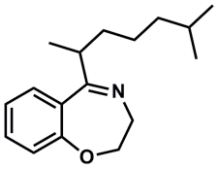
To a solution of 2-aryloyl-phenol (1.00 equiv.) and 2-(*tert*-butoxycarbonylamino)-1-ethanol (1.20 equiv.) in THF (12.0 mL) were added triphenylphosphine (1.20 equiv.) and DMEAD (1.20 equiv.) at room temperature. After being stirred at the same temperature for 12 h, to the reaction mixture was added TFA at room temperature. After being stirred at 60 °C for 25 h, the reaction mixture was poured into triethylamine and the reaction mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to give benzoxazepine analog.

8-Methoxy-5-phenyl-2,3-dihydrobenzo[*f*][1,4]oxazepine (8)[28]



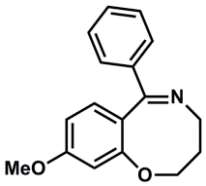
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 6.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.67-6.64 (m, 2H), 4.75 (t, *J* = 4.7 Hz, 2H), 4.00 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 162.5, 158.5, 140.1, 132.5, 130.1, 129.2, 128.2, 119.8, 109.2, 106.3, 78.4, 55.6, 51.5; IR (neat): 3056, 3004, 2937, 1895, 1720, 1603, 1574, 1562, 1497, 1444, 1378, 1323, 1284, 1259, 1238, 1194, 1159, 1123, 1110, 1706, 1059, 1030, 1001, 969, 930, 861, 815, 777, 759, 735, 723, 697, 666, 636, 618, 854, 552, 538, 513, 474 (cm^{-1}).

5-(6-Methylheptan-2-yl)-2,3-dihydrobenzo[*f*][1,4]oxazepine (16)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 8.5 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 4.56-4.51 (m, 2H), 3.66-3.54 (m, 2H), 2.91-2.85 (m, 1H), 1.69-1.62 (m, 1H), 1.52-1.06 (m, 9H), 1.52 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.2, 155.1, 131.1, 130.1, 127.4, 123.6, 121.9, 78.5, 49.9, 41.5, 39.1, 35.4, 27.9, 25.0, 22.7, 22.6, 18.6; IR (neat): 3067, 2953, 2930, 2869, 1725, 1629, 1600, 1571, 1482, 1458, 1445, 1384, 1367, 1335, 1263, 1232, 1205, 1154, 1111, 1048, 998, 943, 881, 795, 761, 737, 704, 683, 636, 572, 458, 510 (cm^{-1}); HRMS (ESI-TOF) calcd for $C_{17}H_{26}NO$ $[M + H]^+$ 260.2014, found 260.2029.

3,4-Dihydro-9-methoxy-6-phenyl-2*H*-benzo[1,5-*b*]oxazocine (18)[28]



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.40-7.34 (m, 3H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.49 (d, *J* = 7.0 Hz, 1H), 6.47 (s, 1H), 4.37 (s, 1H), 4.11-4.05 (m, 2H), 3.52 (s, 1H), 3.80 (s, 3H), 2.10 (s, 1H), 1.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 161.8, 160.3, 141.6, 133.1, 129.8, 129.1, 128.2, 114.2, 108.0, 103.8, 65.9, 55.4, 49.6, 26.5; IR (neat): 2957, 2859, 1720, 1649, 1608, 1577, 1499, 1464, 1445, 1375, 1353, 1317, 1287, 1243, 1226, 1200, 1169, 1125, 1112, 1060, 1039, 1009, 975, 900, 839, 810, 779, 762, 737, 698, 641, 616, 527 (cm^{-1}).

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