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An efficient synthesis of *o*-terphenyls from Morita–Baylis–Hillman adducts of cinnamaldehydes: a consecutive bromination, Wittig reaction, 6π-electrocyclization, and an aerobic oxidation process

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ABSTRACT

An efficient synthetic method of *o*-terphenyls was developed from Morita–Baylis–Hillman adducts. The synthesis was carried out via a sequential bromination of MBH adducts, Wittig reaction with various aldehydes, 6π-electrocyclization, and a base-mediated aerobic oxidation process.

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The synthesis of poly-substituted benzene derivatives including *ortho*- and *para*-terphenyls has received much attention.[1–3] Among the numerous approaches for these compounds, a sequential 6π-electrocyclization of suitably-substituted 1,3,5-trienes to dihydrobenzenes and a following oxidation process is one of the important routes.[4,5] The *Z*-stereochemistry at the 3-position of 1,3,5-trienes is essential for the 6π-electrocyclization. Thus, the synthesis of 1,3(*Z*),5-trienes in a stereoselective manner is very important.

The Morita–Baylis–Hillman (MBH) adducts have been used extensively for the synthesis of poly-substituted benzenes.[2,3,6] Very recently, we reported a synthesis of *p*-terphenyls by a Diels–Alder reaction of 1,3-diene that was prepared from MBH adduct of benzaldehyde, as shown in Scheme 1.[2] As a continuous interest for the synthesis of terphenyls, we presumed that a Wittig reaction of the MBH bromide of cinnamaldehyde could provide 1,3,5-triene **4a**, and the triene could be used for the synthesis of *o*-terphenyl **5a**, as shown in Scheme 1. The two styryl moieties of **4a** are positioned in the same direction around the 2,3-double bond, although the systematic nomenclature of the double bond is *E*, thus a 6π-electrocyclization of **4a** could produce the intermediate **I** by a disrotatory ring-closure.

The MBH bromide **2a** was prepared from the MBH adduct of cinnamaldehyde **1a** as reported.[7,8] The preparation of a phosphonium salt of **2a** and the following Wittig reaction with benzaldehyde (**3a**) in the presence of K_2CO_3 produced methyl 5-phenyl-2-styrylpenta-2,4-dienoate (**4a**) in moderate yield (64%).[9,10] However, the *E*/*Z* selectivity (*E*/*Z* = 4:1) of the styryl substituent at the 2-position during the Wittig reaction was not high,[9a] and the purification of **4a** was somewhat difficult.[9,10] Thus we examined the reaction with an *E*/*Z* mixture of **4a** in CH_3CN in the presence of K_2CO_3 under an O_2 balloon atmosphere. To our delight, *o*-terphenyl **5a** was obtained in good yield (91%) via the 6π-electrocyclization to form a mixture of dihydrobenzene intermediate **I** and its diastereomer, and a concomitant base-mediated aerobic oxidation.[2,5] The result stated that the preparation of **4a** and its conversion to **5a** could be performed in a one-pot. Thus, we examined a one-pot synthesis of **5a** without isolation of the triene **4a**. As shown in Scheme 2, the preparation of a phosphonium salt of **2a** was carried out with PPh_3 in CH_3CN at room temperature for 2 h. After monitoring the formation of a phosphonium salt on TLC, benzaldehyde (1.1 equiv) and K_2CO_3 (2.0 equiv) were added, and the reaction mixture was stirred for 12 h at room temperature to form the triene intermediate **4a**. The reaction mixture was then heated to reflux for 15 h under O_2 balloon atmosphere. The product **5a** was obtained in a one-pot reaction from **2a** in moderate yield (55%).[11] The yield of **5a** was similar to that of the two-step procedure (58%).

Encouraged by the results various *o*-terphenyl derivatives were synthesized analogously, and the results are summarized in Table 1. The reactions between **2a** and various aldehydes such as *p*-chlorobenzaldehyde (**3b**), *p*-anisaldehyde (**3c**), *p*-nitrobenzaldehyde (**3d**), and 4-biphenylcarboxaldehyde (**3e**) afforded the corresponding *o*-terphenyls **5b–e** in a one-pot reaction in reasonable

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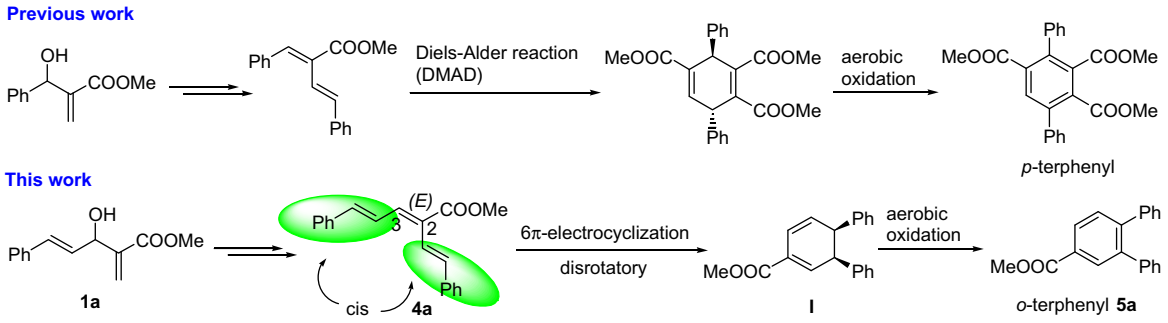
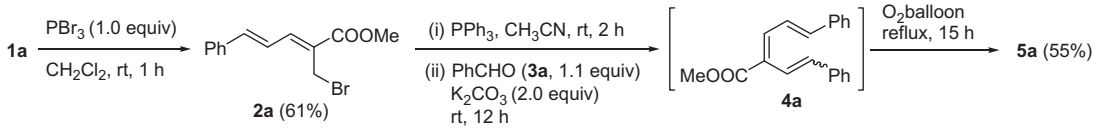
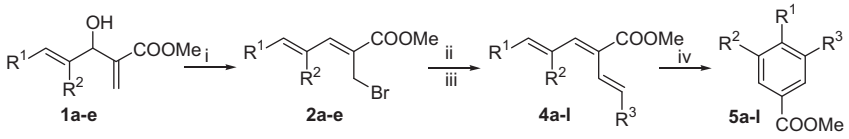


Scheme 1.

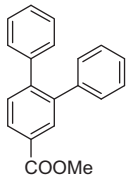


Scheme 2.

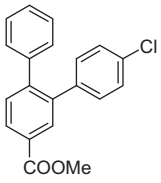
Table 1
One-pot synthesis of *o*-terphenyl derivatives **5** from MBH bromides **2**[a,b]



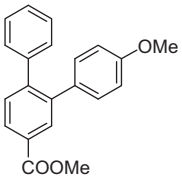
(i): PBr_3 (1.0 equiv), CH_2Cl_2, rt, 1 h (46-78%). (ii): PPh_3 (1.1 equiv), $MgSO_4$, CH_3CN, rt, 2 h. (iii): R^3-CHO (**3a-h**, 1.1 equiv), K_2CO_3 (2.0 equiv), rt, 12-28 h. (iv): reflux, O_2 balloon, 15-22 h.



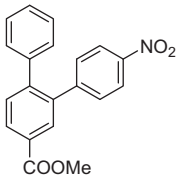
5a (55%)
R^1=Ph, R^2=H
R^3=Ph



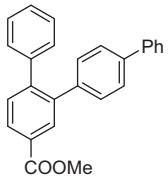
5b (63%)
R^1=Ph, R^2=H
R^3=*p*-ClPh



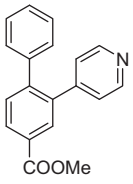
5c (45%)
R^1=Ph, R^2=H
R^3=*p*-MeOPh



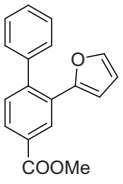
5d (68%)
R^1=Ph, R^2=H
R^3=*p*-NO_2Ph



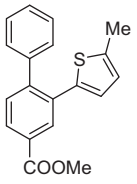
5e (68%)
R^1=Ph, R^2=H
R^3=*p*-PhPh



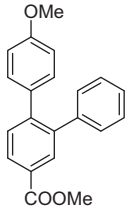
5f (69%)
R^1=Ph, R^2=H
R^3=4-pyridyl



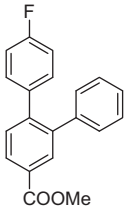
5g (58%)
R^1=Ph, R^2=H
R^3=2-furyl



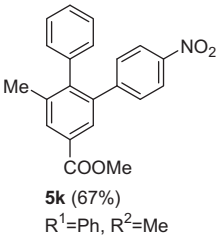
5h (60%)
R^1=Ph, R^2=H
R^3=5-Me-2-thienyl



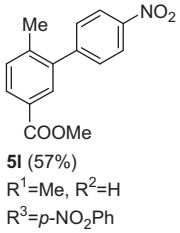
5i (54%)[c]
R^1=*p*-MeOPh, R^2=H
R^3=Ph



5j (59%)
R^1=*p*-FPh, R^2=H
R^3=Ph

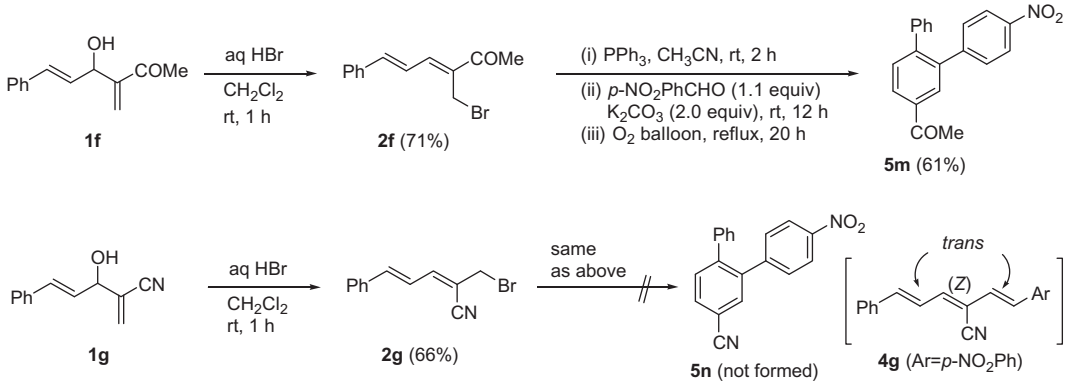


5k (67%)
R^1=Ph, R^2=Me
R^3=*p*-NO_2Ph

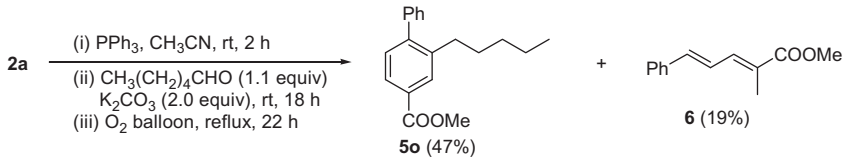


5l (57%)
R^1=Me, R^2=H
R^3=*p*-NO_2Ph

[a] MBH alcohols **1** and the corresponding MBH bromides **2** were prepared as reported.[7,8] For **1a–e** and **2a–e**: **a**: R^1 = Ph, R^2 = H; **b**: R^1 = *p*-MeOPh, R^2 = H; **c**: R^1 = *p*-FPh, R^2 = H; **d**: R^1 = Ph, R^2 = Me; **e**: R^1 = Me, R^2 = H. For **3a–h**: **a**: R^3 = Ph; **b**: R^3 = *p*-ClPh; **c**: R^3 = *p*-MeOPh; **d**: R^3 = *p*-NO_2Ph; **e**: R^3 = *p*-PhPh; **f**: R^3 = 4-pyridyl; **g**: R^3 = 2-furyl; **h**: R^3 = 5-Me-2-thienyl.
[b] The yield of *o*-terphenyl **5** is one of the three-step, one-pot reactions from MBH bromide **2**.
[c] The corresponding MBH acetate was used instead of MBH bromide **2b** for the Wittig reaction.



Scheme 3.



Scheme 4.

yields (45–68%). The yield of **5c** was somewhat low as compared to other entries due to the formation of the hydrolysis product (vide infra).[10] Besides these arylaldehydes, the reactions between **2a** and 4-pyridinecarboxaldehyde (**3f**), 2-furaldehyde (**3g**) and 5-methyl-2-thiophenecarboxaldehyde (**3h**) afforded the corresponding products **5f**–**h** in good yields (58–69%). The use of MBH bromides **2b**-**e**[8j] derived from *p*-methoxycinnamaldehyde, *p*-fluorocinnamaldehyde, α-methylcinnamladehyde, and crotonaldehyde showed similar results, and *o*-terphenyls **5i**–**l** were synthesized in good to moderate yields (54–67%).

The reaction of MBH bromide **2f** bearing an acetyl group showed the same reactivity to produce **5m** in moderate yield (61%) with *p*-nitrobenzaldehyde, as shown in Scheme 3. As compared to the stereochemistry of **2a**–**f**, the MBH bromide **2g** bearing a nitrile moiety was formed in the opposite stereochemistry.[8j] Thus, the intermediate triene **4g** might have a wrong stereochemistry around the second double bond, and the 6π-electrocyclization cannot occur. Actually, the reaction of **2g** did not produce the corresponding *o*-terphenyl **5n** in appreciable amount under the same reaction conditions as expected.

In order to check the scope of the reaction, the reaction of **2a** was examined with *n*-hexanal although the expected product **5o** is not an *o*-terphenyl derivative, as shown in Scheme 4. The yield of **5o** was somewhat low (47%) as compared to *o*-terphenyls **5a**–**m** derived from arylaldehydes. As noted above, an appreciable amount of methyl 2-methyl-5-phenylpenta-2,4-dienoate (**6**), the reduction product of a phosphonium salt of **2a**, were formed during the Wittig reaction even in the presence of $MgSO_4$.[10c]

In summary, various *o*-terphenyl derivatives were synthesized in a one-pot reaction from MBH bromides of cinnamaldehydes via a sequential Wittig reaction, 6π-electrocyclization, and a base-mediated aerobic oxidation process.

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9. For the Wittig type reaction of MBH adducts and their synthetic application, see: (a) Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976–979; (b) Lee, C. G.; Lee, K. Y.; Kim, S. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 719–720; (c) Crist, R. M.; Reddy, P. V.; Borhan, B. *Tetrahedron Lett.* **2001**, *42*, 619–621; (d) Muthiah, C.; Kumar, K. S.; Vittal, J. J.; Swamy, K. C. K. *Synlett* **2002**, 1787–1790; (e) Palmelund, A.; Myers, E. L.; Tai, L. R.; Tisserand, S.; Butts, C. P.; Aggarwal, V. K. *Chem. Commun.* **2007**, 4128–4130; For the synthesis of methyl 5-phenyl-2-styrylpenta-2,4-dienoate (**4a**), see: (f) Kang, S.-K.; Lee, Y.-T.; Lee, S.-H. *Tetrahedron Lett.* **1999**, *40*, 3573–3576; (g) Janecki, T. *Synth. Commun.* **1993**, *23*, 641–650. Although the assignment of stereochemistry and the *E*/*Z* ratio of triene **4a** was not clear from its ^{1}H NMR spectrum, the high yield (91%) of *o*-terphenyl **5a** from **4a** stated that the stereochemistry at the 2-position of **4a** must be *E*, as shown in Scheme 1. In the absence of K_2CO_3 under N_2 balloon atmosphere (CH_3CN, reflux, 40 h), the reaction of **4a** produced *cis*-dihydrobenzene **I** in good yield (74%) by disrotatory 6π-electrocyclization (thermally allowed by the Woodward–Hoffman rules) along with a trace amount of **5a** (7%). The ^{1}H NMR data of **I** were well matched with the reported data of a similar compound:[5d] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H), 3.81 (ddd, J = 9.9, 4.5 and 2.1 Hz, 1H), 4.05 (dd, J = 9.9 and 4.2 Hz, 1H), 6.00 (dd, J = 9.9 and 4.5 Hz, 1H), 6.63–6.73 (m, 5H), 6.94–7.20 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 45.63, 47.24, 51.90, 122.50, 126.66, 126.71, 127.72, 127.82, 127.99, 129.07, 129.09, 130.78, 137.80, 138.28, 139.56, 166.08. The result strongly confirmed that the major isomer of **4a** is an *E,E,E*-triene, as shown in Scheme 1.
10. In addition, an appreciable amount (5–10%) of the hydrolysis product, methyl 2-methyl-5-phenylpenta-2,4-dienoate (**6**, see Scheme 4), was formed during the Wittig reaction. The addition of $MgSO_4$ was helpful for the increase of the yield of **4a** by suppressing the hydrolysis of a phosphonium salt. For the hydrolysis of phosphonium salt, see: (a) Lee, K. Y.; Na, J. E.; Lee, M. J.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 5977–5981; (b) Siegel, B. *J. Am. Chem. Soc.* **1979**, *101*, 2265–2268; For the synthesis of methyl 2-methyl-5-phenylpenta-2,4-dienoate, see: (c) Meier, L.; Ferreira, M.; Sa, M. M. *Heteroat. Chem.* **2012**, *23*, 179–186; (d) Pachamuthu, K.; Vankar, Y. D. *Tetrahedron Lett.* **1998**, *39*, 5439–5442.
11. *Typical procedure for the synthesis of compound* ***5a***: A mixture of MBH bromide **2a** (281 mg, 1.0 mmol),[8j] PPh_3 (288 mg, 1.1 mmol), and $MgSO_4$ (1.0 g) in CH_3CN (3.0 mL) was stirred at room temperature for 2 h to form the phosphonium salt. Benzaldehyde (117 mg, 1.1 mmol) and K_2CO_3 (276 mg, 2.0 mmol) were added into the flask, and the reaction mixture was stirred for 12 h at room temperature to form triene **4a**. The reaction mixture was then heated to reflux for 15 h under O_2 balloon atmosphere. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 100:1) compound **5a** was obtained as a white solid, 159 mg (55%). Other *o*-terphenyls were synthesized similarly, and the spectroscopic data of selected compounds **5a**, **5d**, **5g**, **5i**, **5l**, **5m,** and **5o** are as follows.
Compound ***5a***:[1h,i] 55%; white solid, mp 126–128 °C; IR (KBr) 2982, 1708, 1628, 1265, 1209, 1022 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 3H), 7.05–7.08 (m, 4H), 7.13–7.18 (m, 6H), 7.42 (d, J = 8.1 Hz, 1H), 7.99 (dd, J = 8.1 and 1.8 Hz, 1H), 8.04 (d, J = 1.8 Hz, 1H); ESIMS m/z 289 [M+H]$^+$.
Compound ***5d***: 68%; yellow solid, mp 124–126 °C; IR (KBr) 3005, 2953, 1725, 1511, 1260 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.90 (s, 3H), 7.03–7.05 (m, 2H), 7.18–7.20 (m, 3H), 7.24 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.1 Hz, 1H), 8.01 (s, 1H), 8.04–8.08 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.36, 123.32, 127.72, 128.40, 129.56, 129.59, 129.71, 130.65, 131.09, 131.46, 138.41, 139.55, 145.18, 146.70, 147.48, 166.50; ESIMS m/z 334 [M+H]$^+$. Anal. Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 72.31; H, 4.73; N, 4.11.
Compound ***5g***: 58%; colorless oil; IR (film) 2979, 1708, 1604, 1513, 1237 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H), 5.56 (dd, J = 3.3 and 0.6 Hz, 1H), 6.16 (dd, J = 3.3 and 1.8 Hz, 1H), 7.18–7.22 (m, 2H), 7.26–7.34 (m, 5H), 7.90 (dd, J = 8.1 and 1.8 Hz, 1H), 8.41 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.23, 109.65, 111.34, 127.69, 128.09, 128.23, 128.43, 128.67, 129.38, 129.63, 130.97, 141.06, 141.86, 143.56, 151.80, 166.79; ESIMS m/z 279 [M+H]$^+$. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.49; H, 5.26.
Compound ***5i***: 54%; pale yellow solid, mp 90–92 °C; IR (KBr) 2952, 2926, 1721, 1309, 1265 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70 (s, 3H), 3.86 (s, 3H), 6.69 (d, J = 9.0 Hz, 2H), 6.99 (d, J = 9.0 Hz, 2H), 7.07–7.11 (m, 2H), 7.14–7.19 (m, 3H), 7.40 (d, J = 8.1 Hz, 1H), 7.97 (dd, J = 8.1 and 1.8 Hz, 1H), 8.01 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.13, 55.16, 113.46, 126.76, 128.04, 128.49, 128.75, 129.76, 130.60, 130.83, 131.89, 132.78, 140.54, 140.80, 144.66, 158.77, 166.97; ESIMS m/z 319 [M+H]$^+$. Anal. Calcd for $C_{21}H_{18}O_3$: C, 79.22; H, 5.70. Found: C, 79.15; H, 5.98.
Compound ***5l***: 57%; pale yellow solid, mp 106–108 °C; IR (KBr) 2925, 1722, 1519, 1348 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.25 (s, 3H), 3.85 (s, 3H), 7.32 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.84 (s, 1H), 7.92 (d, J = 7.5 Hz, 1H), 8.24 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.62, 52.20, 123.56, 128.17, 129.43, 130.10, 130.53, 130.90, 139.72, 140.61, 147.08, 147.62, 166.69; ESIMS m/z 272 [M+H]$^+$. Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.72; H, 4.90; N, 5.01.
Compound ***5m***: 61%; pale yellow solid, mp 136–138 °C; IR (KBr) 2951, 1714, 1593, 1515, 1342 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.61 (s, 3H), 7.02–7.06 (m, 2H), 7.17–7.22 (m, 3H), 7.25 (d, J = 9.0 Hz, 2H), 7.51 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 8.1 and 1.8 Hz, 1H), 8.03 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.74, 123.35, 127.78, 128.42, 128.56, 129.55, 130.14, 130.63, 131.24, 136.32, 138.64, 139.44, 145.32, 146.72, 147.50, 197.31; ESIMS m/z 318 [M+H]$^+$. Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.96; H, 4.73; N, 4.19.
Compound ***5o***: 47%; colorless oil; IR (film) 2951, 2924, 1721, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (t, J = 6.6 Hz, 3H), 1.07–1.18 (m, 4H), 1.39–1.44 (m, 2H), 2.53 (t, J = 7.8 Hz, 2H), 3.87 (s, 3H), 7.16–7.24 (m, 3H), 7.28–7.38 (m, 3H), 7.81 (dd, J = 8.1 and 1.8 Hz, 1H), 7.90 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.91, 22.28, 30.87, 31.54, 32.84, 52.08, 126.67, 127.24, 128.11, 128.88, 128.99, 130.14, 130.46, 140.72, 141.02, 146.47, 167.24; ESIMS m/z 283 [M+H]$^+$. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.67; H, 7.93.