An Easy Access to 2-Substituted Azulenes from Azulene-2-boronic Acid Pinacol Ester

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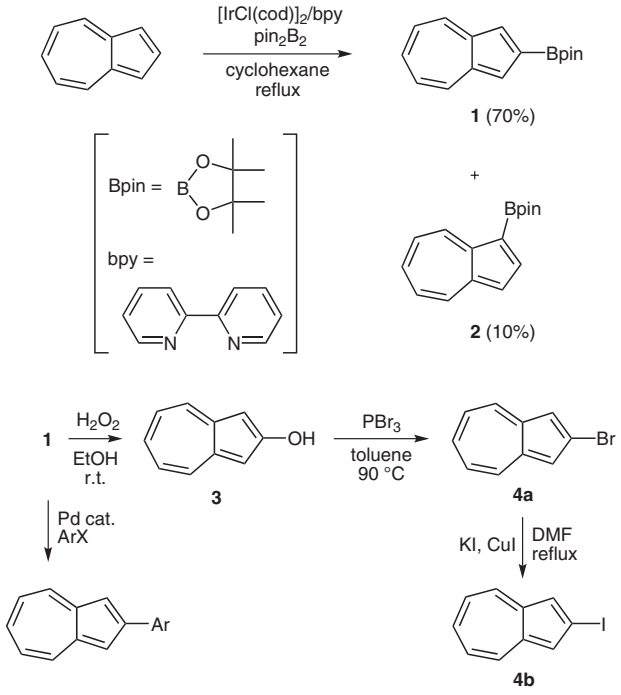
Received 26 June 2008; revised 13 August 2008

Abstract: Azulene-2-boronic acid pinacol ester was conveniently transformed into 2-substituted azulenes bearing carboxyl, formyl, ester, or amino groups, which are difficult to access by conventional methods. Furthermore, the azulene-2-carboxylic acid thus synthesized was subjected to the Ugi four-component condensation to obtain a dipeptide-type product containing an azulene skeleton.

Key words: azulene, borylation, boronic acid ester, cross-coupling, Ugi four-component reaction

Owing to the π-electron polarization, azulene is prone to electrophilic substitution at the 1- and 3-positions and nucleophilic addition at the 4-, 6- and 8-positions.[1] Therefore, the synthesis of azulene derivatives bearing substituents at the 2-, 5- or 7-positions is not trivial, and has traditionally required a multi-step transformation including the construction of the azulene skeleton.[2] As part of our recent efforts to overcome this problem, we reported a new simple method for introducing a boryl group into the 2-position of azulene. In this method, azulene undergoes direct borylation preferentially at this position via the C–H activation with an iridium-based catalyst, giving **1** together with a small quantity of **2** (Scheme 1).[3a] The 4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl group (Bpin) of **1** is converted into a hydroxyl group by oxidation to give **3**. This ensures the easy access to 2-bromoazulene (**4a**)[3b] and 2-iodoazulene (**4b**),[3b] which are key synthetic intermediates in the production of 2-substituted azulenes, such as 2,2′-biazulene,[4a] 2-dialkylaminoazulene,[4b] and 2-diphenylphosphinylazulene,[5] via the organometallic routes involving coupling or halogen–metal exchange. Furthermore, the Miyaura–Suzuki cross-coupling of **1** with aryl halides is an efficient route to 2-arylated azulenes.[6] These successful transformations of **1** based on the transition metal catalyzed reaction prompted us to explore further their synthetic utility. In particular, there is still a need for the development of general and simple methods for the introduction of basic functional groups, such as carboxyl, formyl, ester, or amino substituents, into the 2-position of azulene. In this paper, we report a convenient method for the synthesis of 2-substituted azulenes bearing these functional groups based on the cross-coupling reaction of **1**, as well as the preliminary results of the Ugi four-component reaction using these derivatives.



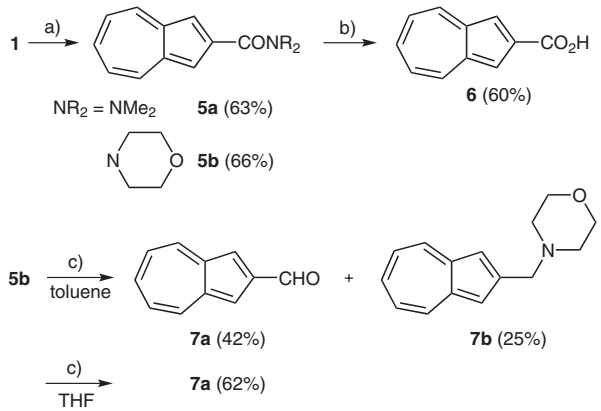
Scheme 1

Recently, Lysén and co-workers reported a new synthetic route to aromatic amides by Pd-catalyzed coupling of arylboronic acid esters with carbamoyl chlorides.[7] When we applied this reaction to **1**, the desired amides **5** were obtained in moderate yields and unreacted **1** (ca. 10%) was recovered (Scheme 2). The subsequent hydrolysis of **5a** gave azulene-2-carboxylic acid (**6**) in 60% yield.

Furthermore, morpholine amides are known to be efficient precursors of aldehydes. The reduction of **5b** with DIBAL-H produced the desired **7a** only in low yield, owing to the concomitant formation of the amine **7b**. However, this reaction was proved to be sensitive to the solvent effect. Thus, the use of THF[8] in the place of toluene improved the yield of **7a** while suppressing the formation of **7b**, indicating that its coordination with the aluminum center decreases the reducing capacity.

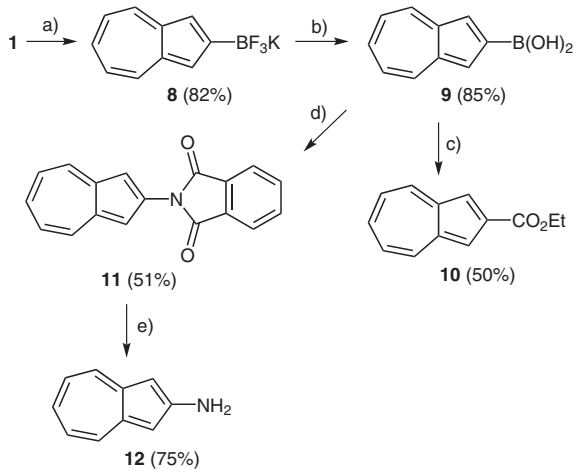
Next, we examined the conversion of **1** into ester **10** (Scheme 3). When **1** was subjected to a coupling reaction

SYNTHESIS 2008, No. 23, pp 3745–3748
Advanced online publication: 14.11.2008
DOI: 10.1055/s-0028-1083224; Art ID: F14108SS



Scheme 2 *Reagents and conditions*: a) $PdCl_2(PPh_3)_2$, $ClCONR_2$, CsF, THF, reflux; b) KOH (excess), **5a**, EtOH–H_2O, reflux; c) DIBAL-H, **5b**, –78 °C.

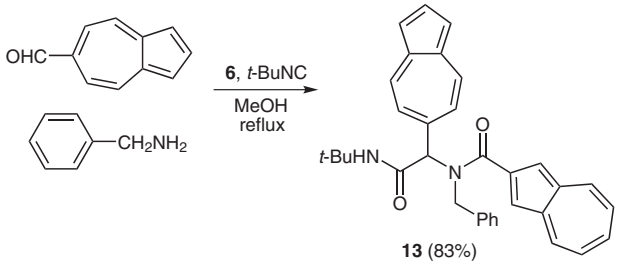
with ethyl chloroformate under the conditions for the synthesis of **5**, no reaction occurred. Duan has reported the Pd-catalyzed coupling reaction of arylboronic acids with ethyl chloroformate, yielding the corresponding ethyl esters.[9] In order to examine the applicability of this reaction to azulene systems, we attempted to perform the conversion of **1** into **9**. Initially, the attempt to treat **1** with an aqueous solution of sodium periodate containing hydrochloric acid[10] resulted in the formation of a complex reaction mixture. On the other hand, when **1** was allowed to react with phenylboronic acid in the presence of hydrochloric acid, transesterification[11] occurred smoothly, giving the desired **9** in 58% yield. The most prominent yield of **9** was obtained by an alternative route via the borate **8**. Thus, the treatment of **1** with KHF_2[12] produced **8**, which was subsequently hydrolyzed to **9**. Furthermore, the Pd-catalyzed coupling reaction of ethyl chloroformate with **9** thus obtained afforded **10**. Although the yield of **10** is not satisfactory, few side products are found (by TLC) in the reaction mixture. In the presence of $Cu(OAc)_2$,[13] **9** reacted with phthalimide to give **11**, whose phthaloyl group was



Scheme 3 *Reagents and conditions*: a) KHF_2, MeOH, r.t.; b) Na_2CO_3, MeCN–H_2O, r.t.; c) $Pd(PPh_3)_4$, $K_3PO_4{\cdot}nH_2O$, $ClCO_2Et$, toluene, 90 °C; d) $Cu(OAc)_2$, phthalimide, pyridine, H_2O, DMF, r.t.; e) NH_2NH_2, THF, r.t.

deprotected by the addition of hydrazine[14] to form **12**. In the Cu-catalyzed amination reaction, insoluble substances due to the decomposition of **9** were formed. The attempt to transform **1** into **11** directly was unsuccessful.

The Ugi four-component condensation between an aldehyde, an amine, carboxylic acid, and an isocyanide allows the rapid preparation of α-aminoacyl amide derivatives.[15] The products of the Ugi reaction can participate in a wide variety of substitution patterns, and constitute peptidomimetics, which have potential pharmaceutical applications. Taking into account the versatile biological activities and medicinal applications of azulene derivatives,[16] we decided to utilize the Ugi reaction using substituted azulenes. Thus, the condensation of **6**, 6-formylazulene, benzylamine, and *tert*-butyl isocyanide proceeded smoothly to give the corresponding Ugi product **13** in good yield (Scheme 4). The attempt to perform a similar condensation using **12** in the place of benzylamine was unsuccessful, which is attributed to the presence of the less nucleophilic amino group of **12**.



Scheme 4

In summary, we have found that the azulenylboronic acid ester **1** can be converted into useful 2-substituted azulenes bearing carboxyl, formyl, ester, or amino groups, whose syntheses by conventional methods are difficult. We believe that these azulene derivatives can be conveniently utilized for the construction of new electronic systems based on the unique electronic and pharmaceutical properties of azulene.

All reactions were carried out under air, unless otherwise noted. THF was distilled from sodium benzophenone ketyl under argon before use. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance 400S spectrometer with TMS as an internal standard. IR spectra were obtained as KBr pellets on a Nicolet Avator 370 DTGS spectrophotometer.

2-Azulenecarboxamides 5a,b; General Procedure

To a flask charged with $(PPh_3)_2PdCl_2$ (12.6 mg, 0.018 mmol), CsF (182 mg, 1.2 mmol), carbamoyl chloride (1.2 mmol), and **1** (152 mg, 0.6 mmol) was added THF (5 mL) under argon. The mixture was heated at 80 °C for 23 h. The reaction was quenched with H_2O (20 mL), and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 5:1) to give the corresponding amide.

***N*,*N*-Dimethyl-2-azulenecarboxamide (5a)**

Yield: 75 mg (63%); blue powder; mp 164–165 °C.

IR (KBr): 2925, 1620, 1517, 1388, 1170 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.14 (3 H, s), 3.18 (3 H, s), 7.21 (2 H, t, *J* = 9.8 Hz), 7.46 (2 H, s), 7.64 (1 H, t, *J* = 9.9 Hz), 8.37 (2 H, d, *J* = 9.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 35.2, 39.3, 116.9, 123.8, 138.4, 138.5, 139.8, 143.6, 169.3.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.29; H, 6.65; N, 7.05.

Morpholino-2-azulenecarboxamide (5b)
Yield: 96 mg (66%); blue powder; mp 141–142 °C.

IR (KBr): 3442, 2965, 2856, 1634, 1431 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.64 (4 H, s), 3.81 (2 H, s), 3.87 (2 H, s), 7.23 (2 H, t, *J* = 9.9 Hz), 7.42 (2 H, s), 7.66 (1 H, t, *J* = 9.9 Hz), 8.38 (2 H, d, *J* = 9.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.4, 48.0, 67.0, 116.6, 124.0, 138.6, 138.8, 139.9, 142.4, 168.1.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.61; H, 6.28; N, 5.77.

Azulene-2-carboxylic Acid (6)
Amide **5a** (99 mg, 0.5 mmol) was dissolved in EtOH–H_2O (4:1) (5 mL), and after addition of KOH (70 mg, 0.9 mmol), the mixture was heated at 80 °C for 23 h. The resulting solution was cooled to r.t. and the reaction was quenched with H_2O (10 mL). The resulting mixture was washed with Et_2O (3 × 10 mL). The aqueous layer was acidified with 10% aq HCl to give a green precipitate of **6**. The precipitate was extracted with Et_2O (3 × 10 mL) and the extracts were dried (Na_2SO_4) and concentrated to leave the pure product **6**; yield: 52 mg (60%); green powder; mp 200–203 °C (dec.) (Lit.[5a] mp 200–203 °C, dec.).

^1H NMR (400 MHz, DMSO-d_6): δ = 7.30 (2 H, t, *J* = 9.9 Hz), 7.72 (2 H, s), 7.80 (1 H, t, *J* = 9.9 Hz), 8.56 (2 H, d, *J* = 10.0 Hz), 12.76 (1 H, br s).

Reduction of 5b to 2-Formylazulene (7a)
To a solution of **5b** (121 mg, 0.5 mmol) in anhyd THF (5 mL) was added dropwise DIBAL-H (1.0 M toluene solution, 0.9 mL, 0.9 mmol) at –78 °C under argon. The mixture was stirred at this temperature for 15 min, and the reaction was quenched with aq AcOH (50%, 1 mL). After 10 min, the resulting solution was neutralized with aq sat. Na_2CO_3 and extracted with Et_2O (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 2:1) to give the desired **7a**; yield: 49 mg (62%); green powder; mp 61–62 °C (Lit.[17] mp 62–63 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (2 H, t, *J* = 9.8 Hz), 7.70 (1 H, t, *J* = 9.9 Hz), 7.77 (2 H, s), 8.48 (2 H, d, *J* = 9.9 Hz), 10.44 (1 H, s).

A similar reduction of **5b** in toluene gave **7a** and **7b** in 42% and 25% yield, respectively.

2-(Morpholinomethyl)azulene (7b)
Yield: 28 mg (25%); purple oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.55 (4 H, t, *J* = 4.7 Hz), 3.77 (4 H, t, *J* = 4.7 Hz), 3.92 (2 H, s), 7.17 (2 H, t, *J* = 9.8 Hz), 7.35 (2 H, s), 7.55 (1 H, t, *J* = 9.9 Hz), 8.26 (2 H, d, *J* = 9.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.0, 59.0, 67.0, 117.8, 123.1, 135.5, 136.3, 140.2, 149.8.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 78.99; H, 7.58; N, 6.25.

Potassium 2-Azulenyltrifluoroborate (8)
To a solution of **1** (254 mg, 1.0 mmol) in MeOH (7 mL) was added aq KHF_2 (2.0 mL, 2.8 M, 5.6 mmol). The solution was stirred at r.t. for 15 min and concentrated in vacuo to leave a residue, which was dissolved in hot acetone (7 mL). The resulting mixture was filtered off and the filtrate was concentrated in vacuo to give a crude product, which was recrystallized from a minimum amount of hot acetone–Et_2O to afford **8** as a pure product; yield: 192 mg (82%); blue powder; mp 260–265 °C (dec.).

IR (KBr): 3449, 2955, 2924, 2854, 1302 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 6.99 (2 H, t, *J* = 9.7 Hz), 7.30 (2 H, s), 7.40 (1 H, t, *J* = 9.8 Hz), 8.12 (2 H, d, *J* = 9.3 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 121.2, 123.2, 133.3, 134.6, 140.4. One azulene skeleton carbon signal was not observed.

Anal. Calcd for $C_{10}H_7BF_3K$: C, 51.31; H, 3.01. Found: C, 51.10; H 2.83.

Azulene-2-boronic Acid (9)
(a) *By Hydrolysis of **8***: To a mixture of **8** (234 mg, 1.0 mmol) and Na_2CO_3 (159 mg, 1.5 mmol) in H_2O (5 mL) was added MeCN (10 mL). The resulting solution was stirred at r.t. for 4 h, acidified with aq 1 M HCl (2 mL) followed by aq sat. NH_4Cl (5 mL), and then extracted with Et_2O (3 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was recrystallized from hexane–EtOAc (30:1) to afford **9** as a pure product; yield: 147 mg (85%); blue powder; mp 256–259 °C (dec.).

IR (KBr): 3404, 2924, 1499, 1458, 1359 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.13 (2 H, t, *J* = 9.7 Hz), 7.61 (1 H, t, *J* = 9.9 Hz), 7.72 (2 H, s), 8.24 (2H, s), 8.35 (2 H, d, *J* = 9.5 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.9, 125.2, 137.8, 138.7, 140.5, 146.1.

Anal. Calcd for $C_{10}H_9BO_2$: C, 69.84; H, 5.27. Found: C, 70.11; H, 5.48.

(b) *By Transesterification of **1***: To a solution of **1** (254 mg, 1.0 mmol) in EtOH (7 mL) was added phenylboronic acid (146 mg, 1.2 mmol) followed by a diluted aq solution of HCl (5 mL, pH 3) at r.t., and the mixture was stirred for 5 h. After concentration of the mixture, 10% aq KOH (10 mL) was added and the resulting mixture was washed with Et_2O (3 × 10 mL). The aqueous layer was acidified with a diluted aq solution of HCl (10 mL, pH 3) and extracted with Et_2O (3 × 10 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give the crude product. Purification by recrystallization from hexane–EtOAc (5:1) afforded the pure product **9**; yield: 100 mg (58%).

Ethyl 2-Azulenecarboxylate (10)
To a flask charged with $Pd(PPh_3)_4$ (10 mg, 0.009 mmol), $K_3PO_4 \cdot nH_2O$ (170 mg, 0.8 mmol), ethyl chloroformate (0.028 mL, 0.3 mmol), and **9** (52 mg, 0.3 mmol) was added toluene (5 mL) under argon. The mixture was heated at 90 °C for 2 h. The reaction was quenched with H_2O (20 mL), and the resulting mixture was extracted with hexane (3 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 10:1) to give **10** as a pure product; yield: 30 mg (50%); blue powder; mp 72–73 °C.

IR (KBr): 2977, 1697, 1320, 1227, 1202 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.44 (3 H, t, *J* = 7.1 Hz), 4.44 (2 H, q, *J* = 7.1 Hz), 7.18 (2 H, t, *J* = 9.8 Hz), 7.65 (1 H, t, *J* = 9.9 Hz), 7.80 (2 H, s), 8.41 (2 H, d, *J* = 9.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 60.7, 118.8, 123.8, 138.6, 139.9, 140.2, 140.5, 165.7.

Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.92; H, 5.89.

2-Azulenylphthalimide (11)

To a flask charged with phthalimide (147 mg, 1.0 mmol), **9** (172 mg, 1.0 mmol), $Cu(OAc)_2$ (9 mg, 0.1 mmol), DMF (7 mL), and H_2O (0.018 mL) was added pyridine (0.08 mL, 1.0 mmol). After stirring the mixture at r.t. for 3 h, the reaction was quenched with H_2O (10 mL). The resulting mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was recrystallized from hot THF–hexane (1:10) to give **11** as a pure product; yield: 140 mg (51%); purple powder; mp 256–258 °C.

IR (KBr): 1721, 1491, 1474, 1377, 1282 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26 (2 H, t, *J* = 9.8 Hz), 7.60 (1 H, t, *J* = 9.9 Hz), 7.80 (2 H, m), 7.99 (2 H, m), 8.03 (2 H, s), 8.39 (2 H, d, *J* = 9.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.5, 123.8, 124.1, 131.9, 134.6, 136.4, 136.6, 138.9, 139.4, 166.9.

Anal. Calcd for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. Found: C, 79.04; H, 3.93; N, 5.11.

2-Aminoazulene (12)

To a solution of **11** (137 mg, 0.5 mmol) in THF (7 mL) was added hydrazine monohydrate (0.025 mL, 0.52 mmol) at r.t., and the resulting solution was stirred for 24 h at this temperature. After the addition of H_2O (5 mL), the mixture was extracted with Et_2O (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated to leave a residue, which was chromatographed (silica gel; hexane–EtOAc, 5:1) to give **12** as a pure product; yield: 54 mg (75%); red crystals; mp 92–93 °C (Lit.[18] mp 93–94 °C).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.54 (2 H, s), 6.68 (2 H, s), 7.19 (2 H, t, *J* = 9.8 Hz), 7.32 (1 H, t, *J* = 9.6 Hz), 7.95 (2 H, d, *J* = 9.2 Hz).

***N*-(*tert*-Butyl)-2-[*N*′-(benzyl)azulene-2-carboxamido]-2-(6-azulenyl)acetamide (13)**

To a flask charged with 6-formylazulene (78 mg, 0.5 mmol) and benzylamine (0.068 mL, 0.625 mmol) was added MeOH (3 mL). After stirring the resulting solution at r.t. for 10 min, **6** (86 mg, 0.5 mmol) was added and the mixture was stirred at r.t. for 5 min. Then, *tert*-butyl isocyanide (0.056 mL, 0.5 mmol) was added and the mixture was stirred at 60 °C for 24 h. The solvent was concentrated to leave a residue, which was recrystallized from THF–hexane (1:2) to give **13** as a pure product; yield: 208 mg (83%); blue powder; mp 236–238 °C.

The ^1H NMR spectra of **13** suffered extreme peak broadening due to rotational isomerism. This compound was characterized by variable-temperature ^1H NMR spectrum. Only one set of the signals was observed at 60 °C.

IR (KBr): 3418, 3306, 2925, 2854, 1660, 1636 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6, 60 °C): δ = 1.21 (9 H, s), 4.70 (1 H, br s), 5.12 (1 H, d, *J* = 16.4 Hz), 5.98 (1 H, br s), 6.94–7.00 (5 H, m), 7.17 (2 H, br s), 7.30 (2 H, t, *J* = 9.9 Hz), 7.32 (2 H, d, *J* = 3.8 Hz), 7.45 (2 H, s), 7.68 (1 H, br s), 7.74 (1 H, t, *J* = 10.0 Hz), 7.84 (1 H, t, *J* = 3.8 Hz), 8.26 (2 H, d, *J* = 10.1 Hz), 8.44 (2 H, d, *J* = 9.5 Hz).

^{13}C NMR (100 MHz, DMSO-d_6, 60 °C): δ = 28.1, 49.2 (br), 50.4, 66.9 (br), 116.0, 117.8, 123.6, 124.0, 125.8, 126.5, 127.3, 135.0, 136.9, 138.4, 138.6, 138.9, 139.0, 139.3, 143.3, 146.1 (br), 168.0, 169.9.

Anal. Calcd for $C_{34}H_{32}N_2O_2$: C, 81.57; H, 6.44; N, 5.60. Found: C, 81.44; H, 6.49; N, 5.55.

Acknowledgment

Support from the Japan Society for the Promotion of Science (Grant-in-Aid for Scientific Research, No. 19550043) is gratefully acknowledged.

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