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A Practical Synthesis of Highly Hindered Biphenyl-2-carboxylates via Nucleophilic Aromatic Substitution of *tert*-Butyl 2-Methoxybenzoates with Aryl Grignard Reagent

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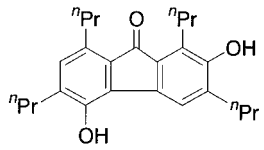
Abstract:

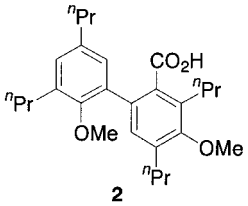
The fluorenone derivative (OPC-34165) has potent repairing and protecting activities for peripheral and central nervous system degeneration. A synthesis of the biphenyl-2-carboxylic acid derivative, which is the key intermediate of OPC-34165, is described employing the S_NAr reaction of *tert*-butyl 2-methoxybenzoate with aryl Grignard reagent in refluxing THF−toluene.

Introduction

The fluorenone derivative **OPC-34165** (**1**), discovered in our research institute, has potent repairing and protecting activities for peripheral and central nervous system degeneration.[1] To provide the drug substance for pharmacological and toxicological evaluation, we searched for a suitable process for the large-scale production of **1**. As **1** can be easily derived from the biphenyl-2-carboxylic acid derivative **2** by the intramolecular Friedel−Crafts cyclization,[2] obtaining sterically congested **2** was the most challenging problem to overcome. Herein, we disclose an efficient method of synthesis of **2** by using a nucleophilic aromatic substitution (S_NAr) reaction.



1 (OPC-34165)



2

Results and Discussion

Although several useful methods of realizing aryl−aryl coupling reaction for the construction of the biphenyl framework are known,[3] we have applied Meyers' S_NAr reaction to the methoxy group adjacent to the electron-withdrawing group in aryloxazoline derivatives.[4] This method was selected since the essential carboxylic acid moiety was contained as the protected form in the starting material, and an expensive reagent such as Ni or Pd catalyst was not used.

Treating the oxazoline derivative **3a** with the aryl Grignard reagent **4a**[5a,b] gave the corresponding biphenyl compound **5a** in 71% yield. However, the hydrolysis of the oxazoline ring of **5a** gave the corresponding 3-hydroxy-2-methylpropan-2-yl amide which resisted further hydrolysis. The drawback of this procedure was the difficulty in deprotecting an oxazoline moiety to the parent carboxylic acid. As an alternative procedure, Miyano and co-workers report that 2,6-dialkyl-substituted phenyl esters serve as convenient activating groups to carry out ortho-substitutions. These esters are easily deprotected to the parent carboxylic acid by transesterification [NaOMe in toluene and 1-methyl-2-piperidone (NMP) or HMPA] followed by hydrolysis of the methyl ester.[6] Hence, we have applied Miyano's procedure and treated **3b** (R = Me) with **4a** to give **5b** (R = Me) in 92% yield. Unfortunately, **5b** (R = Me) had no reactivities toward either hydrolytic or the recommended transesterification conditions,[7] and only a moderate result was obtained for 2,6-di-*tert*-butyl-4-methoxyphenyl ester **5b** (R = OMe) under the oxidative cleavage conditions using ceric ammonium nitrate (CAN)[8] in giving 54% of **2** (Scheme 1). With our compound, sterically congested esters to give the desired biphenyls on S_NAr reactions were resistant to deprotection to the parent carboxylic acids.

Next, we investigated alkyl instead of phenyl esters, since an *i*-propyl group was shown to be an effective activating group for the synthesis of congested 1,1′-binaphthyl-2-carboxylate;[9,10] however, it was not applicable for the

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(1) Tanaka, T.; Sakurai, Y.; Fujisawa, N.; Hongoh, O.; Nishi, T. WO95, 1995, 00468; *Chem. Abstr.*, **1995**, *122*, 239345r.

(2) For examples, see: (a) Wassmundt, F. W. *J. Org. Chem.* **1968**, *33*, 3322. (b) Suzuki, H.; Enya, T.; Hisamatsu, Y. *Synthesis* **1997**, 1273.

(3) For general reviews, see: (a) Bringman, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Altenbavh, H.-J. In *Organic Synthesis Highlights*; Mulzer, J., Ed.; VCH: Weinheim, 1991; Vol. 1, p 181.

(4) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383. (b) Meyers, A. I.; Mihelich, E. D. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 270. (c) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837.

(5) The synthetic procedure was reported, see: (a) Aki, S.; Haraguchi, Y.; Tone, H.; Fujioka, T.; Ishigami, M.; Sakikawa, H.; Minamikawa, J.; Nishi, T.; Tanaka, T.; Watanabe, K. Jpn. Kokai Tokkyo Koho JP11-217348, 1999; *Chem. Abstr.* **1999**, *131*, 129765f. (b) Scammells, P. J.; Baker, S. P.; Beauglehole, A. R. *Bioorg. Med. Chem.* **1998**, *6*, 1517. (c) Hong, F.-T.; Lee, K.-S.; Tsai, Y.-F.; Liao, C.-C. *J. Chin. Chem. Soc. (Taipei)* **1998**, *45*, 1.

(6) Hattori, T.; Suzuki, T.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1375. (b) Hattori, T.; Suzuki, T.; Hayashizaka, N.; Koike, N.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3034. (c) Hattori, T.; Hayashizaka, N.; Miyano, S. *Synthesis* **1995**, 41. (d) Hattori, T.; Koike, N.; Miyano, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2273. (e) Hattori, T.; Miyano, S. *Yuki Gosei Kagaku Kyokaishi* **1997**, *55*, 121. (f) Hattori, T.; Koshiishi, E.; Wada, S.; Koike, N.; Yamabe, O.; Miyano, S. *Chirality* **1998**, *10*, 619.

(7) Due to the toxicity, we the authors did not examine the reaction in HMPA.

(8) Pirrung, M. C.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1727.

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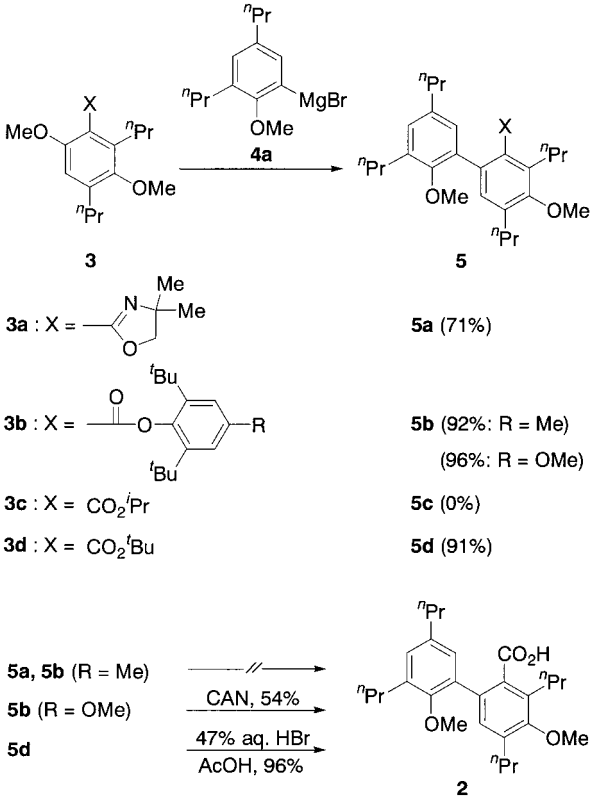
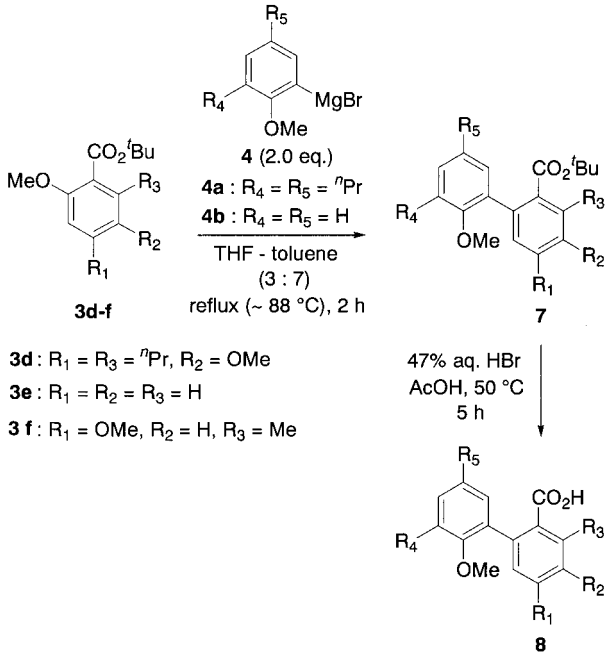
Scheme 1



construction of a simple biphenyl system.[11] As our compounds **3** and **4** were sterically congested, we expected that the carbonyl group of the *i*-propyl ester moiety might be resistant to nucleophilic attack of the Grignard reagent **4a**, however, the product from the reaction between the *i*-propyl ester **3c** (X = CO_2 *i*-Pr in Scheme 1) and Grignard reagent **4a** yielded undesired 2′-(2,5-dimethoxy-4,6-dipropylbenzoyl)-2-methoxy-3,5,4′,6′-tetrapropylbiphenyl[12] in 31% yield and recovered **3c** in 42% yield.

After several trials, we found that this problem could be solved by using a *tert*-butyl ester.[13] To our knowlege, this is the first example of the use of an alkyl ester for the construction of a biphenyl system using S_NAr methodology. Thus, the reaction of **3d**[5a,c] with the Grignard reagent **4a** (2.0 equiv) in refluxing THF−toluene (3:7, at about 88 °C)[14] for 2 h gave the biphenyl ester **5d**[15] in 91% yield. Subsequent treatment of this compound with 47% aqueous HBr in AcOH at 50 °C[16] easily furnished the desired biphenyl-2-carboxylic acid **2** as a colorless solid in 96% yield (Scheme 1 and Table 1, entry 1). The efficiency of this improved method was established in a scale-up trial. **3d** (4.73 kg) gave the desired **2** (5.86 kg) after a simple purification (acid/base extraction) in 94% yield from **3d**.

Table 1. **Treatment of *tert*-butyl 2-methoxybenzoates with aryl Grignard reagents**



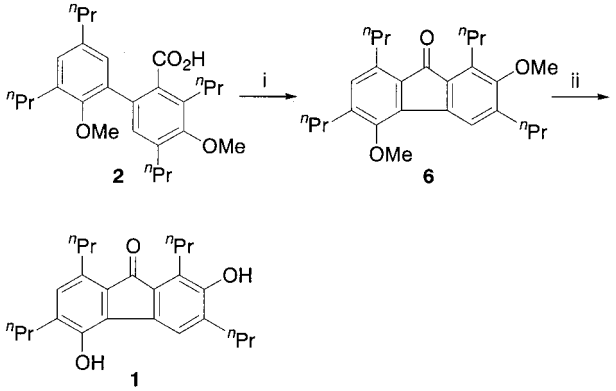
			yield (%)	
entry	**3**	**4**	**7**[a]	**8**[b]
1	**3d**	**4a**	91 (**5d**)	96 (**2**)
2	**3d**	**4b**	26[c]	97
3	**3e**	**4a**	38[d]	84
4	**3e**	**4b**	∼0[e]	−
5	**3f**	**4a**	91	85

[a] Isolated yield of pure product from **3**. [b] Isolated yield of pure product from **7**. [c] The major side product was 2′-(2,5-dimethoxy-4,6-dipropylbenzoyl)-2-methoxybiphenyl (yield <39%; unseparable undetermined impurity was contaminated); see: ref 12. [d] The complex mixture was obtained. [e] The major product was tri(2-methoxyphenyl)methanol (61% yield).

We further investigated the scope and limitation of this method. The results obtained for some other combinations of *o*-methoxybenzoates and aryl Grignard reagents are summarized in Table 1. (1) The combination of the crowded **3** and the crowded **4** was effective to give the corresponding highly congested *tert*-butyl biphenyl-2-carboxylate derivatives, which were readily converted to the parent carboxylic acids in good yields (entries 1, 5). (2) When the steric crowd of either reagent **3** or **4** was reduced, the yields of **7** decreased

(9) Hotta, H.; Suzuki, T.; Miyano, S. *Chem. Lett.* **1990**, 143.
(10) The S_NAr reaction of *N*-alkyl-substituted benzaldimine with aryl Grignard reagents was reported, see: (a) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732. (b) Flippin, L. A.; Carter, D. S.; Dubree, N. J. P. *Tetrahedron Lett.* **1993**, *34*, 3255. (c) Goubet, D.; Meric, P.; Dormoy, J.-R.; Moreau, P. *J. Org. Chem.* **1999**, *64*, 4516.
(11) The following result was reported: treating *i*-propyl 2-methoxybenzoate with phenylmagnesium bromide gave diphenyl(2-methoxyphenyl)methanol in 75% yield; see: ref 6a.
(12) A similar type of reaction was reported, see: Fuson, R. C.; Speck, S. B. *J. Am. Chem. Soc.* **1942**, *64*, 2446.
(13) The required *tert*-butyl ester **3d** was readily prepared by esterification of the corresponding carboxylic acid with thionyl chloride followed by treatment with *tert*-butyl alcohol and potassium carbonate in dichloromethane in 91% yield. For preparation of **3e**, the transesterification technique was more effective, see: (a) Rossi, R. A.; de Rossi, R. H. *J. Org. Chem.* **1974**, *39*, 855. (b) Stanton, M. G.; Gagne, M. R. *J. Org. Chem.* **1997**, *62*, 8240.
(14) The use of THF−toluene as a cosolvent gave better results; the reaction of **3d** with **4a** (3 equiv) in THF gave 82% of **5d** after refluxing for 15 h.
(15) IR (film): 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89−1.08 (m, 12H), 1.22 (s, 9H), 1.49−1.78 (m, 8H), 2.49 (t, J = 8.8 Hz, 2H), 2.52−2.80 (m, 6H), 3.36 (s, 3H), 3.78 (s, 3H), 6.86 (d, J = 2.3 Hz, 1H), 6.94 (d, J = 2.3 Hz, 1H), 7.09 (s, 1H); HRMS results: calcd for $C_{31}H_{46}O_4$, 482.3398; found 482.3367.
(16) Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; John Wiley & Sons: New York, 1991; p 245.

Scheme 2[a]



[a] Reagents and conditions: (i) MsOH, 50−60°C, 1.5 h, 93%; (ii) 47% aq. HBr, AcOH, reflux, 14 h, 93%.

significantly (entries 2, 3). (3) When the steric crowding of both reagent **3** and **4** was relieved, the desired biphenyl derivative could not be obtained; instead, tri(2-methoxyphenyl)methanol was obtained in 56% yield as a major product (entry 4). The presented method is particularly effective for the synthesis of sterically congested biphenyl-2-carboxylic acid derivatives with limited synthesis of less hindered ones.

2 was converted into the desired product **1** as shown in Scheme 2. After Friedel−Crafts cyclization, the resultant methyl ether of the fluorenone (**6**) was deprotected to give **1** in high yield.

Conclusions

We have developed a practical and efficient method for preparing the highly hindered biphenyl-2-carboxylic acid derivative **2**, which was the key intermediate for the synthesis of **OPC-34165** (**1**), by taking advantage of aryl−aryl coupling reaction using *tert*-butyl *o*-methoxybenzoate and an aryl Grignard reagent. Consequently, we have achieved the large-scale production of **1**.

Experimental Section

NMR spectra were recorded on a Bruker DPX-300 spectrometer (chemical shifts were given in ppm from TMS as an internal standard in $CDCl_3$). IR spectra were performed on either a Perkin-Elmer FT-IR 1640 or a Nicolet FT-IR Magna 560 spectrometer. Melting points were measured with a Büchi 535 and were uncorrected. HPLC was performed on a Waters LC Module I Plus using a Tosoh TSKgel ODS-80T_S column (4.6 × 150 mm) and $CH_3CN/H_2O/H_3PO_4$ (850/150/1) phase at 270 nm.

2-(3,5-Dipropyl-2-methoxy)phenyl-4,6-dipropyl-5-methoxybenzoic Acid (2). A toluene (33.1 L) solution of 2-bromo-4,6-dipropylanisole[5a,b] (5.96 kg, 22.0 mol) was added to a suspension of Mg (534 g, 22.0 mol) and 1,2-dibromoethane (47 mL) in THF (9.5 L). The mixture was refluxed for 6 h under N_2. To this solution was added a solution of **3d**[5a,c] (4.73 kg, 14.7 mol) in toluene (4.7 L), and the mixture was refluxed for 2 h under N_2. After completion of the reaction, the mixture was poured into 3% aqueous HCl (38.1 L) at 3 °C and extracted with ethyl acetate (23.7 L). The combined extracts were washed with brine (2 × 47.3 L) and water (47.3 L) and concentrated in vacuo to give the crude product (9.04 kg) as an oil. HBr (47% aqueous, 11.3 L) was added to the solution of the residual oil containing **5d**[15] in acetic acid (37.2 L). After stirring for 5.5 h at 50 °C, the reaction mixture was poured into H_2O (70.6 L) and extracted with hexane (2 × 70.6 L). The organic layer was washed with aqueous $NaHCO_3$ (2 × 42.4 L) and H_2O (42.4 L) and extracted with aqueous KOH (KOH: 1.30 kg in 70.6 L of H_2O). The aqueous KOH layer was washed with hexane (42.4 L), neutralized with aqueous HCl (concd HCl: 3.1 L in 10.6 L of H_2O), and extracted with ethyl acetate (42.4 L). The ethyl acetate layer was washed with brine (42.4 L) and H_2O (42.4 L) and concentrated in vacuo to give **2** (5.86 kg, 94% yield from **3d**) as a solid: mp 73.4−74.0 °C (unrecryst.); IR (KBr) 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86−1.15 (m, 12H), 1.50−1.75 (m, 8H), 2.49 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.8 Hz, 2H), 2.60−2.82 (m, 4H), 3.35 (s, 3H), 3.79 (s, 3H), 6.87 (d, J = 2.1 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.0, 14.1, 14.4, 23.6, 23.9, 24.4, 24.6, 30.2, 31.9, 32.1, 37.4, 60.6, 61.5, 128.8, 129.8, 130.4, 132.1, 132.4, 133.3, 133.9, 135.1, 137.1, 138.0, 153.0, 156.1, 172.2. HRMS results: calcd for $C_{27}H_{38}O_4$, 426.2771; found 426.2743.

2,5-Dimethoxy-1,3,6,8-tetrapropyl-9-fluorenone (6). A solution of **2** (5.85 kg, 13.7 mol) in methanesulfonic acid (46.8 L) was stirred at 50−60 °C for 1.5 h. After completion of the reaction, the mixture was poured into water (175.4 L) at 0 °C and extracted with ethyl acetate (87.7 L). The extract was combined further with ethyl acetate (58.5 L), washed with water (87.7 and 58.5 L), aqueous $NaHCO_3$ (58.5 L), and H_2O (58.5 L), and concentrated in vacuo to give **6** (5.20 kg, 93% yield) as a deep orange oil: IR (film) 1698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H), 1.48−1.78 (m, 8H), 2.61 (t, J = 7.8 Hz, 2H), 2.65 (t, J = 7.8 Hz, 2H), 2.94 (t, J = 7.8 Hz, 2H), 3.01 (t, J = 7.6 Hz, 2H), 3.75(s, 3H), 3.82 (s, 3H), 6.82 (s, 1H), 7.50 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.1, 14.2, 14.6, 23.7, 23.8 (×2), 24.1, 27.0, 31.7, 32.6, 32.7, 60.6, 61.7, 123.0, 130.8, 131.1, 132.2, 135.3, 137.9, 138.9, 139.8, 141.6, 143.2, 151.8, 157.4, 194.7; M^+ 408.

2,5-Dihyroxy-1,3,6,8-tetrapropyl-9-fluorenone (1). A solution of **6** (5.19 kg, 12.7 mol) and 47% aqueous HBr (15.1 L) in acetic acid (62.3 L) was refluxed for 6 h. HBr (47% aqueous, 5.2 L) was further added to the reaction mixture and refluxed for 8 h. After completion of the reaction, the mixture was poured into a solution of water (186.9 L) and ethyl acetate (62.3 L) at 10 °C. The aqueous layer was extracted with ethyl acetate (51.9 and 21.0 L). The extracts were combined, washed with water (87.7 and 58.5 L), brine (3 × 51.9 L), and aqueous $NaHCO_3$ (2 × 51.9 L). The organic layer was treated with active-C, dried with anhydrous magnesium sulfate, and concentrated in vacuo to give **1** (4.81 kg, quantitative, HPLC purity: 93%) as a deep red solid. For purification, **1** (4.79 kg) was treated with acetic anhydride (3.32 L, 35.2 mol) in pyridine (31.2 L) at room temperature for 1.3 h to derive the corresponding diacetate (5.12 kg, 86% yield from **6**). The diacetate (5.10 kg) was recrystallized

twice from 80% aqueous acetone (38.0 L was used for 1.0 kg of the diacetate) to give 4.42 kg (87% yield) of light yellow needles.[17] After deprotection of the acetyl group by treating with concentrated HCl (19.7 L) in EtOH (75.0 L) under reflux for 15 h to give **1** (3.54 kg, 98% yield), the recrystallization from 65% aqueous EtOH (35.4 L) gave **1** (3.10 kg, 88% yield) with high purity (HPLC analysis indicated 99.75% purity; $t_R = 8.7$ min.) as deep red prisms: mp 115.8−117.2 °C; IR (KBr) 1677, 3484 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91−1.06 (m, 12H), 1.51−1.76 (m, 8H), 2.54 (t, $J = 7.7$ Hz, 2H), 2.59 (t, $J = 7.7$ Hz, 2H), 2.90 (t, $J = 7.7$ Hz, 2H), 3.06 (t, $J = 7.7$ Hz, 2H), 4.85 (br.s, 1H), 4.94 (br.s, 3H), 6.69 (s, 1H), 7.46 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 14.1, 14.2, 22.7 (×2), 22.9, 23.9, 25.8, 31.9, 32.5, 33.1, 123.2, 129.6, 129.7, 130.2, 130.8, 131.2, 133.3, 135.3, 136.2, 136.5, 146.9, 151.9, 195.7. $C_{25}H_{32}O_3$ requires C 78.91, H 8.48. Found C 79.04, H 8.37%.

(17) Mp 148.0−148.5 °C; IR (KBr): 1705, 1754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, $J = 7.3$ Hz, 3H), 0.99 (t, $J = 7.3$ Hz, 9H), 1.46−1.76 (m, 8H), 2.30−3.40 (br. m, 2H), 2.35 (s, 3H), 2.45 (s, 3H), 2.45 (t, $J = 7.7$ Hz, 4H), 2.97 (t, $J = 7.6$ Hz, 2H), 6.91 (s, 1H), 7.20 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 14.1 (×2), 14.5, 20.5, 20.9, 22.3, 22.8, 23.1, 23.7, 27.2, 32.4, 32.8, 33.1, 121.5, 130.7, 130.8, 132.5, 134.9, 136.8, 140.2, 140.3, 141.8, 142.0, 142.1, 148.5, 168.7, 169.2, 193.6; M^+ 464.

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