(Supporting information)

Efficient Synthesis of Phenanthridinone Derivatives *via* a Palladium-Catalyzed Coupling Process

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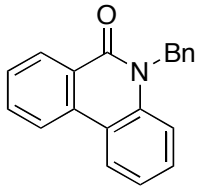
General Information

^{1}H NMR spectra were obtained on JEOL ECA-500 at 500 MHz or JEOL EX-270 at 270 MHz with chemical shifts being reported as ppm from tetramethylsilane as an internal standard. ^{13}C NMR spectra were measured on JEOL ECA-500 at 125 MHz or JEOL EX-270 at 68 MHz. The mass spectra were measured on a JEOL MStation JMS-700 spectrometer. The GC-MS analysis was performed on Agilent Technologies 6890N (GC) combined with JEOL JMS-AMSUN (MS). Unless otherwise noted, all reactions were run under an argon atmosphere. Column chromatography was carried out with silica gel 60N spherical (63-210 mesh, KANTO CHEMICAL).

General procedure for domino reaction (general procedure (I)).

$Pd(OAc)_2$ (6.0 mol%) was added to a solution of ligand **1** (5.0 mol%) in 1,4-dioxane (concentration of **1**: 0.15 M) under an argon atmosphere. After sonicating the solution, the substrate (1.0 equiv.) and Cs_2CO_3 (1.0 equiv.) were added to the solution at rt and the mixture was stirred for 24 h at 100 °C. After stirring, H_2O was added, and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel to afford the corresponding phenanthridinone derivative.

Experimental details and spectroscopic data of phenanthridinone derivatives in Tables 1 – 3.



12

According to the general procedure (I), 5-benzylphenanthridin-6(5*H*)-one (**12**) (19 mg, 77%) was obtained from *N*-benzyl-2-bromobenzamide (**11**) (50 mg, 0.17 mmol) as a colorless solid.

R*f* = 0.68 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.32 – 8.29 (m, 2H), 7.85 – 7.75 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.35 (m, 1H), 7.40 – 7.20 (m, 7H), 5.67 (brs, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.9, 137.4, 136.6, 133.8, 132.7, 129.5, 129.2, 128.8, 128.0, 127.2, 126.5, 125.4, 123.3, 122.6, 121.7, 119.5, 116.0, 46.5; **MS** (FAB) *m*/*z* 286 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{20}H_{16}NO$ $(M+H)^+$ 286.1231, found 286.1209.

The structure of **12** was unambiguously determined by X-ray analysis as shown in Figure 1.

Crystallographic data for **12**: $C_{20}H_{15}NO$, *M* = 285.34, monoclinic, space group $P2_1/a$ (#14), *T* = 298 K, *a* = 17.573(3) Å, *b* = 9.0671(14) Å, *c* = 9.6002(16) Å, *β* = 97.633(13)°, *V* = 1516.1(4) Å^3, *Z* = 4, *D* = 1.300 g/cm^3, *λ*(Cu *Ka*) = 1.54178 Å, *R* = 0.0550, *wR*2[F^2] = 0.1832 for 606 unique reflections.

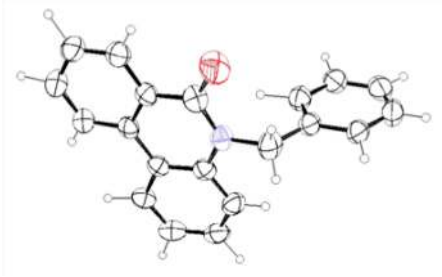
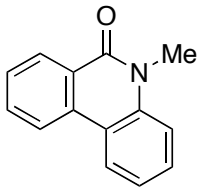
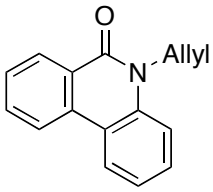


Figure 1. Ortep view of **12**.



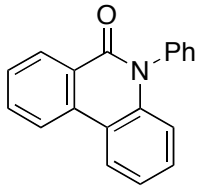
14a

According to the general procedure (I), 5-methylphenanthridin-6(5*H*)-one (**14a**) (14 mg, 28%) was obtained from 2-bromo-*N*-methylbenzamide (**13a**) (50 mg, 0.23 mmol) as a colorless solid. Spectral data for **13a** : See, Ref. [1].



14b

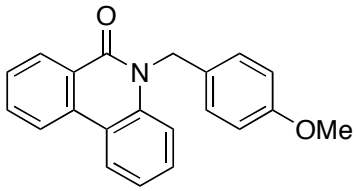
According to the general procedure (I), 5-allylphenanthridin-6(5*H*)-one (**14b**) (8 mg, 32%) was obtained from *N*-allyl-2-bromobenzamide (**13b**) (50 mg, 0.21 mmol) as a colorless solid. Spectral data for **14b** : See, Ref. [2].



14c

According to the general procedure (I), 5-phenylphenanthridin-6(5*H*)-one (**14c**) (11 mg, 23%) was obtained solids from 2-bromo-*N*-phenylbenzamide (**13c**) (100 mg, 0.36 mmol) as a colorless solid.

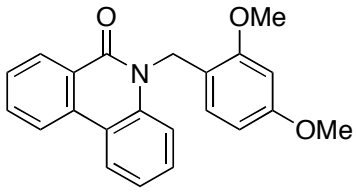
R*f* = 0.63 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.40 - 8.25 (m, 2H), 7.85 – 7.75 (m, 1H), 7.65 – 7.55 (m, 3H), 7.55 – 7.52 (m, 1H), 7.40 – 7.28 (m, 4H), 6.71 – 6.69 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.7, 139.2, 138.3, 134.0, 132.8, 130.2, 129.1, 129.0, 128.8, 128.1, 125.9, 123.0, 122.6, 121.8, 119.0, 117.0; **MS** (FAB) *m*/*z* 272 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{19}H_{14}NO$ $(M+H)^+$ 272.1075, found 272.1070.



14d

According to the general procedure (I), 5-(4-methoxybenzyl)phenanthridin-6(5*H*)-one (**14d**) (63 mg, 64%) was obtained from 2-bromo-*N*-(4-methoxybenzyl)benzamide (**13d**) (200 mg, 0.63 mmol) as a colorless solid.

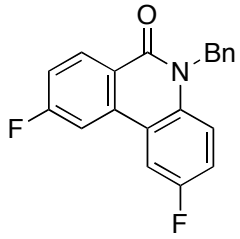
R*f* = 0.70 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.35 - 8.25 (m, 2H), 7.85 – 7.75 (m, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.61 (brs, 2H), 3.75 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.9, 158.8, 137.4, 133.8, 132.6, 129.5, 129.2, 128.7, 128.0, 127.9, 125.5, 123.3, 122.5, 121.7, 119.5, 116.0, 114.2, 55.2, 45.9; **MS** (FAB) *m*/*z* 316 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{21}H_{18}NO_2$ $(M+H)^+$ 316.1337, found 316.1342.



14e

According to the general procedure (I), 5-(2,4-dimethoxybenzyl)phenanthridin-6(5*H*)-one (**14e**) (29 mg, 72%) was obtained from 2-bromo-*N*-(2,4-dimethoxybenzyl)benzamide (**13e**) (80 mg, 0.23 mmol) as a colorless solid.

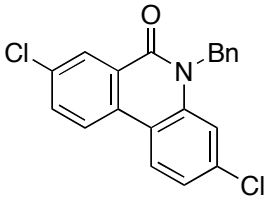
R*f* = 0.47 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 1.2, 7.9 Hz, 1H), 8.35 - 8.25 (m, 2H), 7.85 – 7.75 (m, 1H), 7.65 – 7.55 (m, 1H), 7.45 – 7.35 (m, 1H), 7.32 – 7.20 (m, 2H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.28 (dd, *J* = 2.4, 8.5 Hz, 1H), 5.58 (brs, 2H), 3.95 (s, 3H), 3.73 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.0, 160.0, 157.6, 137.4, 133.9, 132.5, 129.6, 129.1, 127.9, 127.5, 125.6, 123.1, 122.4, 121.6, 119.4, 116.8, 116.2, 104.4, 98.5, 55.5, 55.3, 40.9; **MS** (FAB) *m*/*z* 346 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{22}H_{20}NO_3$ $(M+H)^+$ 346.1444, found 346.1438.



16c

According to the general procedure (I), 5-benzyl-2,9-difluorophenanthridin-6(5*H*)-one (**16c**) (12 mg, 45%) was obtained from *N*-benzyl-2-bromo-4-fluorobenzamide (**15c**) (50 mg, 0.16 mmol) as a colorless solid.

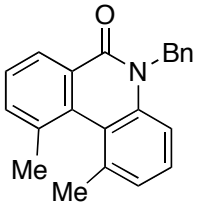
R*f* = 0.73 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.64 (dd, *J* = 5.8, 8.8 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.40 – 7.20 (m, 7H), 7.20 – 7.10 (m, 1H), 5.63 (brs, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.8, 136.1, 134.2, 132.7, 132.6, 129.1, 128.9, 128.5, 127.4, 126.4, 122.2, 117.81, 117.77, 117.6, 117.1, 116.9, 109.6, 109.4, 108.0, 107.9, 46.7; **MS** (FAB) *m*/*z* 322 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{20}H_{14}F_2NO$ $(M+H)^+$ 322.1043, found 322.1011.



16d

According to the general procedure (I), 5-benzyl-3,8-dichlorophenanthridin-6(5*H*)-one (**16d**) (14 mg, 37%) was obtained from *N*-benzyl-2-bromo-5-chlorobenzamide (**15d**) (71 mg, 0.22 mmol) as a colorless solid.

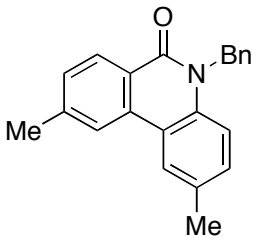
R*f* = 0.71 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.57 (d, *J* = 2.4 Hz, 1H), 8.20 – 8.10 (m, 2H), 7.74 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.35 – 7.20 (m, 7H), 5.60 (brs, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 160.8, 138.2, 135.8, 135.7, 134.6, 133.3, 131.6, 129.0, 128.9, 127.6, 126.6, 126.5, 124.5, 123.4, 123.1, 117.4, 116.1, 46.8; **MS** (FAB) *m*/*z* 354 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{20}H_{14}Cl_2NO$ $(M+H)^+$ 354.0452, found 354.0488.



16e

According to the general procedure (I), 5-benzyl-1,10-dimethylphenanthridin-6(5*H*)-one (**16e**) (25 mg, 81%) was obtained from *N*-benzyl-2-bromo-3-methylbenzamide (**15e**) (60 mg, 0.20 mmol) as a colorless solid.

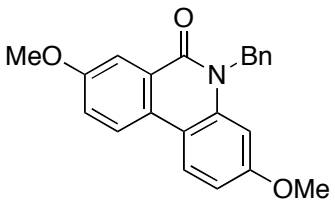
R*f* = 0.80 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.39 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 6.7 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.30 – 7.15 (m, 6H), 7.10 – 7.00 (m, 2H), 5.70 (brs, 1H), 5.38 (brs, 1H), 2.47 (s, 3H), 2.45 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 162.4, 137.7, 136.9, 136.5, 135.2, 134.4, 133.8, 128.7, 128.4, 127.8, 127.1, 127.0, 126.5, 125.7, 124.9, 119.8, 112.0, 46.6, 22.2, 21.8; **MS** (FAB) *m*/*z* 314 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{22}H_{20}NO$ $(M+H)^+$ 314.1545, found 314.1545.



16f

According to the general procedure (I), 5-benzyl-2,9-dimethylphenanthridin-6(5*H*)-one (**16f**) (52 mg, 67%) was obtained from *N*-benzyl-2-bromo-4-methylbenzamide (**15f**) (150 mg, 0.49 mmol) as a colorless solid.

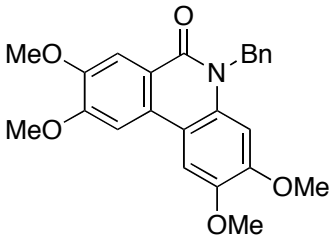
R*f* = 0.47 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 8.6 Hz, 1H), 8.15 - 8.00 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.13 (m, 7H), 5.64 (brs, 2H), 2.58 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.8, 143.1, 136.8, 135.3, 133.7, 131.8, 130.4, 129.3, 129.2, 128.7, 127.1, 126.5, 123.3, 123.2, 121.7, 119.3, 115.9, 46.3, 22.2, 20.9; **MS** (FAB) *m*/*z* 314 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{22}H_{20}NO$ $(M+H)^+$ 314.1545, found 314.1545.



16g

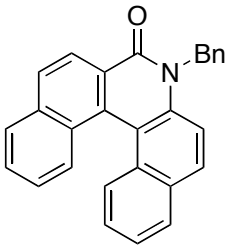
According to the general procedure (I), 5-benzyl-3,8-dimethoxyphenanthridin-6(5*H*)-one (**16g**) (18 mg, 41%) was obtained from *N*-benzyl-2-bromo-5-methoxybenzamide (**15g**) (80 mg, 0.25 mmol) as a colorless solid.

R*f* = 0.57 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.15 - 8.05 (m, 2H), 8.00 (d, *J* = 2.9 Hz, 1H), 7.35 (dd, *J* = 2.9, 9.2 Hz, 1H), 7.32 – 7.20 (m, 5H), 6.83 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.80 (d, *J* = 2.3 Hz, 1H), 5.64 (brs, 2H), 3.96 (s, 3H), 3.75 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.2, 159.8, 158.8, 137.6, 136.6, 128.8, 127.7, 127.2, 126.6, 125.3, 123.9, 122.9, 122.8, 113.2, 109.3, 109.2, 101.1, 55.6, 55.3, 46.8; **MS** (FAB) *m*/*z* 346 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{22}H_{20}NO_3$ $(M+H)^+$ 346.1443, found 346.1396.



16h

According to the general procedure (I), 5-benzyl-2,3,8,9-tetramethoxyphenanthridin-6(5*H*)-one (**16h**) (27 mg, 92%) was obtained from *N*-benzyl-2-bromo-4,5-dimethoxybenzamide (**15h**) (50 mg, 0.14 mmol) as a colorless solid. Spectral data for **16h** : See, Ref. [3].



16i

According to the general procedure (I), binaphtyl derivative (**16i**) (20 mg, 59%) was obtained from *N*-benzyl-1-bromo-2-naphthamide (**15i**) (60 mg, 0.18 mmol) as a colorless solid.

R*f* = 0.79 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.6 Hz, 1H), 8.10 - 8.02 (m, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.90 – 7.80 (m, 2H), 7.65 – 7.58 (m, 1H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.45 – 7.37 (m, 1H), 7.35 – 7.18 (m, 7H), 5.89 (brs, 1H), 5.63 (brs, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 162.3, 136.7, 136.5, 135.5, 132.9, 130.5, 129.6, 129.3, 129.2, 128.8, 128.6, 128.14, 128.06, 127.8, 127.2, 126.5, 125.7, 125.4, 124.94, 124.86, 123.7, 115.4, 113.6, 46.8; **MS** (FAB) *m*/*z* 386 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{28}H_{20}NO$ $(M+H)^+$ 386.1545, found 386.1506.

Experimental procedure for GC-MS analysis for detection of benzyl isocyanate (Table 1, entry 1).

The GC-MS analysis of the reaction mixture of entry 1 in Table 1 was performed. The direct introduction of the mixture showed the peak having *m/z* 313 (Chart 1) at 3.55 min, which is identical with the standard sample of benzyl isocyanate (Chart 2) both on the retention time as well as the mass fragmentations.

GC conditions: Column: Agilent Technologies HP-5 (30 m x 0.32 mm x 0.25 μm); Flow rate of the carrier gas (He): 1.0 mL/min.

The initial temperature of the column was set at 40 °C and ramped at 25 °C/min to a final temperature of 170 °C.

Chart 1

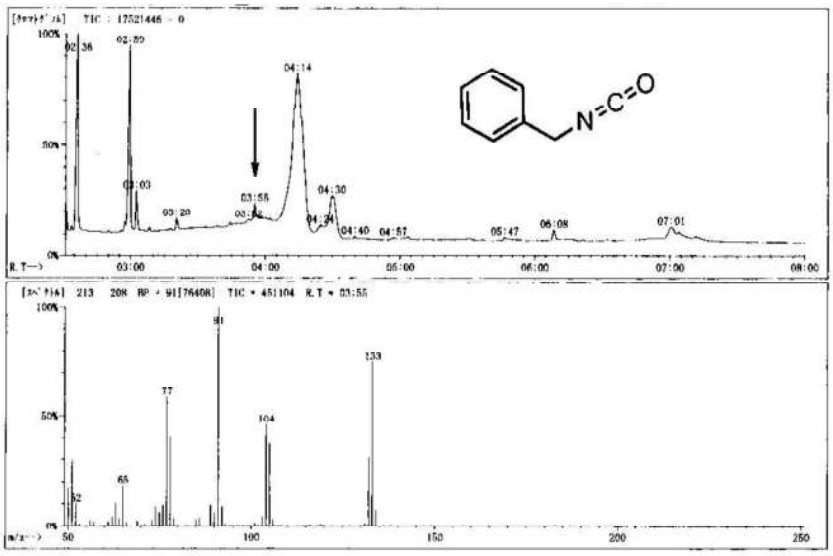
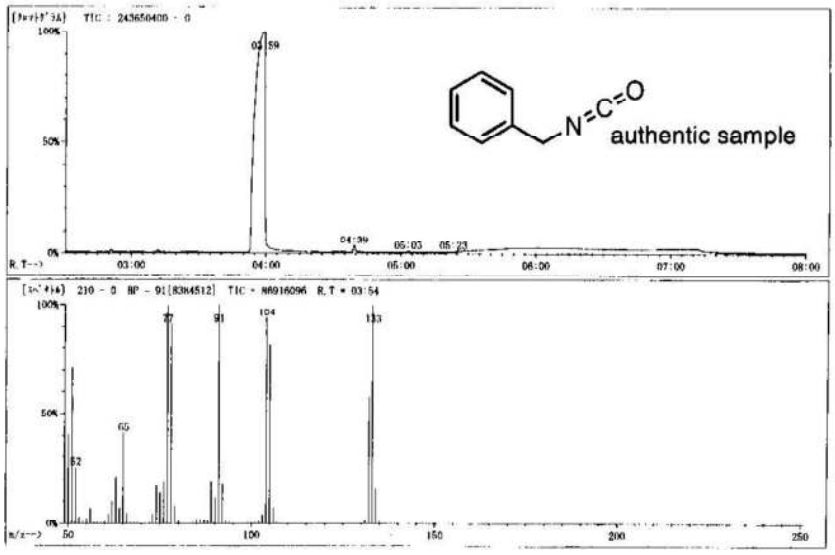


Chart 2



Experimental procedure for isolation of di-*p*-methoxybenzyl urea (Table 2, entry 4).

According to general procedure for domino reaction, the duplicate reaction was preformed. After the chromatography on silica gel (CH_2Cl_2/MeOH, 19:1), di-*p*-methoxybenzyl urea **25** was isolated in 40% yield.

Experimental procedure for diversity oriented synthesis of phenanthridinone derivatives (Scheme 3A).

According to the general procedure (I), the reaction was performed by the use of equimolar amounts of *N*-benzyl-2-bromo-5-chlorobenzamide (**15d**) (105 mg, 0.323 mmol) and *N*-benzyl-2-bromo-5-methoxybenzamide (**15g**). The coupling products, 5-benzyl-3,8-dichlorophenanthridin-6(5*H*)-one (**16d**) (14 mg, 25%), 5-benzyl-3,8-dimethoxyphenanthridin-6(5*H*)-one (**16g**) (17 mg, 26%) and the mixture (22 mg) containing 5-benzyl-3-chloro-8-methoxyphenanthridin-6(5*H*)-one (**19**) and 5-benzyl-8-chloro-3-methoxyphenanthridin-6(5*H*)-one (**20**) were obtained by column chromatography on silica gel (hexane/AcOEt, 1:3). The yields of products **19** and **20** were caluculated by ^{1}H NMR integration of the mixture (Figure 2). Further purification of the part of the mixture by column chromatography on silica gel afforded **19**.

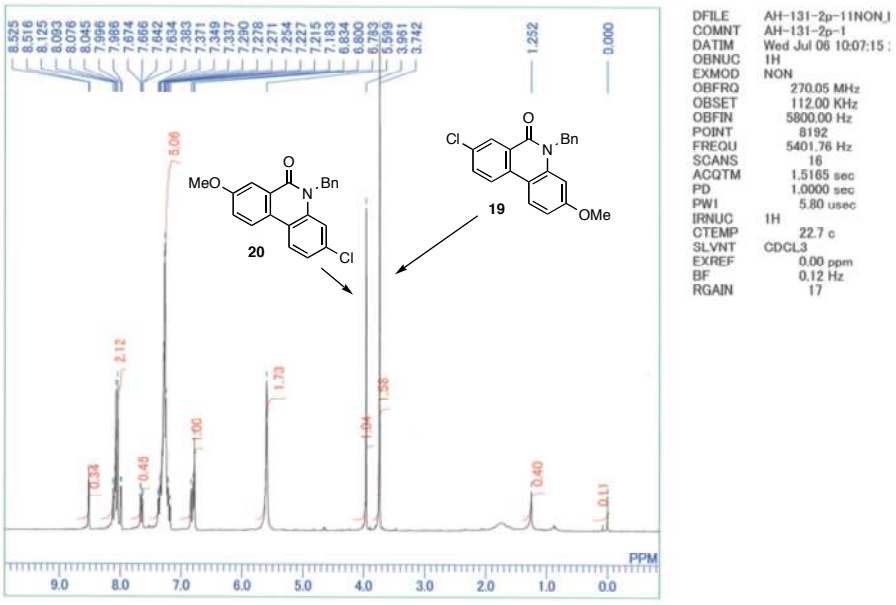
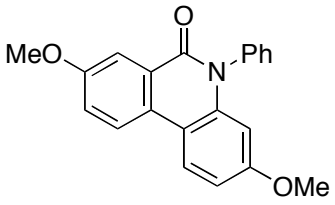


Figure 2. ^{1}H NMR of the mixture containing **19** and **20**.

Spectral data for **19**: **R*f*** = 0.61 (hexane/AcOEt, 7:3); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.0 Hz, 1H), 8.20 – 7.95 (m, 2H), 7.69 (dd, *J* = 2.0, 8.6 Hz, 1H), 7.40 – 7.15 (m, 5H), 6.90 – 6.70 (m, 2H), 5,62 (brs, 2H), 3.76 (s, 3H); **MS** (FAB) *m*/*z* 350 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{21}H_{17}ClNO_2$ $(M+H)^+$ 350.0948, found 350.0902.

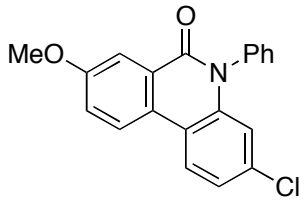
Experimental procedure for Scheme 3B.

According to the general procedure (I), the reaction was performed by the use of equimolar amounts of *N*-benzyl-2-bromo-5-chlorobenzamide (**15d**) (95 mg, 0.294 mmol) and 2-bromo-5-methoxy-*N*-phenylbenzamide (**21**) (90 mg, 0.294 mmol). The products, 5-benzyl-3,8-dichlorophenanthridin-6(5*H*)-one (**16d**) (16 mg, 30%), 3,8-dimethoxy-5-phenylphenanthridin-6(5*H*)-one (**22**) (4.4 mg, 9%), 5-benzyl-8-chloro-3-methoxyphenanthridin-6(5*H*)-one (**19**) (7.6 mg, 7%) and 3-chloro-8-methoxy-5-phenylphenanthridin-6(5*H*)-one (**23**) (2.2 mg, 2%) were obtained by column chromatography on silica gel (hexane/AcOEt, 3:1).



22

Spectral data for **22**: colorless solid; **R*f*** = 0.46 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 - 8.10 (m, 2H), 7.93 (d, *J* = 2.9 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.38 (dd, *J* = 2.9, 9.2 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 2H), 6.86 (dd, *J* = 2.3, 8.6 Hz, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H), 3.68 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.9, 159.5, 158.8, 139.5, 138.4, 130.2, 128.9, 128.8, 127.9, 125.8, 123.7, 123.0, 122.7, 112.9, 109.3, 109.2, 102.0, 55.6, 55.3; **MS** (FAB) *m*/*z* 332 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{21}H_{18}NO_3$ $(M+H)^+$ 332.1286, found 332.1287.



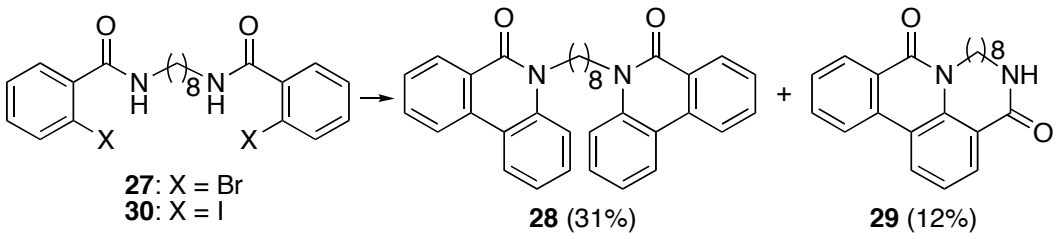
23

Spectral data for **23**: colorless solid; **R*f*** = 0.56 (hexane/AcOEt, 7:3); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 9.1 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 3.0 Hz, 1H), 7.70 – 7.60 (m, 2H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.41 (dd, *J* = 3.0, 9.1 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.24 (dd, *J* = 2.0, 8.5 Hz, 1H), 3.95 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 161.7, 159.9, 139.1, 137.9, 133.8, 130.4, 129.1, 128.9, 127.0, 126.9, 123.7, 123.6, 123.0, 122.9, 117.8, 116.7, 109.6, 55.7; **MS** (FAB) *m*/*z* 336 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{20}H_{15}ClNO_2$ $(M+H)^+$ 336.0791, found 336.0804.

Deprotection of PMB group (Scheme 4).

The solution of **14d** (20 mg, 0.063 mmol) in trifluoroacetic acid (1 mL) was refluxed for 14 h, then the soluion was evaporated to give a residue. To the residue, H_2O was added and extracted with AcOEt. The organic layer was washed with H_2O, brine, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 19:1) to afford **24** (11 mg, 92%) as a colorless solid.

Experimental details for Ref. (12) in Notes and References.



According to the general procedure (I), the reaction with *N*-tethered 2-bromobenzamide **27** (150 mg, 0.29 mmol) was performed. The phenanthridinone dimer (**28**) (15 mg, 31%) and intramolecular coupling product **29** (12 mg, 12%) were obtained by column chromatography on silica gel (hexane/AcOEt, 1:1) as colorless solids.

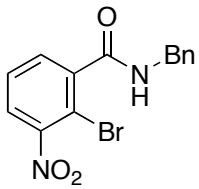
The product **28** was derived from the intermolecular coupling reaction between two and/or three molecules of the substrates **27**. The yield (31%) was calculated based on the three-component coupling reaction.

On the other hand, the product **29** was derived from the intramolecular coupling reaction of **27**. The same product was previously reported on the Pd catalyzed reaction from the corresponding iodide **30**.[4]

Compound **28:** **R*f*** = 0.71 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 8.56 (d, *J* = 7.9 Hz, 2H), 8.35 – 8.20 (m, 4H), 7.76 (t, *J* = 7.6 Hz, 2H), 7.65 – 7.50 (m, 4H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 4.39 (t, *J* = 7.9 Hz, 4H), 1.85 – 1.40 (m, 12H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 161.3, 137.1, 133.6, 132.3, 129.5, 128.8, 127.9, 125.6, 123.4, 122.2, 121.5, 119.5, 115.1, 42.7, 29.3, 27.4, 27.0; **MS** (FAB) *m*/*z* 501 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{34}H_{33}N_2O_2$ $(M+H)^+$ 501.2542, found 501.2534.

<u>General procedure for synthesis of *N*-benzyl 2-bromobenzamide derivatives (general procedure (II)).</u>

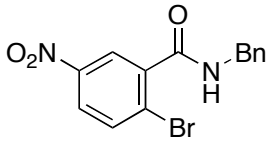
To a solution of 2-bromobenzoic acid derivative in toluene were added thionyl chloride (1.1 equiv.) and catalytic amount of DMF at 0 °C under an argon atmosphere. The mixture was stirred for 10 min at 70 °C, then the solution was evaporated to give a residue. The residue was dissolved in CH_2Cl_2, then benzylamine (1.2 eq) and triethyamine (3.0 eq) were added to the solution at 0 °C. After stirring the mixture for 2 h at rt, H_2O was added, and extracted with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ aq., 2 N HCl, brine, dried over $MgSO_4$ and evaporated to afford corresponding *N*-benzyl 2-bromobenzamide derivative.



15a

According to the general procedure (II), *N*-benzyl-2-bromo-3-nitrobenzamide (**15a**) (365 mg, 89%) was obtained solids from 2-bromo-3-nitrobenzoic acid (300 mg, 1.2 mmol) as a colorless solid.

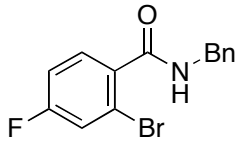
R*f* = 0.68 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.45 – 7.30 (m, 5H), 6.14 (brs, 1H), 4.66 (d, *J* = 5.9 Hz, 2H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 166.0, 141.2, 137.0, 132.4, 131.6, 128.9, 128.6, 128.1, 128.0, 125.8, 111.4, 44.4; **MS** (FAB) *m*/*z* 335 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{14}H_{12}{}^{79}BrN_2O_3$ $(M+H)^+$ 335.0031, found 335.0017.



15b

According to the general procedure (II), *N*-benzyl-2-bromo-5-nitrobenzamide (**15b**) (323 mg, 79%) was obtained from 2-bromo-5-nitrobenzoic acid (300 mg, 1.2 mmol) as a colorless solid.

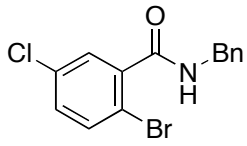
R*f* = 0.76 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.40 (d, *J* = 2.4 Hz, 1H), 8.12 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.25 (m, 5H), 6.26 (brs, 1H), 4.68 (d, *J* = 5.5 Hz, 2H); **^{13}C NMR** (68 MHz, acetone) δ 166.3, 141.3, 139.6, 135.4, 129.3, 128.6, 128.0, 127.5, 126.0, 124.4, 44.1 ; **MS** (FAB) *m*/*z* 335 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{14}H_{12}{}^{79}BrN_2O_3$ $(M+H)^+$ 335.0031, found 335.0001.



15c

According to the general procedure (II), *N*-benzyl-2-bromo-4-fluorobenzamide (**15c**) (399 mg, 71%) was obtained from 2-bromo-4-fluorobenzoic acid (400 mg, 1.8 mmol) as a colorless solid.

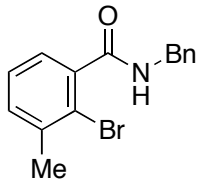
R*f* = 0.68 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 5.8, 8.6 Hz, 1H), 7.40 – 7.27 (m, 6H), 7.10 – 7.00 (m, 1H), 6.40 (brs, 1H), 4.62 (d, *J* = 5.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.6, 163.9, 161.8, 137.4, 133.79, 133.76, 131.3, 131.2, 128.8, 128.0, 127.7, 120.8, 120.6, 120.0, 119.9, 115.0, 114.8, 44.3; **MS** (FAB) *m*/*z* 308 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{14}H_{12}{}^{79}BrFNO$ $(M+H)^+$ 308.0086, found 308.0118.



15d

According to the general procedure (II), *N*-benzyl-2-bromo-5-chlorobenzamide (**15d**) (290 mg, quant.) was obtained from 2-bromo-5-chlorobenzoic acid (200 mg, 0.85 mmol) as a colorless solid.

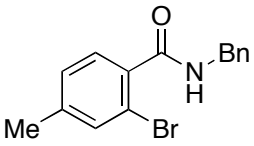
R*f* = 0.61 (hexane/AcOEt, 9:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 3.0 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.25 (m, 5H), 7.25 (dd, *J* = 3.0, 8.5 Hz, 1H), 6.24 (brs, 1H), 4.65 (d, *J* = 5.5 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 166.0, 138.9, 137.3, 134.6, 133.9, 131.4, 129.7, 128.8, 128.0, 127.8, 117.2, 44.4; **MS** (FAB) *m*/*z* 324 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{14}H_{12}{}^{79}BrClNO$ $(M+H)^+$ 323.9790, found 323.9749.



15e

According to the general procedure (II), *N*-benzyl-2-bromo-3-methylbenzamide (**15e**) (385 mg, 54%) was obtained from 2-bromo-3-methylbenzoic acid (500 mg, 2.3 mmol) as a colorless solid.

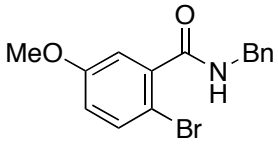
R*f* = 0.68 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 7.35 – 7.10 (m, 8H), 6.37 (brs, 1H), 4.55 (d, *J* = 5.3 Hz, 2H), 2.39 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 168.3, 139.1, 138.9, 137.7, 131.8, 128.6, 127.9, 127.6, 127.2, 126.2, 121.6, 44.0, 23.5; **MS** (FAB) *m*/*z* 304 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{15}H_{15}{}^{79}BrNO$ $(M+H)^+$ 304.0337, found 304.0306.



15f

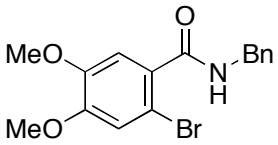
According to the general procedure (II), *N*-benzyl-2-bromo-4-methylbenzamide (**15f**) (266 mg, 94%) was obtained from 2-bromo-3-methylbenzoic acid (200 mg, 0.93 mmol) as a colorless solid.

R*f* = 0.40 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.3 Hz, 1H), 7.45 – 7.20 (m, 6H), 7.15 (d, *J* = 7.9 Hz, 1H), 6.32 (brs, 1H), 4.65 (d, *J* = 5.9 Hz, 2H), 2.34 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 167.4, 142.0, 137.7, 134.5, 133.8, 129.7, 128.7, 128.3, 127.9, 127.6, 119.1, 44,2, 20.9; **MS** (FAB) *m*/*z* 304 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{15}H_{15}{}^{79}BrNO$ $(M+H)^+$ 304.0337, found 304.0316.



15g

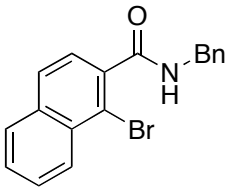
According to the general procedure (II), *N*-benzyl-2-bromo-5-methoxybenzamide (**15g**) (246 mg, quant.) was obtained from 2-bromo-5-methoxybenzoic acid (200 mg, 0.87 mmol) as a colorless solid. Spectral data for **15g**: See, Ref. [5].



15h

According to the general procedure (II), *N*-benzyl-2-bromo-4,5-dimethoxybenzamide (**15h**) (305 mg, 76%) was obtained from 2-bromo-4,5-dimethoxybenzoic acid (300 mg, 1.2 mmol) as a colorless solid.

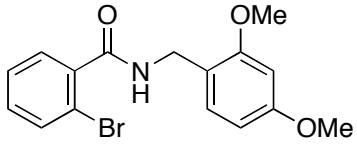
R*f* = 0.47 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 5H), 6.99 (s, 1H), 6.60 (brs, 1H), 4.66 (d, *J* = 5.3 Hz, 2H), 3.89 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 166.6, 150.8, 148.4, 137.7, 128.8, 128.7, 127.9, 127.6, 115.7, 113.1, 109.8, 56.2, 56.1, 44.3; **MS** (FAB) *m*/*z* 350 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{16}H_{17}{}^{79}BrNO_3$ $(M+H)^+$ 350.0392, found 350.0348.



15i

According to the general procedure (II), *N*-benzyl-1-bromo-2-naphthamide (**15i**) (362 mg, 89%) was obtained from 1-bromo-2-naphthoic acid (300 mg, 1.2 mmol) as a colorless solid.

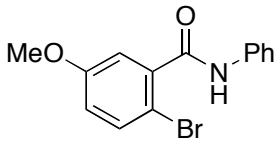
R*f* = 0.47 (hexane/AcOEt, 1:1); **^{1}H NMR** (270 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.80 (m, 2H), 7.70 – 7.20 (m, 8H), 6.26 (brs, 1H), 4.71 (d, *J* = 4.8 Hz, 2H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 168.5, 137.6, 136.2, 134.6, 131.9, 128.8, 128.30, 128.25, 128.2, 128.1, 127.9, 127.7, 127.6, 125.1, 119.9, 44.3; **MS** (FAB) *m*/*z* 340 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{18}H_{15}{}^{79}BrNO$ $(M+H)^+$ 340.0337, found 340.0373.



13e

To a solution of 2,4-dimethoxybenzylamine (457 mg, 2.73 mmol) in CH_2Cl_2 were added triethylamine (962 μL, 6.83 mmol) and 2-bromobenzoyl chloride (500 mg, 2.28 mmol) at 0 °C under an argon atmosphere. The mixure was stirred for 4 h at rt. After stirring, H_2O was added, and extracted with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ aq., 2 N HCl, brine, dried over $MgSO_4$ and evaporated to give a residue. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 1:1) to afford 2-bromo-*N*-(2,4-dimethoxybenzyl)benzamide (**13e**) as a colorless solid (750 mg, 94%).

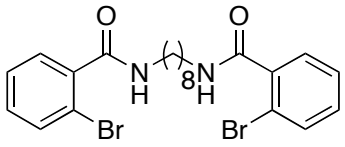
R*f* = 0.56 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.45 (m, 2H), 7.40 – 7.20 (m, 3H), 6.50 – 6.40 (m, 3H), 4.57 (d, *J* = 6.1 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.1, 160.7, 158.7, 138.0, 133.3, 131.0, 130.7, 129.7, 127.4, 119.3, 118.3, 103.9, 98.6, 55.4, 55.3, 39.6; **MS** (FAB) *m*/*z* 350 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{16}H_{17}{}^{79}BrNO_3$ $(M+H)^+$ 350.0392, found 350.0377.



21

To a solution of 2-bromo-5-methoxybenzoic acid (100 mg, 0.433 mmol) in toluene (1.5 mL) were added thionyl chloride (29 μL, 0.476 mmol) and catalytic amount of DMF at 0 °C under an argon atmosphere. The mixure was stirred for 10 min at 70 °C, then evaporated to give a residue. The residue was dissolved in CH_2Cl_2, then aniline (33 μL, 0.519 mmol) and triethyamine (179 μL, 1.30 mmol) in CH_2Cl_2 (0.5 mL) were added to the solution at 0 °C. After stirring the mixture for 2 h at rt, H_2O was added, and extracted with CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ aq., 2 N HCl, brine, dried over $MgSO_4$, then evaporated to afford 2-bromo-5-methoxy-*N*-phenylbenzamide (**21**) as a colorless solid (84 mg, 64%).

R*f* = 0.68 (hexane/AcOEt, 1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.75 (brs, 1H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.49 (d, *J* = 9.1 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 7.25 – 7.10 (m, 2H), 6.88 (dd, *J* = 3.0, 9.1 Hz, 1H), 3.82 (s, 3H); **^{13}C NMR** (68 MHz, $CDCl_3$) δ 165.2, 159.1, 138.3, 137.5, 134.3, 129.1, 124.9, 120.1, 118.4, 114.9, 109.3, 55. 7; **MS** (FAB) *m*/*z* 306 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{14}H_{13}{}^{79}BrNO_2$ $(M+H)^+$ 306.0130, found 306.0134.



27

To a solution of 2-bromobenzoyl chloride (0.27 mL, 2.00 mmol) in CH_2Cl_2 (5.0 mL) were added 1,8-diaminooctane (148 mg, 1.00 mmol) and triethylamine (0.56 mL, 4.00 mmol) in CH_2Cl_2 (5.0 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred for 2.5 h at rt. The colorless precipitate was filtered off through short silica gel column, and the filtrate was evaporated to give a residue. The residue was dissolved with CH_2Cl_2 and washed with sat. $NaHCO_3$ aq., 2 N HCl, brine, and dried over $MgSO_4$. Then the organic layer was evaporated to give a residue. The residue was purified by column chromatography on silica gel (hexane/AcOEt, 7:3) to afford **27** (495 mg, 97%) as a colorless solid.

R*f* = 0.75 (CH_2Cl_2/MeOH, 10:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 4H), 7.40 – 7.20 (m, 4H), 5.97 (brs, 2H), 3.46 (q, *J* = 7.3 Hz, 4H), 1.67 – 1.55 (m, 4H), 1.50 – 1.30 (m, 8H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 167.5, 138.1, 133.3, 131.1, 129.6, 127.6, 119.2, 40.1, 29.4, 29.1, 26.8; **MS** (FAB) *m*/*z* 511 $(M+H)^+$; **HRMS** (FAB) calcd for $C_{22}H_{27}{}^{79}Br^{81}BrN_2O_2$ $(M+H)^+$ 511.0419, found 511.0388.

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