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NOVEL PHOTOSENSITIZED CYCLIZATION REACTIONS OF ETHYL 3-AMINO-3-PHENYL-2-PROPENOATE DERIVATIVES TO HIGHLY SUBSTITUTED PYRROLES

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Abstract – Irradiation of nitrogen-saturated acetonitrile solutions containing ethyl 3-amino-3-phenyl-2-propenoate derivatives with the (*Z*)-configuration [(*Z*)-**1**] and 10-methylacridinium perchlorate (MAP) at wavelengths longer than 340 nm afforded the corresponding pyrrole derivatives in good to high yields without exhibiting a profound effect related to the substituents. An analysis of the Stern–Volmer plots for the fluorescence quenching of MAP by (*Z*)-**1** showed that this sensitizer fluorescence is efficiently quenched, and hence electron transfer is confirmed to be involved in the primary process of the MAP-sensitized cyclization reactions of **1**.

Recently, photoinduced electron transfer (PET)-initiated cyclization reactions have received considerable attentions because of their wide range of synthetic applications.[1] In addition, a systematic study of these PET reactions proceeding through exciplexes or radical ions has provided new and interesting mechanistic information about organic photochemistry. In the course of our study of the PET reactions of *N*-acyl-α-dehydroarylalaninamides and *N*-acyl-α-dehydroarylalanine alkyl esters (α-dehydroamino acid derivatives), we found that these derivatives readily undergo one-electron reduction in the presence of a tertiary aliphatic amine to enable the highly selective construction of 3,4-dihydroquinolinone and 4,5-dihydrooxazole ring systems, respectively, through the corresponding reactive radical ion pair intermediates.[2,3] The finding that PET reactions of these α-dehydroamino acid derivatives efficiently construct pharmaceutically useful heterocyclic rings allows us to confidently expect that β-dehydroamino acid derivatives also undergo PET reactions to enable the construction of such heterocyclic rings. However, a careful literature survey revealed that no study on the photochemical reactions of β-dehydroamino acid derivatives has been reported. Thus, the development of the PET reactions of these amino acid derivatives as an extension of the PET-initiated cyclization reactions of substituted α-

dehydroamino acids would be significant. Because a simple and efficient method for the synthesis of *N*-unsubstituted and *N*-alkyl substituted ethyl 3-amino-3-aryl-2-propenoates (β-dehydroarylalanine ethyl ester derivatives) has been established,[4] we conducted a preliminary study regarding the reactivity and product distribution of several β-dehydroarylalanine ethyl ester derivatives **1a**–**g** activated by 10-methylacridinium perchlorate (MAP) as a photosensitizer (Chart 1). In this communication, we present results demonstrating that selective excitation of MAP enables the progress of efficient electron transfer from the ground-state **1** to the singlet-excited-state MAP in order to result in a novel cyclization to substituted pyrroles.

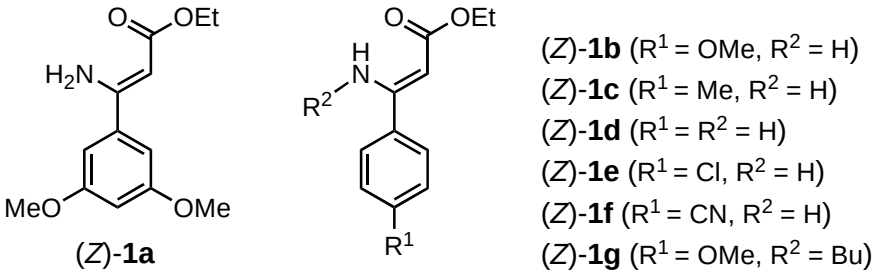
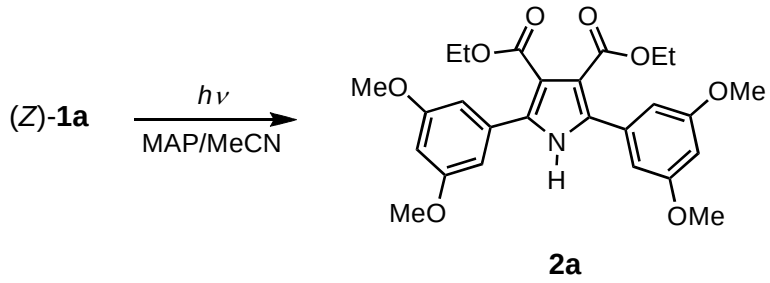


Chart 1

The starting β-dehydroarylalanine ethyl ester derivatives **1a**–**g** with the (*Z*)-configuration were prepared in 30–45% overall yields by reactions between ethyl acetoacetate and substituted benzoyl chlorides, followed by a heat treatment of the resultant ethyl aroyl acetates in ethanol that contained a five-fold molar excess of acetic acid and ammonia (**1a**–**f**) or acetic acid and butylamine (**1g**).[5] To examine the distribution and composition of the products generated from the photosensitized reaction of **1**, a nitrogen-saturated acetonitrile solution (100 mL) that contained (*Z*)-**1a** (5.0×10^{-3} mol dm^{-3}) and MAP (1.0×10^{-2} mol dm^{-3}) was irradiated at wavelengths longer than 340 nm for 24 h at room temperature (light source: 500-W high-pressure Hg lamp). Because MAP exhibits fairly low solubility in ethyl acetate, repeated extraction of the photoproducts with this solvent from the reaction mixture (concentrated to dryness in vacuo) and subsequent preparative thin-layer chromatography using silica gel (eluent: EtOAc–hexane) enabled us to isolate 2,5-bis(3,5-dimethoxyphenyl)-3,4-bis(ethoxycarbonyl)-pyrrole (**2a**) in 46% yield, along with a small amount of **1a**.[6] ^{1}H NMR spectral analysis of this mixture showed that it contained small amounts of byproducts in addition to **1a**, **2a**, and MAP, which strongly suggests the occurrence of a side reaction, although no attempt was made to isolate these byproducts (Scheme 1). In addition, we were able to revaluate the yield (^{1}H NMR yield) of **2a** and the conversion of **1a** to be 60% and 96%, respectively, on the basis of the internal standard method using 1,3,5-trimethoxybenzene. The structure of the pyrrole derivative **2a** was confirmed by the following three experimental results: (1) proton signals for the two ethoxycarbonyl groups and for the two 3,5-dimethoxyphenyl groups gave the same chemical

shift values, respectively; (2) the calculated molecular weight for **2a** ($[M + Na]^+$ 506.19) was consistent with its observed value ($[M + Na]^+$ 505.99); and (3) a large difference NOE (35% in $CDCl_3$) was observed between the NH proton in the pyrrole ring and the proton at the 2-position on the benzene ring.



Scheme 1

Next, we focused on the effects of the substituent on the photoreactivity (conversion) of the starting β-dehydroarylalanine ethyl ester **1** as well as on the ^{1}H NMR yield of the pyrrole product **2**; the results are summarized in Table 1. Although the pyrrole yield tended to increase with an increase in the electron-withdrawing ability of the substituent introduced onto the benzene ring, the photoreactivity indicated no correlation with this electron-withdrawing ability. In addition, the replacement of the amino hydrogen in **1b** by the butyl group (**1g**) slightly enhanced the conversion of **1** without affecting the yield of **2**. The contribution of a side reaction that affords byproducts likely complicates the relationship between the reactant conversion and the ^{1}H NMR yield of the pyrrole product.

Table 1. Effects of the substituent on the conversion of (*Z*)-**1** and the ^{1}H NMR yield of pyrrole derivative **2**, obtained by the 24 h irradiation of a nitrogen-saturated acetonitrile solution of **1** (5.0×10^{-3} mol dm^{-3}) containing MAP (1.0×10^{-2} mol dm^{-3}) at room temperature

(*Z*)-**1**	Conversion of (*Z*)-**1** (%)	^{1}H NMR yield of **2** (%)
1a	96	60
1b	96	60
1c	94	66
1d	94	66
1e	88	74
1f	96	96
1g	100	60

The observations that MAP exhibits its first UV absorption band at a much longer wavelength compared to that of **1** and undergoes no decomposition during irradiation confirm that MAP functions as a photosensitizer with the ability to accept an electron from the β-dehydroamino acid ester **1**. To explore the relationship between the photoreactivity of ester **1** and the efficiency of electron transfer (ET) from **1** to the excited-state MAP, we estimated quenching constants (K_{SV}'s) through the fluorescence quenching of MAP by **1a**–**g** in argon-saturated acetonitrile at room temperature. As shown in Figure 1, the fluorescence of MAP ([MAP] = 1.0×10^{-4} mol dm^{-3} and excitation wavelength = 366 nm) was quenched by **1a** according to the Stern–Volmer equation: $I_0/I = 1 + K_{SV}$[**1a**], where I and I_0 are the fluorescence intensities of MAP with and without **1a**, respectively. Because similar results were obtained for the other β-dehydroamino acid esters, the K_{SV} values were determined from the slopes of the linear Stern–Volmer plots: K_{SV} (dm^3 mol^{-1}) = 7.0×10^2 (**1a**), 8.9×10^2 (**1b**), 7.0×10^2 (**1c**), 7.8×10^2 (**1d**), 7.7×10^2 (**1e**), 3.2×10^3 (**1f**), and 7.8×10^2 (**1g**). Clearly, the ET fluorescence quenching of MAP occurs with a high efficiency irrespective of the electronic properties of the substituents introduced; however, the magnitude of K_{SV}, which is a measure of ET efficiency, does not correlate with the observed photoreactivity of **1** (Table 1). Because prolonged irradiation is required to complete the examined photoreactions, this finding suggests that at least two regeneration processes of the starting dehydroamino acid ester reactants occur prior to the appearance of the pyrrole products. Interestingly, the presence of the electron-withdrawing cyano group in **1** enhanced the efficiency of ET from this amino acid ester to MAP by a factor of approximately 4–5. The strong ability of the cyano group to accept an electron may assist ET to the sensitizer in the singlet-excited state.

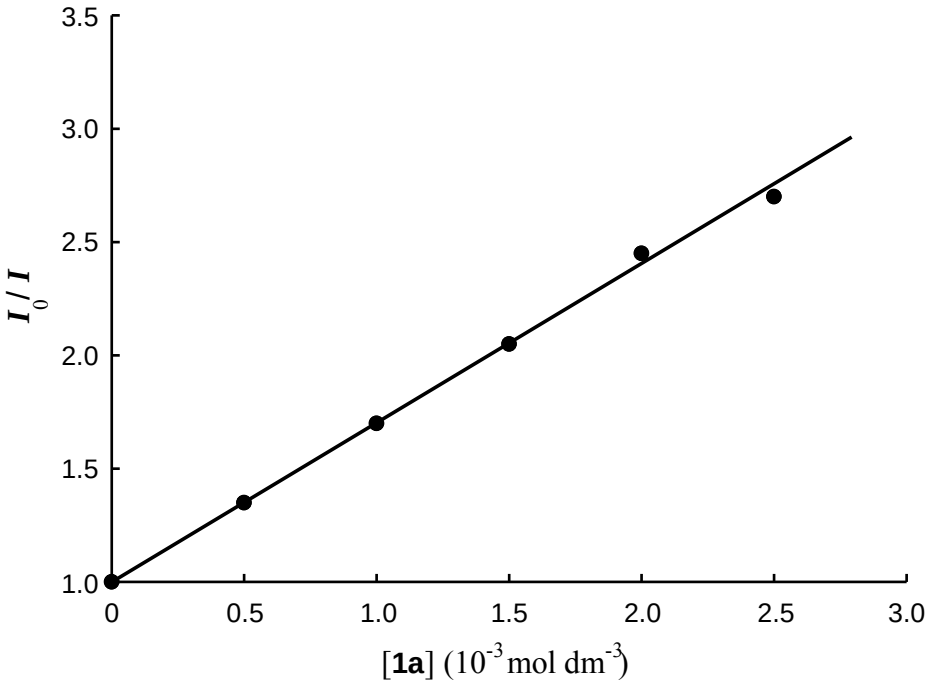
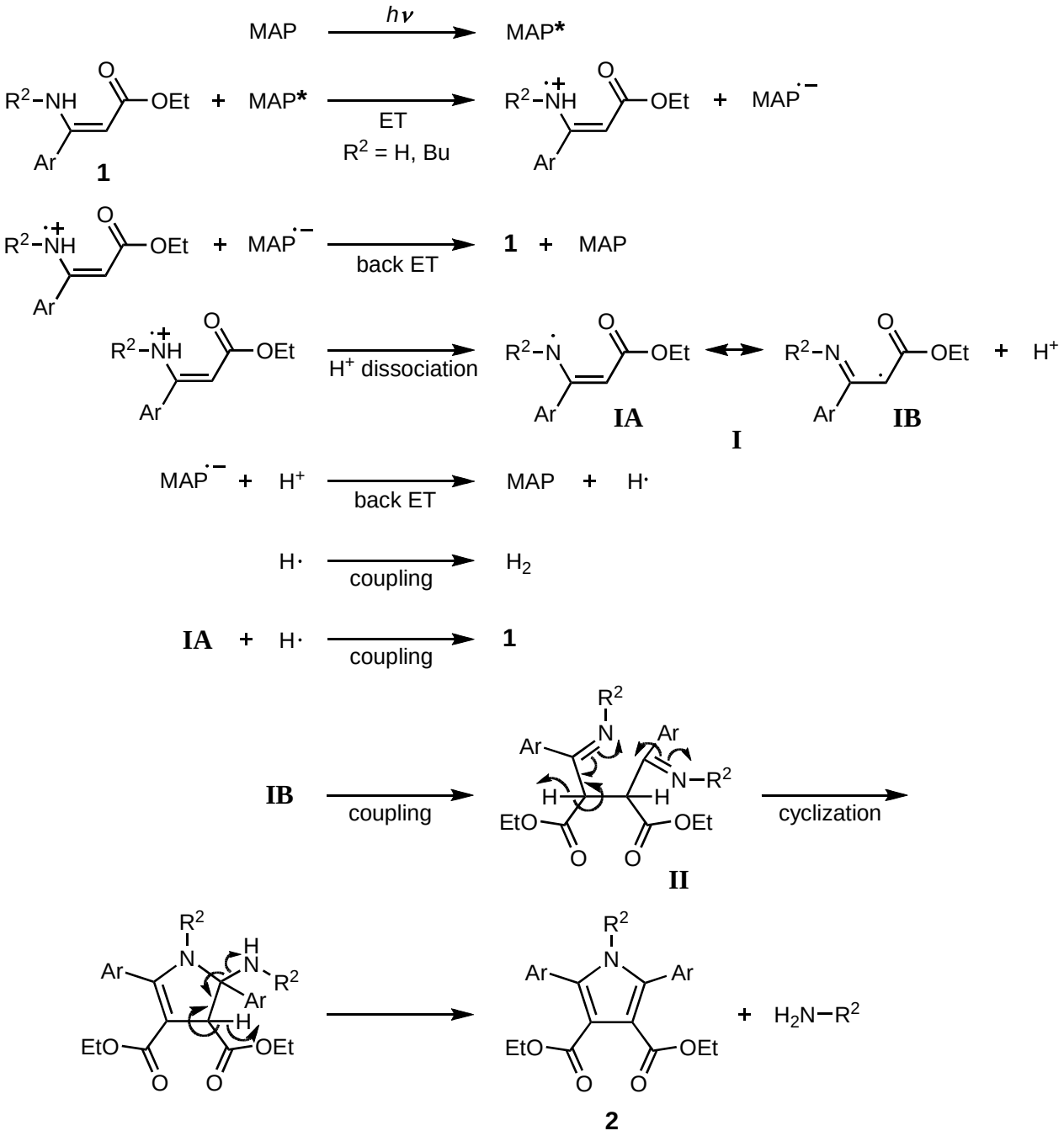


Figure 1. Stern–Volmer plot for the fluorescence quenching of MAP by **1a** in acetonitrile.



Scheme 2

On the basis of the previously discussed results of the ET fluorescence quenching, we propose a mechanism that explains the formation of the pyrrole derivatives **2a**–**g** (Scheme 2). As shown in Scheme 2, in competition with the regeneration of β-dehydroamino acid ester **1** by back ET from the MAP anion radical to the **1** cation radical, this strongly acidic cation radical formed in the primary process of the photosensitized reaction is dissociated into a proton and the imino radical **I**, in which the nitrogen-centered radical **IA** and the carbon-centered radical **IB** resonate with each other. The coupling reaction of the former imino radical with a hydrogen atom, which is produced by back ET from the MAP anion radical to the proton, regenerates the amino acid ester **1** to result in a decrease in the

sensitized reaction efficiency along with the back ET reaction that regenerates **1** and MAP. In addition, the coupling reaction of the latter imino radical that occurs in competition with the regeneration of **1** yields the dimerized intermediate **II**. The cyclization of this intermediate and the subsequent release of amine from the 2-pyrroline ring furnish the highly substituted pyrrole derivative **2**. No attempt was made to detect the liberated amine.

Although numerous thermal routes to pyrrole derivatives are known,[7] the number of photochemical routes to these derivatives is limited.[8] The procedure for the preparation of the variously substituted (*Z*)-β-dehydroarylalanine ethyl ester derivatives (*Z*)-**1a**–**g** is simple and readily applicable to their related compounds. Although prolonged irradiation is required to complete the PET reactions of **1** in the presence of MAP, the pyrrole photoproducts **2** that undergo only a small extent of secondary decomposition can be obtained in good to high yields by the brief post-treatment of the irradiated reaction mixtures. Therefore, the MAP-sensitized cyclization reaction of **1** provides a novel photochemical method for constructing the pyrrole ring, which is the structural unit of naturally occurring chlorophylls, porphyrins, and bilirubins.

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5. Data for (*Z*)-**1a**: oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.30 (3H, t, *J* = 7.5 Hz), 3.81 (6H, s), 4.18 (2H, q, *J* = 7.5 Hz), 4.95 (1H, s), 6.52 (1H, d, *J* = 2.5 Hz), 6.67 (2H, d, *J* = 2.5 Hz), 7.25 (1H, br

s), 8.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.6, 55.5 (2C), 58.9, 84.6, 102.1, 104.2 (2C), 139.8, 160.4, 161.0 (2C), 170.3.

Data for (*Z*)-**1g**: oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 0.85 (3H, t, *J* = 6.5 Hz), 1.28 (3H, t, *J* = 7.0 Hz), 1.30 (2H, tq, *J* = 6.5, 6.5 Hz), 1.46 (2H, tt, *J* = 6.5, 6.5 Hz), 3.08 (2H, dt, *J* = 6.5, 6.5 Hz), 3.84 (3H, s), 4.14 (2H, q, *J* = 7.0 Hz), 4.57 (1H, s), 6.90 (2H, d, *J* = 8.5 Hz), 7.29 (2H, d, *J* = 8.5 Hz), 8.53 (1H, t, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 13.7, 14.6, 19.8, 33.0, 44.3, 55.2, 58.5, 84.5, 113.6 (2C), 128.6, 129.2 (2C), 160.2, 165.0, 170.5.

6. Data for **2a**: 46% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.26 (6H, t, *J* = 7.5 Hz), 3.78 (12H, s), 4.25 (4H, q, *J* = 7.5 Hz), 6.45 (2H, d, *J* = 2.5 Hz), 6.71 (4H, d, *J* = 2.5 Hz), 8.76 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.1 (2C), 55.4 (4C), 60.7 (2C), 100.7 (2C), 106.3 (4C), 114.6 (2C), 132.5 (2C), 133.7 (2C), 160.7 (4C), 165.2 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{26}H_{29}NNaO_8$ $[M + Na]^+$: 506.19. Found: 505.99.

Data for **2b**: 41% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.25 (6H, t, *J* = 7.0 Hz), 3.81 (6H, s), 4.22 (4H, q, *J* = 7.0 Hz), 6.90 (4H, d, *J* = 9.0 Hz), 7.47 (4H, d, *J* = 9.0 Hz), 8.61 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.1 (2C), 55.3 (2C), 60.6 (2C), 113.5 (2C), 113.8 (4C), 123.3 (2C), 129.5 (4C), 134.1 (2C), 159.7 (2C), 165.4 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{24}H_{25}NNaO_6$ $[M + Na]^+$: 446.17. Found: 445.84.

Data for **2c**: 43% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.25 (6H, t, *J* = 7.0 Hz), 2.37 (6H, s), 4.23 (4H, q, *J* = 7.0 Hz), 7.20 (4H, d, *J* = 9.0 Hz), 7.43 (4H, d, *J* = 9.0 Hz), 8.51 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.1 (2C), 21.3 (2C), 60.6 (2C), 114.0 (2C), 128.0 (6C), 129.2 (4C), 134.2 (2C), 138.5 (2C), 165.3 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{24}H_{25}NNaO_4$ $[M + Na]^+$: 414.18. Found: 414.41.

Data for **2d**: 37% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.26 (6H, t, *J* = 7.5 Hz), 4.24 (4H, q, *J* = 7.5 Hz), 7.35–7.38 (2H, m), 7.39–7.44 (4H, m), 7.55–7.56 (4H, m), 8.57 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.0 (2C), 60.7 (2C), 114.5 (2C), 128.1 (4C), 128.5 (4C), 130.9 (2C), 134.2 (2C), 165.2 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{22}H_{21}NNaO_4$ $[M + Na]^+$: 386.15. Found: 385.93.

Data for **2e**: 49% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.27 (6H, t, *J* = 7.0 Hz), 4.26 (4H, q, *J* = 7.0 Hz), 7.39 (4H, d, *J* = 9.0 Hz), 7.50 (4H, d, *J* = 9.0 Hz), 8.69 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 13.7 (2C), 60.4 (2C), 114.5 (2C), 128.1 (4C), 129.2 (2C), 129.5 (6C), 133.9 (2C), 164.9 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{22}H_{19}Cl_2NNaO_4$ $[M + Na]^+$: 454.07. Found: 454.36.

Data for **2f**: 70% isolated yield; oily liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ= 1.26 (6H, t, *J* = 7.0 Hz), 4.23 (4H, q, *J* = 7.0 Hz), 7.59 (4H, d, *J* = 9.0 Hz), 7.66 (4H, d, *J* = 9.0 Hz), 9.92 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 13.9 (2C), 61.3 (2C), 111.6 (2C), 116.2 (2C), 128.7 (4C), 132.0 (6C), 133.0

(2C), 134.8 (2C), 164.7 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{24}H_{19}N_3NaO_4$ $[M + Na]^+$: 436.14. Found: 435.88.

Data for **2g**: 40% isolated yield; oily liquid; ^1H NMR (500 MHz, $CDCl_3$) δ = 0.55 (3H, t, J = 6.5 Hz), 0.87 (2H, tq, J = 6.5, 6.5 Hz), 1.14 (6H, t, J = 7.0 Hz), 1.15 (2H, tt, J = 6.5, 6.5 Hz), 3.67 (2H, t, J = 6.5 Hz), 3.87 (6H, s), 4.13 (4H, q, J = 7.0 Hz), 6.97 (4H, d, J = 9.0 Hz), 7.34 (4H, d, J = 9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 13.3, 14.0 (2C), 19.4, 32.4, 44.5, 55.3 (2C), 60.2 (2C), 113.6 (4C), 114.2 (2C), 123.4 (2C), 131.9 (4C), 136.1 (2C), 159.7 (2C), 165.1 (2C). MALDI TOF-MS *m*/*z* calcd for $C_{28}H_{33}NNaO_6$ $[M + Na]^+$: 502.23. Found: 502.56.

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