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AZULENO[6,5-*b*]INDOLES: PALLADIUM-CATALYZED OXIDATIVE RING-CLOSING REACTION OF 6-(ARYLAMINO)AZULENES

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Abstract – 6-Bromoazulene derivative with two *n*-butoxycarbonyl groups was prepared by the modification procedure of Nozoe's azulene synthesis. The aromatic nucleophilic substitution reaction of the 6-bromoazulene derivatives having two-ester functions with aniline derivatives proceeded to give the corresponding 6-(arylamino)azulene derivatives. Palladium-catalyzed oxidative ring-closing reaction of the 6-(arylamino)azulene derivatives provided the azuleno[6,5-*b*]indoles in moderate to good yields.

Dedicated to Professor Somsak Ruchirawat on the occasion of his 80th birthday

INTRODUCTION

Indole derivatives are important components of a number of natural products such as alkaloids and many bioactive and pharmaceutical compounds.¹ Therefore, their synthetic and modification methods of such compounds have been continually explored. Classically, indole derivatives have been prepared by the condensation of hydrazines with ketones under acidic conditions, following sequential [3,3]-sigmatropic rearrangement and eventual intramolecular cyclization reactions, so-called Fischer indole synthesis.² Meanwhile, in modern methods, transition metal-catalyzed reactions are frequently applied for the synthesis of indoles and their derivatives.³

Since azulene and its derivatives are of interest not only from the viewpoint of physical organic chemistry for their unique properties, but also as pharmaceuticals for their bioactivity,⁴ so that the numerous synthetic and modification methods have been developed to date.⁵ From the interest in material and medicinal chemistry, azulene derivatives incorporating the indole substructure have also been prepared by several groups (Figure 1). In 2012, our group reported the synthesis of indole-substituted azulene derivatives **A** at the 1- or 1,3-positions, which was achieved by a Vilsmeier-type reaction using 2-indolinones and triflic anhydride (Tf₂O).⁶ Meanwhile, several synthetic methods for indole-fused azulene derivatives have been reported in the literature. In 2007, Yamamura *et al.* reported the synthesis of azuleno[1,2-*b*]indole **B** and azuleno[2,1-*b*]indole **C** by the ionization of the tropylium group of methylfuryl-2-tropyliindoles followed by intramolecular nucleophilic ring-opening reaction of the furan ring.⁷ More recently, the synthesis of guaiazulene-fused indole by Cadogan cyclization has been reported by Gao and Swager,⁸ in which guaiazulene with an *o*-nitrophenyl group at the 2-position reacts with triphenylphosphine under the microwave irradiation conditions to form azulenoindole **D**.

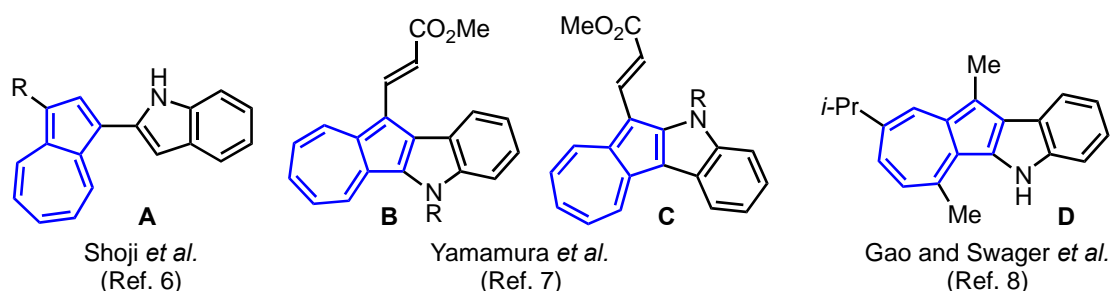
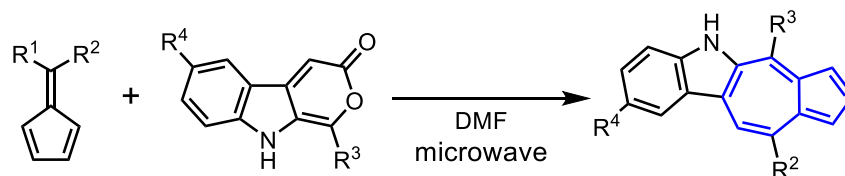


Figure 1. Azulene-substituted and fused indole derivatives reported in the literature

The preparation of azulenoindole derivatives, in which indole is fused at the seven-membered ring of azulene, was reported by Hong *et al.* (Scheme 1). In their study, azuleno[5,6-*b*]indoles were prepared by microwave-assisted [6 + 4] cycloaddition of 6-dimethylaminofulvene with indole-fused α -pyrone and their antitumor activities were also evaluated.⁹ As a result, the prepared azuleno[5,6-*b*]indoles revealed good antitumor activity against a variety of cancer cells (melanoma, leukemia, lung, colon, renal, ovarian, brain, breast and prostate). However, this is the only one report for the preparation of indole-fused azulene derivatives at the seven-membered ring. Thus, there is no report for the synthesis of their derivatives utilizing more readily available azulene derivatives as starting materials. Therefore, the development of the new synthetic methods for the azulenoindoles using azulene derivatives as precursors could contribute to the progress of medicinal chemistry.

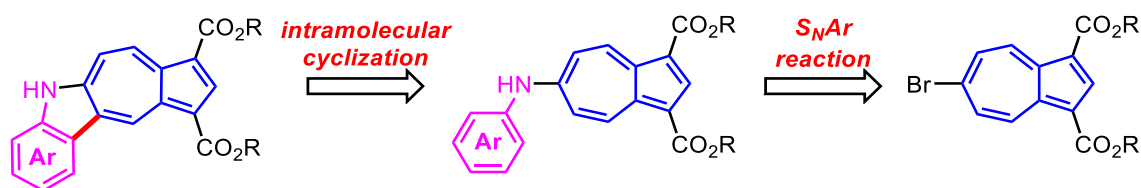


Scheme 1. Synthesis of azuleno[5,6-*b*]indoles by microwave-assisted [6 + 4] cycloaddition of 6-dimethylaminofulvene with indole-fused α -pyrone derivatives

In this paper, we describe the synthesis of azuleno[6,5-*b*]indoles *via* palladium-catalyzed oxidative ring-closing reaction of 6-(arylamino)azulenes, which were prepared from 6-bromoazulenes by aromatic nucleophilic substitution (S_NAr) reaction with aniline derivatives.

RESULTS AND DISCUSSION

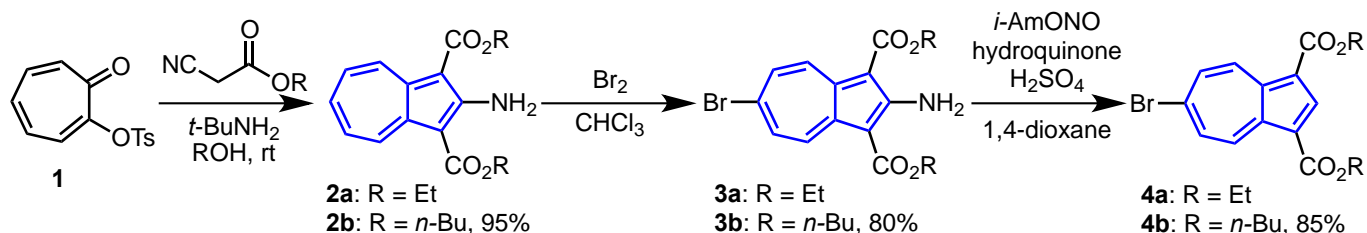
In 2008, Fagnou *et al.* reported a new oxidative carbon-carbon bond formation reaction in which diarylamines can be converted to carbazoles using palladium(II) catalyst, i.e., palladium acetate [$Pd(OAc)_2$], in pivalic acid (PivOH) as the solvent under the aerobic conditions.¹⁰ This reaction is versatile and applicable to the synthesis of natural products, so that we adapted this approach to the synthesis of indole-fused azulene derivatives at the seven-membered ring. The overview of the planned synthetic pathway is shown in Scheme 2. The preparation of the precursors, 6-(arylamino)azulenes and 6-haloazulenes, was initially investigated prior to the implementation of the palladium-catalyzed cyclization reaction.



Scheme 2. Planned synthetic pathway to azuleno[6,5-*b*]indoles

Synthesis of 6-bromoazulenes: As appropriate precursors for the synthesis of azuleno[6,5-*b*]indoles, we selected the 6-bromoazulenes with two ester groups at the 1,3-positions, because they could be utilized amination reaction by aromatic nucleophilic substitution (S_NAr) at the 6-position.¹¹ 6-Bromoazulene **4a** with two ethyl ester groups was prepared according to the method reported by Nozoe *et al.* in three step protocol using tosyloxytropone (**1**) as a starting material (Scheme 3).¹² The synthesis of the butyl ester derivative **4b** was accomplished in a similar manner. The reaction of **1** with butyl cyanoacetate in the presence of *tert*-butylamine (*t*-BuNH₂) gave the 2-aminoazulene derivative **2b** in high yield. The solubility of **2b** in organic solvents was higher than that of **2a** owing to the substituted two

butoxycarbonyl substituents. Bromination at the 6-position of the azulene ring was attained by the treatment of **2b** with Br₂ in chloroform as a solvent, affording **3b** in 80% yield. Since compound **3a** is relatively insoluble toward the reaction solvent, the product can be easily obtained in high purity by the simple filtration of the generated precipitate after the completion of the reaction. On the other hand, **3b** did not show precipitation in the reaction solvent during the reaction and thus required a tedious work-up process, such as extraction and chromatographic purification. The eventual deamination of **3b** proceeded under Sandmeyer condition to provide **4b** in 85% yield.



Scheme 3. Synthesis of 6-bromoazulenes **4a** and **4b** with two ester functions from tosyloxypyrone (**1**)

Synthesis of 6-(arylamino)azulenes by S_NAr reaction: The obtained 6-bromoazulenes **4a** and **4b** were used as starting materials for the transformation to 6-(arylamino)azulenes via S_NAr substitution reaction with aniline derivatives. The product yields for the S_NAr reaction are summarized in Table 1. We have previously reported that a similar reaction does not proceed in toluene as a solvent, resulting in the recovery of the starting material **4a**.¹³ However, we found the S_NAr reaction of **4a** with *p*-toluidine in ethanol under reflux conditions afforded **5a** in 68% yield. Therefore, we selected ethanol as the suitable solvent for the S_NAr reaction of **4a** and **4b** and examined the generality by utilizing two other aniline derivatives. Compound **6a** was obtained in excellent yield (91%) by the reaction of **4a** with *p*-anisidine. Whereas the yield of the product **7a** by the reaction of **4a** with 3,4,5-trimethoxyaniline was only 36%. A similar reaction was also examined in DMSO and DMF as the solvent, but only complete decomposition proceeded in these solvents, and no obvious product could be obtained. The S_NAr reaction of the butoxy ester derivative **4b** with *p*-anisidine and 3,4,5-trimethoxyaniline was also performed and the reaction provided **6b** and **7b** in 74% and 65% yields, respectively. Compounds **5a–7a** were relatively insoluble in common organic solvents (hexane, toluene, ethyl acetate, methanol and so on), whereas **6b** and **7b** showed high solubility because of the presence of the long alkoxy groups in the ester functions (i.e., two butoxycarbonyl groups).

Table 1. Synthesis of 6-(arylamino)azulenes by the S_NAr reaction with aniline derivatives

4a
4b

EtOH
reflux

5a–7a: R = Et
6b and 7b: R = *n*-Bu

entry	substrate		Product, yield [%]
1	4a		5a , 68
2	4a		6a , 91
3	4a		7a , 36
4	4b		6b , 74
5	4b		7b , 65

Synthesis of azuleno[6,5-*b*]indoles by metal-catalyzed ring-closing reaction: Next, the transformation to azuleno[6,5-*b*]indoles by the ring-closing reaction of the obtained 6-(arylamino)azulenes was investigated. The product yields for the ring-closing reaction are summarized in Table 2. Initially, the oxidative ring-closing reaction of **5a** was conducted under the same conditions as those of Fagnou *et al.* However, the reaction resulted in the recovery of the starting material due to the low solubility of **5a** toward PivOH as the solvent. To resolve this problem, a small amount of toluene was used as an auxiliary solvent, but the reaction was also resulted in the recovery of the starting material **5a**. Since the nature of the substituted aryl group might be responsible for the low reactivity, we investigated the same reaction by utilizing **6a** and **7a**, both of which have more electron-rich aryl groups. As a result, azuleno[6,5-*b*]indoles **8a** and **9a** could be obtained by the oxidative ring-closing reaction, although the product yields were moderate in these cases (**8a**: 35%, **9a**: 41%).

However, the low solubility problem was not fully resolved even with a toluene addition, so that the ring-closing reaction was performed by using **6b** and **7b**, which have longer alkoxy groups in the ester

functions that showed high solubility to PivOH. As expected, **6b** and **7b** could be completely dissolved in PivOH under the reaction conditions and giving azuleno[6,5-*b*]indoles **8b** and **9b** in 81% and 21% yields, respectively. Since significant decomposition was observed in the reaction of **7b**, the low yield of **9b** should be ascribed to the result on the undesirable over oxidation reaction derived from the electron-rich trimethoxybenzene moiety under the highly soluble conditions.

Table 2. Synthesis of azuleno[6,5-*b*]indoles by palladium-catalyzed oxidative ring-closing reaction

Pd(OAc)_2
 K_2CO_3
 PivOH, O_2
 $110\text{ }^\circ\text{C}$

5a–7a: R = Et
6b, 7b: R = *n*-Bu

8a, 9a: R = Et
8b, 9b: R = *n*-Bu

entry	substrate		Product, yield [%]
1 ^a	5a		no reaction
2 ^a	6a		8a , 35
3 ^a	7a		9a , 41
4	6b		8b , 81
5	7b		9b , 21

^a Small amount of toluene was employed as an auxiliary solvent.

CONCLUSION

In conclusion, we have demonstrated herein the first synthesis of azuleno[6,5-*b*]indoles *via* palladium-catalyzed intramolecular ring-closing reaction. The 6-bromoazulene derivative **4b** with longer alkoxy groups in the ester functions were prepared by an improved method of Nozoe's protocol, i.e., the reaction of tosyloxypone (**1**) with *n*-butyl cyanoacetate in the presence of *t*-BuNH₂ and the subsequent bromination and deamination reactions. The S_NAr reaction of 6-bromoazulenes **4a** and **4b** with aniline

derivatives gave the corresponding 6-(arylamino)azulenes **5a**, **6a,b** and **7a,b**, which could be converted to azuleno[6,5-*b*]indoles by palladium-catalyzed oxidative ring-closing reaction, except for **5a**. Although there are several limitations on the method we have presented in this paper, such as the low solubility of the starting material and the tolerability of substituents on the aryl group, the procedure should be the straightforward way to obtain azuleno[6,5-*b*]indoles for which no synthetic route has existed so far. To overcome these problems the more efficient synthetic procedure for the azuleno[6,5-*b*]indoles is currently under investigation in our laboratory.

EXPERIMENTAL

General. Melting points were determined with a Yanagimoto MPS3 micro melting apparatus and are uncorrected. High-resolution mass spectra were obtained with AB SCIEX TOF/TOF 5800 instrument (dithranol as a matrix substance and/or CF₃CO₂Ag as an auxiliary agent). IR spectrum was measured with JASCO FT/IR-4100 spectrophotometer. ¹H and ¹³C NMR spectra were recorded in CDCl₃ with a JEOL ECA500 at 500 MHz and 125 MHz, respectively.

Compound 2b: *n*-Butyl cyanoacetate (31.0 g, 220 mmol) in *tert*-butylamine (30 mL) was added to a solution of 2-tosyloxypone (**1**) (27.6 g, 100 mmol) in 1-butanol (300 mL) and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice-cooled water and the generated precipitate was collected by filtration to give **2b** (32.6 g, 95%) as yellow crystals. Mp 63–64 °C; IR (AT-IR): ν_{\max} = 3485 (w), 3343 (w), 2957 (w), 2930 (w), 2871 (w), 1682 (m), 1660 (s), 1597 (s), 1575 (m), 1528 (w), 1509 (m), 1496 (m), 1473 (w), 1458 (w), 1426 (m), 1413 (w), 1395 (w), 1375 (w), 1336 (w), 1317 (w), 1278 (w), 1264 (w), 1232 (m), 1204 (w), 1171 (s), 1149 (m), 1110 (s), 1100 (m), 1063 (w), 1038 (w), 998 (w), 975 (w), 951 (w), 915 (w), 887 (w), 865 (w), 847 (w), 807 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ_{H} = 9.15 (d, *J* = 10.3 Hz, 2H, H-4,8), 7.79 (s, 2H, NH₂), 7.54 (t, *J* = 10.3 Hz, 2H, H-5,7), 7.43 (t, *J* = 10.3 Hz, 1H, H-6), 4.41 (t, *J* = 7.4 Hz, 3H, CO₂*n*-Bu), 1.83 (quint, *J* = 7.4 Hz, 3H, CO₂*n*-Bu), 1.53 (sext, *J* = 7.4 Hz, 3H, CO₂*n*-Bu), 1.01 (t, *J* = 7.4 Hz, 4H, CO₂*n*-Bu) ppm; ¹³C NMR (125 MHz, CDCl₃): δ_{C} = 166.76, 162.57, 146.24, 132.95, 132.72, 131.49, 99.94, 63.85, 31.13, 19.60, 13.92 ppm; HRMS (MALDI-TOF, positive): calcd for C₂₀H₂₅NO₄ + H⁺ [M + H]⁺, 344.1856; found: 344.1263; HRMS (MALDI-TOF, positive): calcd for C₂₀H₂₅NO₄ + Ag⁺ [M + Ag]⁺, 450.0829; found: 450.0171.

Compound 3b: Bromine (98.0 g, 66.1 mmol) in CHCl₃ (30 mL) was added to a solution of **2b** (10.8 g, 31.5 mmol) in CHCl₃ (95 mL) and the resulting mixture was stirred at room temperature for 12 h. The

reaction mixture was poured into sat. Na_2SO_3 and extracted with CHCl_3 . The organic layer was washed with brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with toluene/AcOEt (4:1) to give **3b** (10.6 g, 80%) as orange crystals. Mp 110–112 °C; IR (AT-IR): ν_{max} = 3486 (w), 3349 (w), 2956 (w), 2928 (w), 2870 (w), 1685 (m), 1660 (m), 1596 (s), 1577 (m), 1521 (m), 1500 (m), 1471 (m), 1424 (m), 1374 (m), 1326 (w), 1280 (w), 1236 (m), 1165 (s), 1133 (m), 1110 (m), 1079 (m), 1062 (m), 1035 (m), 1008 (m), 987 (w), 943 (w), 919 (w), 890 (w), 876 (w), 858 (w), 835 (m) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ_{H} = 8.80 (d, J = 11.6 Hz, 2H, H-4,8), 7.80 (br.s, NH_2), 7.78 (d, J = 11.6 Hz, 2H, H-5,7), 4.39 (t, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.81 (quint, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.51 (sext, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.01 (t, J = 7.4 Hz, 6H, $\text{CO}_2n\text{-Bu}$) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ_{C} = 166.41, 162.44, 144.39, 135.37, 129.49, 128.41, 101.14, 77.37, 77.11, 76.86, 64.07, 31.07, 19.60, 13.91 ppm; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{20}\text{H}_{24}\text{BrNO}_4 + \text{H}^+ [\text{M} + \text{H}]^+$, 422.0961; found: 422.0392.

Compound 4b: The mixture of **3b** (3.58 g, 8.47 mmol), hydroquinone (1.04 g, 9.45 mmol), and H_2SO_4 (0.5 mL) was dissolved in mixed solvent of 1,4-dioxane (210 mL) and THF (16.5 mL). The solutions of hydroquinone (18.9 g, 171 mmol) in 1,4-dioxane (186 mL) and isopentyl nitrite (21.0 g, 179 mmol) in 1,4-dioxane (62 mL) were added dropwise to the mixture at the same time and the resulting solution was stirred at room temperature for 17 h. The reaction mixture was added sat. Na_2SO_3 (500 mL) and the generated precipitate was collected by filtration to give **4b** (2.93 g, 85%) as red solid. Mp 117–118 °C; IR (AT-IR): ν_{max} = 3491 (w), 3334 (w), 3064 (w), 2958 (w), 2872 (w), 1680 (s), 1606 (w), 1568 (w), 1552 (w), 1524 (w), 1506 (w), 1428 (s), 1389 (w), 1361 (w), 1299 (w), 1238 (w), 1205 (s), 1168 (w), 1115 (w), 1067 (m), 1035 (m), 1011 (m), 972 (w), 910 (w), 876 (w), 853 (m), cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ_{H} = 9.49 (d, J = 11.2 Hz, 2H, H-4,8), 8.80 (s, 1H, H-2), 8.03 (d, J = 11.2 Hz, 2H, H-5,7), 4.38 (t, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.81 (quint, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.52 (sext, J = 7.4 Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.01 (t, J = 7.4 Hz, 6H, $\text{CO}_2n\text{-Bu}$) ppm; ^{13}C NMR (125 MHz, CDCl_3): δ_{C} = 164.85, 143.69, 142.30, 138.61, 137.32, 133.81, 117.95, 64.32, 31.05, 19.46, 13.91 ppm; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{20}\text{H}_{23}\text{BrO}_4 + \text{H}^+ [\text{M} + \text{H}]^+$, 407.0852; found: 407.0309; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{20}\text{H}_{23}\text{BrO}_4 + \text{Ag}^+ [\text{M} + \text{Ag}]^+$, 512.9825; found: 512.9586.

Compound 6a: 4-Methoxyaniline (*p*-anisidine) (2.10 g, 20.9 mmol) was added to a solution of **4a** (2.71 g, 7.73 mmol) in EtOH (60 mL) and the resulting mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and generated precipitate was collected by filtration to give **6a** (2.78 g, 91%) as orange solid. Mp 209–210 °C; IR (AT-IR): ν_{max} = 3275 (m), 3069 (w), 2988 (w), 2950 (w), 1679 (m), 1656 (s), 1614 (w), 1588 (m), 1577 (m), 1547 (w), 1509 (m), 1475 (w), 1463 (m), 1427 (s), 1387 (m),

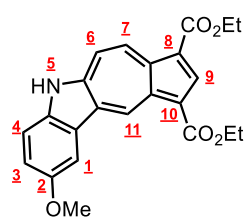
1374 (m), 1352 (m), 1333 (m), 1305 (m), 1270 (w), 1246 (m), 1228 (s), 1200 (s), 1172 (m), 1146 (m), 1102 (m), 1038 (s), 1001 (m), 962 (w), 939 (w), 904 (w), 887 (w), 865 (w), 837 (m), 810 (m) (w) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta_{\text{H}} = 9.33$ (d, $J = 11.5$ Hz, 2H, H-4,8), 8.31 (s, 1H, H-2), 7.20 (m, 3H, H_{meta} of Ar and NH), 7.02 (d, $J = 11.5$ Hz, 2H, H-5,7), 6.95 (d, $J = 8.6$ Hz, 2H, H_{ortho} of Ar), 4.35 (q, $J = 7.1$ Hz, 4H, CO_2Et), 3.84 (s, 3H, OMe), 1.39 (t, $J = 7.1$ Hz, 6H, CO_2Et) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta_{\text{C}} = 165.90, 158.78, 158.62, 139.29, 137.15, 136.15, 130.75, 126.87, 116.22, 116.01, 115.27, 59.71, 55.66, 14.68$ ppm; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_5 - \text{H}^+$ $[\text{M} - \text{H}]^+$, 392.1492; found: 392.0928; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_5 + \text{Ag}^+$ $[\text{M} + \text{Ag}]^+$, 500.0622; found: 500.0595.

Compound 6b: 4-Methoxyaniline (*p*-anisidine) (256 mg, 2.08 mmol) was added to a solution of **4b** (408 mg, 1.00 mmol) in EtOH (5 mL) and the resulting mixture was refluxed for 18 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with $\text{CHCl}_3/\text{AcOEt}$ (10:1) as an eluent to give **6b** (333 mg, 74%) as orange solid. Mp 113–114 °C; IR (AT-IR): $\nu_{\text{max}} = 3318$ (w), 2958 (w), 1683 (w), 1660 (m), 1613 (w), 1588 (m), 1537 (w), 1509 (m), 1459 (w), 1432 (s), 1386 (w), 1371 (m), 1334 (m), 1304 (w), 1261 (w), 1248 (m), 1223 (m), 1196 (s), 1146 (m), 1103 (m), 1065 (w), 1041 (s), 1015 (m), 958 (w), 904 (w), 870 (w), 832 (m) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta_{\text{H}} = 9.32$ (d, $J = 11.7$ Hz, 2H, H-4,8), 8.28 (s, 1H, H-2), 7.41 (s, 1H, NH), 7.19 (dd, $J = 6.7, 2.2$ Hz, 2H, H_{meta} of Ar), 7.04 (d, $J = 11.7$ Hz, 2H, H-5,7), 6.93 (dd, $J = 6.7, 2.2$ Hz, 2H, H_{ortho} of Ar), 4.28 (t, $J = 7.5$ Hz, 4H, $\text{CO}_2n\text{-Bu}$), 3.83 (s, 3H, OMe), 1.75 (quint, $J = 7.5$ Hz, 4H, $\text{CO}_2n\text{-Bu}$), 1.47 (sext, $J = 7.5$ Hz, 4H, $\text{CO}_2n\text{-Bu}$), 0.97 (t, $J = 7.5$ Hz, 6H, $\text{CO}_2n\text{-Bu}$) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta_{\text{C}} = 166.04, 158.92, 158.57, 139.27, 137.09, 136.01, 130.80, 126.81, 116.27, 115.99, 115.24, 63.69, 55.64, 31.13, 19.46, 13.93$ ppm; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_5 + \text{H}^+$ $[\text{M} + \text{H}]^+$, 450.2275; found: 450.2204; HRMS (MALDI-TOF, positive): calcd for $\text{C}_{27}\text{H}_{31}\text{NO}_5 + \text{Ag}^+$ $[\text{M} + \text{Ag}]^+$, 556.1248; found: 556.1180.

Compound 7a: 3,4,5-Trimethoxyaniline (729 mg, 3.98 mmol) was added to a solution of **4a** (714 mg, 2.03 mmol) in EtOH (25 mL) and the resulting mixture was refluxed for 16 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with $\text{CHCl}_3/\text{AcOEt}$ (10:1) as an eluent to give **7a** (327 mg, 36%) as orange solid. Mp 192–193 °C; IR (AT-IR): $\nu_{\text{max}} = 3301$ (w), 3287 (w), 2980 (w), 2939 (w), 1660 (m), 1601 (m), 1578 (m), 1550 (w), 1504 (m), 1462 (m), 1430 (s), 1389 (m), 1374 (m), 1352 (m), 1313 (m), 1262 (w), 1201 (s), 1158 (m), 1127 (s), 1103 (m), 1041 (m), 992 (m), 903 (w), 841 (m), 822 (w), 807 (w) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta_{\text{H}} = 9.37$ (d, $J = 11.4$ Hz, 2H, H-4,8), 8.33 (s, 1H, H-2), 7.20 (s, 1H, NH), 7.10 (d, $J = 11.4$ Hz, 2H, H-5,7),

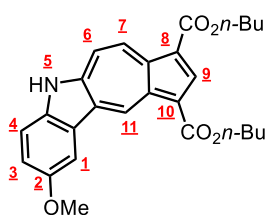
6.51 (s, 2H, Ar), 4.36 (q, $J = 7.2$ Hz, 4H, CO₂Et), 3.88 (s, 3H, OMe), 3.81 (s, 6H, OMe), 1.40 (t, $J = 7.2$ Hz, 6H, CO₂Et) ppm; ¹³C NMR (125 MHz, CDCl₃): $\delta_C = 165.86, 158.00, 154.28, 139.29, 137.44, 136.95, 136.53, 133.99, 116.62, 116.13, 102.30, 61.13, 59.78, 56.35, 14.68$ ppm; HRMS (MALDI-TOF, positive): calcd for C₂₅H₂₇NO₇ [M + H]⁺, 454.1860; found: 454.1534; HRMS (MALDI-TOF, positive): calcd for C₂₅H₂₇NO₇ + Ag⁺ [M + Ag]⁺, 560.0833; found: 560.0434.

Compound 7b: 3,4,5-Trimethoxyaniline (736 mg, 4.02 mmol) was added to a solution of **4b** (817 mg, 2.01 mmol) in EtOH (15 mL) and the resulting mixture was refluxed for 17 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl₃ (10:1) as an eluent to give **7b** (660 mg, 65%) as orange solid. Mp 140–142 °C; IR (AT-IR): $\nu_{\max} = 3269$ (w), 2947 (w), 1677 (m), 1652 (m), 1604 (m), 1577 (m), 1548 (w), 1505 (m), 1458 (m), 1425 (s), 1390 (m), 1371 (m), 1315 (m), 1302 (m), 1268 (w), 1200 (s), 1161 (m), 1125 (m), 1099 (m), 1043 (m), 1015 (m), 998 (m), 925 (w), 901 (w), 840 (m), 820 (w) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): $\delta_H = 9.39$ (d, $J = 11.7$ Hz, 2H, H-4,8), 8.33 (s, 1H, H-2), 7.10 (d, $J = 11.7$, 2H, H-5,7), 7.00 (s, 1H, NH), 6.53 (s, 2H, Ar), 4.31 (t, $J = 7.5$ Hz, 4H, CO_{2n}-Bu), 3.89 (s, 3H, OMe), 3.83 (s, 6H, OMe), 1.77 (quint., $J = 7.5$ Hz, 4H, CO_{2n}-Bu), 1.49 (sext, $J = 7.5$ Hz, 4H, CO_{2n}-Bu), 0.98 (t, $J = 7.5$ Hz, 6H, CO_{2n}-Bu) ppm; ¹³C NMR (125 MHz, CDCl₃): $\delta_C = 166.04, 158.92, 158.57, 139.27, 137.09, 136.01, 130.80, 126.81, 116.27, 115.99, 115.24, 63.69, 55.64, 31.13, 19.46, 13.93$ ppm; HRMS (MALDI-TOF, positive): calcd for C₂₉H₃₅NO₇ + H⁺ [M + H]⁺, 510.2486; found: 510.1724; HRMS (MALDI-TOF, positive): calcd for C₂₉H₃₅NO₇ + Ag⁺ [M + Ag]⁺, 616.1459; found: 616.0754.



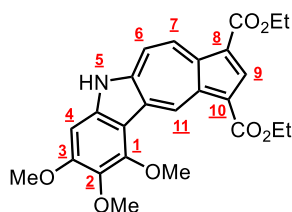
Compound 8a: A solution of **6a** (393 mg, 1.00 mmol), Pd(OAc)₂ (43 mg, 0.193 mmol), K₂CO₃ (28 mg, 0.202 mmol) in pivalic acid (2 mL) and toluene (8 mL) was stirred at 110 °C for 43 h under an O₂ atmosphere. The reaction mixture was cooled to room temperature and generated precipitate was collected by filtration. The precipitate was washed with sat. K₂CO₃ solution to give compound **8a** (117 mg, 30%) as orange solid. The filtrate was also extracted with toluene, washed with brine and dried with Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl₃ (10:1) as an eluent to give **8a** (20 mg, 5%). Overall yield of **8a** was 35% yield (137 mg). Mp 280–282 °C; IR (AT-IR): $\nu_{\max} = 3247$ (w), 2979 (w), 2905 (w), 1644 (s), 1602 (w), 1556 (w), 1510 (m), 1480 (m), 1463 (w), 1426 (m), 1385 (m), 1359 (w), 1314 (m), 1299 (m), 1272 (w), 1219 (s), 1139 (m), 1106 (m), 1045 (m), 1030 (m), 1005 (w), 986 (w), 938 (w), 834 (m) cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): $\delta_H = 10.43$ (s, 1H, H-11), 9.49 (d, $J = 11.2$ Hz, 1H, H-7), 8.29 (s, 1H, H-9), 7.99 (d, $J = 10.9$ Hz, 1H, H-6), 7.62–7.67 (m, 2H, H-3,4), 7.26 (dd, $J = 8.9, 2.6$ Hz, 1H, H-3), 4.35 (q, $J = 7.1$ Hz, 2H,

CO₂Et), 4.31 (d, $J = 7.2$ Hz, 2H, CO₂Et), 3.93 (s, 3H, OMe), 1.40 (t, $J = 7.2$ Hz, 3H, CO₂Et), 1.35 (t, $J = 7.1$ Hz, 3H, CO₂Et) ppm; ¹³C NMR (125 MHz, DMSO-*d*₆): $\delta_C = 165.20, 165.15, 155.91, 147.62, 138.61, 136.50, 134.51, 134.13, 133.87, 132.61, 126.68, 123.37, 118.54, 117.36, 115.47, 115.06, 113.81, 101.88, 59.95, 59.83, 56.12, 15.03, 14.99$ ppm; HRMS (MALDI-TOF, positive): calcd for C₂₃H₂₁NO₅ [M]⁺, 391.1420; found: 391.1420; HRMS (MALDI-TOF, positive): calcd for C₂₃H₂₁NO₅ + Ag⁺ [M + Ag]⁺, 498.0465; found: 497.9760.



Compound 8b: A solution of **6b** (115 mg, 0.255 mmol), Pd(OAc)₂ (12 mg, 0.0526 mmol), K₂CO₃ (7 mg, 0.0523 mmol) in pivalic acid (1.4 mL) and toluene (8 mL) was stirred at 110 °C for 17 h under an O₂ atmosphere. The reaction mixture was cooled to room temperature and generated precipitate was collected by filtration.

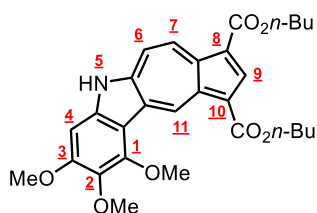
The precipitate was washed with sat. K₂CO₃ solution to give **8b** (92 mg, 81%) as orange solid. Mp 238–239 °C; IR (AT-IR): $\nu_{\max} = 3243$ (w), 2960 (w), 2874 (w), 1681 (m), 1646 (s), 1595 (w), 1553 (w), 1508 (m), 1474 (m), 1458 (m), 1437 (m), 1383 (m), 1351 (w), 1305 (m), 1271 (w), 1227 (s), 1187 (m), 1141 (m), 1103 (m), 1068 (w), 1033 (m), 981 (w), 938 (w), 898 (w), 833 (m), 810 (m), 787 (m), 764 (m), 744 (w), 725 (w), 713 (w), 665 (w) cm⁻¹; ¹H NMR (500 MHz, , CDCl₃) $\delta_H = 10.67$ (s, 1H, H-11), 9.72 (d, $J = 11.2$ Hz, 1H, H-7), 9.15 (s, 1H, NH), 8.63 (s, 1H, H-9), 7.84 (d, $J = 2.3$ Hz, 1H, H-1), 7.79 (d, $J = 11.2$ Hz, 1H, H-6), 7.48 (d, $J = 8.6$ Hz, 1H, H-4), 7.23 (dd, $J = 8.6, 2.3$ Hz, 1H, H-3), 4.42 (m, 4H, CO₂*n*-Bu), 3.99 (s, 3H, OMe), 1.80–1.91 (m, 4H, CO₂*n*-Bu), 1.52–1.61 (m, 4H, CO₂*n*-Bu), 1.01–1.05 (m, 6H, CO₂*n*-Bu) ppm; ¹³C NMR (125 MHz, CDCl₃): $\delta_C = 166.16, 166.02, 156.09, 146.45, 139.42, 138.22, 136.12, 134.17, 133.30, 132.91, 127.34, 123.61, 118.34, 116.61, 115.88, 115.62, 112.06, 102.38, 63.87, 56.19, 31.23, 31.20, 19.56, 19.53, 13.97$ ppm; HRMS (MALDI-TOF, positive): calcd for C₂₇H₂₉NO₅ + [M]⁺, 447.2046; found: 447.1304; HRMS (MALDI-TOF, positive): calcd for C₂₇H₂₉NO₅ + Ag⁺ [M + Ag]⁺, 554.1091; found: 554.0253.



Compound 9a: A solution of **7a** (113 mg, 0.249 mmol), Pd(OAc)₂ (12 mg, 0.0519 mmol), K₂CO₃ (7 mg, 0.0509 mmol) in pivalic acid (0.5 mL) and toluene (1 mL) was stirred at 110 °C for 15 h under an O₂ atmosphere. The reaction mixture was cooled to room temperature, dissolved in CHCl₃ and insoluble matter was separated by filtration. The filtrate was poured into sat. K₂CO₃ and

extracted with CHCl₃. The organic layer was washed with brine and dried with Na₂SO₄. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with CHCl₃/AcOEt (10:1) as an eluent to give **9a** (46 mg, 41%) as orange solid. Mp 178–180 °C; IR (AT-IR): $\nu_{\max} = 3518$ (w), 3366 (w), 2989 (w), 2942 (w), 1627 (m), 1570 (w), 1504 (m), 1468 (m), 1421

(s), 1401 (w), 1384 (m), 1352 (w), 1318 (s), 1289 (w), 1275 (m), 1253 (w), 1212 (s), 1200 (s), 1181 (s), 1153 (w), 1136 (m), 1118 (m), 1105 (m), 1065 (s), 1038 (m), 993 (m), 981 (m), 944 (w), 925 (w), 851 (w) cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): $\delta_{\text{H}} = 11.06$ (s, 1H, H-11), 9.82 (s, 1H, NH), 9.58 (d, $J = 11.2$ Hz, 1H, H-7), 8.63 (s, 1H, H-9), 7.70 (d, $J = 11.2$ Hz, 1H, H-6), 6.57 (s, 1H, H-4), 4.49 (q, $J = 7.2$ Hz, 2H, CO_2Et), 4.43 (q, $J = 7.2$ Hz, 2H, CO_2Et), 4.29 (s, 3H, OMe), 3.91 (s, 3H, OMe), 3.82 (s, 3H, OMe), 1.44–1.49 (m, 6H, CO_2Et) ppm; ^{13}C NMR (125 MHz, CDCl_3): $\delta_{\text{C}} = 166.26, 166.02, 155.39, 149.62, 146.09, 139.24, 137.99, 136.95, 136.05, 135.69, 132.26, 124.34, 115.45, 115.25, 115.16, 112.30, 89.53, 61.62, 61.07, 59.88, 59.82, 56.26, 14.81, 14.75$ ppm; HRMS (MALDI–TOF, positive): calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_7$ $[\text{M} + \text{H}]^+$, 451.1631; found: 451.1334; HRMS (MALDI–TOF, positive): calcd for $\text{C}_{25}\text{H}_{25}\text{NO}_7 + \text{Ag}^+$ $[\text{M} + \text{Ag}]^+$, 558.0676; found: 558.0328.



Compound 9b: A solution of **7b** (130 mg, 0.255 mmol), $\text{Pd}(\text{OAc})_2$ (12 mg, 0.0517 mmol), K_2CO_3 (7 mg, 0.0511 mmol) in pivalic acid (1.5 mL) was stirred at 110 °C for 20 h under an O_2 atmosphere. The reaction mixture was cooled to room temperature, dissolved in CHCl_3 and insoluble matter was separated by filtration. The filtrate was poured into sat. K_2CO_3 and extracted with CHCl_3 . The organic layer was washed with brine and dried with Na_2SO_4 . The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel with $\text{CHCl}_3/\text{AcOEt}$ (10:1) as an eluent to give **9b** (27 mg, 21%) as orange solid. Mp 154–156 °C; IR (AT–IR): $\nu_{\text{max}} = 3273$ (w), 2958 (w), 2872 (w), 1685 (m), 1658 (m), 1626 (m), 1578 (m), 1503 (m), 1463 (m), 1420 (s), 1378 (m), 1356 (m), 1315 (m), 1287 (m), 1267 (m), 1212 (s), 1200 (s), 1153 (m), 1130 (m), 1103 (m), 1063 (m), 1041 (m), 1014 (m), 996 (m), 956 (w), 926 (w), 885 (w), 839 (m), 785 (m), 768 (m), 738 (w), 707 (w), 695 (w), 679 (w), 668 (m), 659 (w) cm^{-1} ; ^1H NMR (500 MHz, $\text{DMSO}-d_6$): $\delta_{\text{H}} = 11.00$ (s, 1H, H-11), 9.53 (d, $J = 11.1$ Hz, 1H, H-7), 8.35 (s, 1H, H-9), 8.05 (d, $J = 11.1$ Hz, 1H, H-6), 7.04 (s, 1H, H-4), 4.32 (t, $J = 6.6$ Hz, 2H, $\text{CO}_2n\text{-Bu}$), 4.28 (t, $J = 6.6$ Hz, 2H, $\text{CO}_2n\text{-Bu}$), 4.19 (s, 3H, OMe), 3.95 (s, 3H, OMe), 3.83 (s, 3H, OMe), 1.69–1.77 (m, 4H, $\text{CO}_2n\text{-Bu}$), 1.42–1.48 (m, 4H, $\text{CO}_2n\text{-Bu}$), 0.91–0.97 (m, 6H, $\text{CO}_2n\text{-Bu}$) ppm; Measurement of ^{13}C NMR was hampered by the low solubility of this compound; HRMS (MALDI–TOF, positive): calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_7 + \text{H}^+$ $[\text{M} + \text{H}]^+$, 507.2252; found: 507.1881; HRMS (MALDI–TOF, positive): calcd for $\text{C}_{29}\text{H}_{33}\text{NO}_7 + \text{Ag}^+$ $[\text{M} + \text{Ag}]^+$, 614.1302; found: 614.0723.

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