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Synthesis and cyclo-oligomerization of 2-(bromomethyl)-3-aryl-2-propenoic acid derivatives

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ABSTRACT

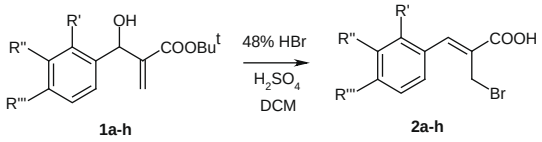
2-Bromomethyl-3-aryl-2-propenoic acids have been synthesized from Baylis–Hillman adducts derived from aromatic aldehydes and *t*-butyl acrylates as new precursors in MBH chemistry. Further triolides were synthesized by the cyclo-oligomerization of 2-bromomethyl-3-aryl-2-propenoic acids in the presence of Cs_2CO_3 demonstrating the synthetic utility of these motifs.

Morita Baylis–Hillman (MBH) reaction[1–4] has found wide applicability by virtue of its functional density, the diversity of functionality realized by the widening of the substrate scope,[1] and further functionalization by nucleophilic substitution.[5] These striking features have contributed to the synthesis of multifunctional derivatives,[6] heterocycles,[7] carbocycles[8], and several biologically relevant molecules[1e,h] through MBH chemistry.

In continuation of our interest in MBH chemistry,[9] in this Letter we report the synthesis of 2-bromomethyl-3-aryl prop-2-enoic acids as new precursor in Baylis–Hillman chemistry and have demonstrated their utility in the synthesis of triolides.

MBH acetates[10] and halides[11] as precursors have dominated the arena of BH chemistry. Most chemical transformations in the MBH chemistry essentially involved hydrolysis of the ester functionality.[12] It occurred to us that carboxylic acid functionality instead of ester would be more suited for further chemical transformations. Schneider et al. have reported the synthesis of 2-bromomethyl-2-butenoic acid moiety via a three-step procedure starting from the MBH adducts of acetaldehyde and methyl acrylate.[13] Ciganek obtained a mixture of 2-(methoxymethyl)-3-aryl-2-propenoic acid and methyl 2-(methoxymethyl)-3-aryl-2-propenoate by the tandem vicinal difunctionalization of methyl acrylate with sodium methoxide and aromatic aldehydes. The ester was subsequently treated with HBr in acetic acid at 60 °C to furnish the 2-(bromomethyl)-3-aryl-2-propenoic acid.[14] Thus we envisaged the synthesis of 2-bromomethyl-3-aryl-2-propenoic acids from *t*-butyl acrylate derived MBH adduct as depicted in Scheme 1 in a single step intending to add a new entry to the list of existing MBH precursors (MBH acetates and bromides).

To this end, we added HBr (8 mL) dropwise followed by H_2SO_4 (8 mL) to a solution of **1a**[15] in DCM at 0 °C and continued the stirring of the reaction mixture until the TLC indicated the disappearance of the starting compounds. The absence of signals



1a-h **2a-h**

Scheme 1.

corresponding to the *t*-butyl group and the presence of allylic protons at δ 4.22 ppm in the ^{1}H NMR spectrum confirmed the formation of the desired product **2a**.[16] Analogously 2-bromomethyl-3-aryl-2-propenoic acid derivatives (**2b–h**) were synthesized and the results are assembled in Table 1.

Difference NOE experiment was carried out to assign the stereochemistry of **2a** (Fig. 1). Irradiation of methylene protons led to the enhancement of the aromatic peak at δ 7.62 ppm by 26.3%. Further irradiation of the olefinic proton led to enhancement of the aromatic proton at δ 7.62 ppm by 7.2%. No enhancement was observed in the olefinic signal on irradiating the methylene protons indicating that they are trans and thus possess *E* stereochemistry.

The synthesis of γ-butyrolactones and γ-butyrolactams from 2-bromomethylacrylic acid clearly highlights the synthetic utility of the structural framework.[17] In addition Schneider et al. oligomerized 2-bromomethyl-3-phenyl-2-propenoic acid in acetonitrile using DBU as base to tri- and tetrolides at room temperature. They also obtained triolides, tetrolides, pentolides, and heptolides when the reaction was carried out at 45 °C.[13]

Intrigued by this report and realizing the role of Cs_2CO_3 as an efficient macrocyclization reagent in organic synthesis,[18] we treated a solution of 2-bromomethyl-3-phenyl-2-propenoic acid (**2a**) in DMF with one equivalent of Cs_2CO_3. Stirring the reaction mixture at room temperature for an hour furnished product **3a** in 30% yields. The ^{1}H NMR spectrum of the product displayed shift in the position of the allylic protons but did not give any clue on the degree of oligomerization. Single-crystal XRD studies[19] of **3b**

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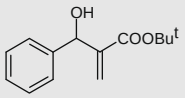
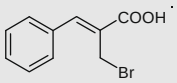
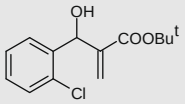
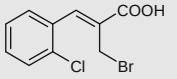
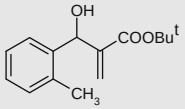
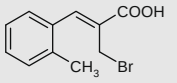
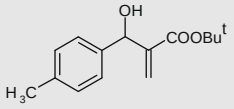
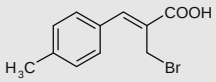
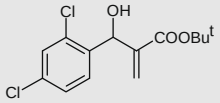
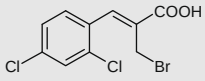
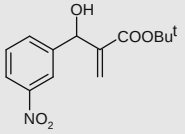
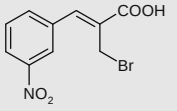
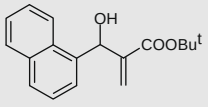
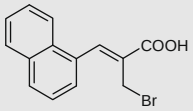
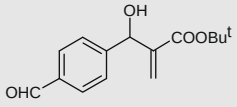
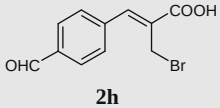
Table 1
Syntheses of 2-(bromomethyl)-3-aryl-2-propenoic acid derivatives

Entry	MBH adduct	2-Bromomethyl-3-aryl-2-propenoic acid	Mp (°C)	Yield (%)[b]
1	 **1a**	 **2a**[14]	158 160[a]	75
2	 **1b**	 **2b**	190	78
3	 **1c**	 **2c**	170	76
4	 **1d**	 **2d**	188	73
5	 **1e**	 **2e**	198	75
6	 **1f**	 **2f**	180	70
7	 **1g**	 **2g**[14]	216 218[a]	71
8	 **1h**	 **2h**	245	60

[a] Literature melting point.
[b] Isolated yield.

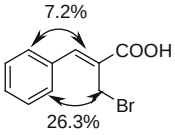


Figure 1. Difference NOE studies of **2a**.

and **3c** (Fig. 2 and 3) obtained by crystallizing the respective pure products from acetone confirmed the products as triolides.

Having established the products as triolides, next it was our concern to improve the yields. Cyclo-oligomerization of **2e** was

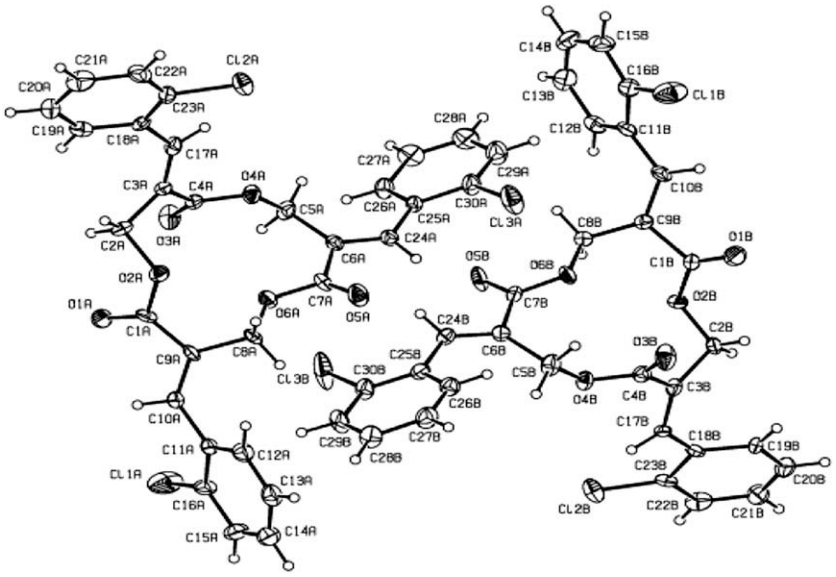


Figure 2. ORTEP diagram of **3b**.

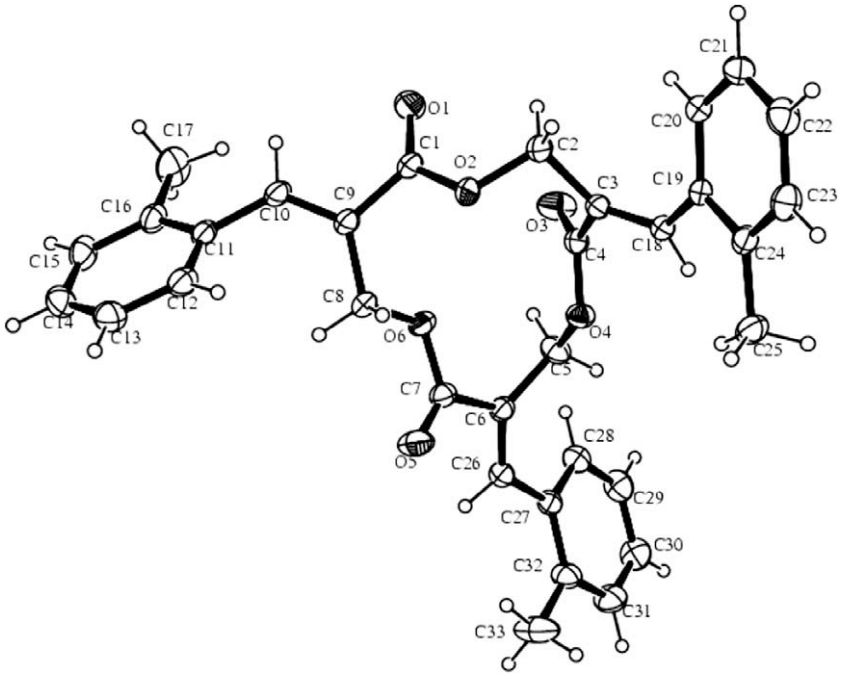
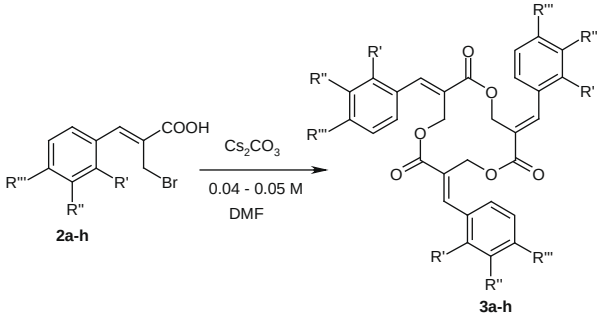


Figure 3. ORTEP diagram of **3c**.

Table 2
Optimization studies for the cyclo-oligomerization of **2e**

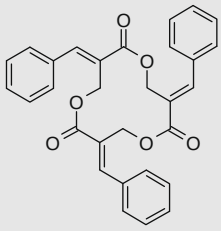
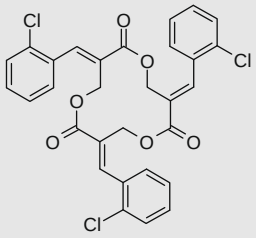
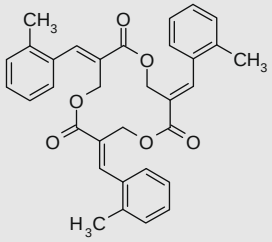
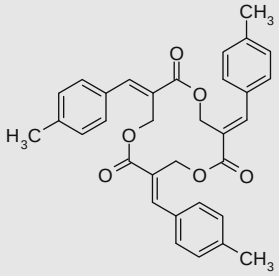
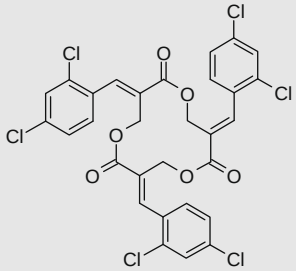
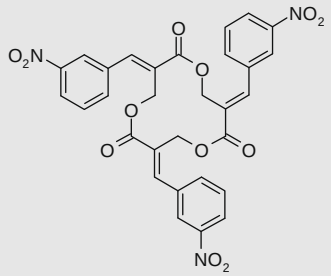
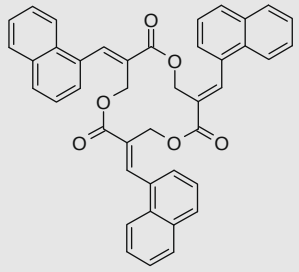
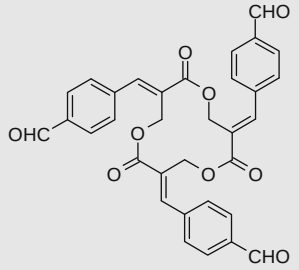
Entry	Concentration	Yield (%)
1	0.03	30
2	0.04	46
3	0.05	61
4	0.12	31

carried out at various concentrations and the results are presented in Table 2. It is evident from the Table 2 that good yields of the triolides were obtained only when the cyclo-oligomerization was conducted in 0.04–0.05 M DMF solution.[20] The triolides **3a**–**h** were synthesized under optimized conditions (Scheme 2 and Table 3).



Scheme 2.

Table 3
Cyclo-oligomerization of 2-(bromomethyl)-3-aryl-2-propenoic acid derivatives

Entry	Triolide	Melting point (°C)	Yield (%)[a]
1	 **3a**[13]	137	61
2	 **3b**	170	65
3	 **3c**	126	63
4	 **3d**	62	61
5	 **3e**	182	64
6	 **3f**	160	55
7	 **3g**	120	57
8	 **3h**	159	53

[a] Isolated yield.

In conclusion, we have synthesized 2-bromomethyl-3-aryl-2-propenoic acid derivatives (**2**) as promising precursors in MBH chemistry and cyclo-oligomerized the 2-bromomethyl-3-aryl-2-propenoic acid to triolides (**3**) using Cs_2CO_3 illustrating its synthetic utility. Further work is underway in our laboratory to explore the synthetic utility of 2-bromomethyl-3-aryl-2-propenoic acids in the synthesis of heterocyclic frameworks.

Acknowledgement

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References and notes

1. For reviews see: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001; (c)*Organic Reactions*; Ciganek, E., Ed.; John Wiley: New York, 1997; Vol. 51, p 201. Chapter 2; (d) Almeida, W. P.; Coelho, F. *Quim. Nova* **2000**, *23*, 98. *Chem. Abstr.* **2000**, *132*, 236532e; (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (f) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627; (g) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481; (h) Basavaiah, D.; Venkateswara Rao, K.; Jannapu Reddy, R. *Chem. Soc. Rev.* **2007**, *36*, 1581; (i) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511.
2. For the mechanism of Baylis–Hillman reaction see: (a) Bode, M. L.; Kaye, P. T. *Tetrahedron Lett.* **1991**, *32*, 5611; (b) Drewes, S. E.; Emslie, N. D.; Field, J. S.; Khan, A. A.; Ramesar, N. S. *Tetrahedron Lett.* **1993**, *34*, 1205; (c) Santos, L. S.;

Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330; (d) Price, K. E.; Broadwater, S. J.; Jung, H. M.; Mcquade, D. T. *Org. Lett.* **2005**, *7*, 147; (e) Price, K. E.; Broadwater, S. J.; Walker, B. J.; Mcquade, D. T. *J. Org. Chem.* **2005**, *70*, 3980; (f) Aggarwal, V. K.; Fulford, S. Y.; Lioyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706.

3. For a review on Aza Baylis–Hillman reaction see: Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.
4. For review on asymmetric Baylis–Hillman reaction see: (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049; (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614.
5. (a) Srihari, P.; Singh, A. P.; Jain, R.; Yadav, J. S. *Synthesis* **2006**, *16*, 2772; (b) Kim, J. M.; Kim, S. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 2505; (c) Sá, M. M.; Fernandes, L.; Ferreira, M.; Bortoluzzi, A. J. *Tetrahedron Lett.* **2008**, *49*, 1228; (d) Liu, Y. K.; Xu, X. S.; Zheng, H.; Xu, D. Q.; Xu, Z. Y.; Zhang, Y. M. *Synlett* **2006**, 571.
6. (a) Basavaiah, D.; Sarma, P. K. S.; Bhavani, A. K. D. *Chem. Commun.* **1994**, 1091; (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803; (c) Navarre, L.; Darses, S.; Genet, J.-P. *Adv. Synth. Catal.* **2006**, *348*, 317; (d) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, *70*, 9207; (e) Das, B.; Banerjee, J.; Mahender, G.; Majhi, A. *Org. Lett.* **2004**, *6*, 3349; (f) Ranu, B. C.; Chattopadhyay, K.; Jana, R. *Tetrahedron Lett.* **2007**, *48*, 3847.
7. (a) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6645; (b) Park, D. Y.; Kim, S. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6315; (c) Kim, J. N.; Im, Y. J.; Gong, J. H.; Lee, K. Y. *Tetrahedron Lett.* **2001**, *42*, 4195; (d) Basavaiah, D.; Aravindu, K. *Org. Lett.* **2007**, *9*, 2453.
8. (a) Chandrasekhar, S.; Basu, D.; Rambabu, Ch. *Tetrahedron Lett.* **2006**, *47*, 3059; (b) Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. *Synthesis* **2006**, 1953; (c) Singh, V.; Batra, S. *Eur. J. Org. Chem.* **2007**, 2970; (d) Song, Y. S.; Lee, K.-J. *J. Heterocycl. Chem.* **2006**, *43*, 1721.
9. Zulykama, Y.; Perumal, P. T. *Aust. J. Chem.* **2007**, *60*, 205.
10. (a) Mandal, S. K.; Paira, M.; Roy, S. C. *J. Org. Chem.* **2008**, *73*, 3823; (b) Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2007**, *9*, 2525; (c) Badkar, P. A.; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2007**, *9*, 3619; (d) Jiang, Y.-Q.; Shi, Y.-L.; Shi, Min. *J. Am. Chem. Soc.* **2008**, *130*, 7202.
11. (a) Sá, M. M.; Ramos, M. D.; Fernandes, L. *Tetrahedron* **2006**, *62*, 11652; (b) Sreedhar, B.; Reddy, P. S.; Kumar, N. S. *Tetrahedron Lett.* **2006**, *47*, 3055.
12. (a) Gowrisankar, S.; Lee, M. J.; Lee, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2004**, *25*, 1963; (b) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619; (c) Singh, V.; Batra, S. *Synthesis* **2006**, 63.
13. Schneider, M. F.; Blechert, S.; Matuszak, A.; Pickardt, J. *Synlett* **1999**, 638.
14. Ciganek, E. *J. Org. Chem.* **1995**, *60*, 4635.
15. Compounds **1a**–**h** were prepared according to the reported procedure Basavaiah, D.; Mallikarjuna Reddy, R. *Indian J. Chem., Sect B* **2001**, *40B*, 985.
16. *Typical procedure for the synthesis of* **2a**: To a 100 mL RB flask containing *t*-butyl 3-hydroxy-2-methylene-3-phenylpropanoate (6 g, 25 mmol) (**1a**) in dichloromethane (20 mL) was added HBr (48%, 8 mL) at 0 °C followed by the dropwise addition of concentrated sulfuric acid (8 mL). The reaction temperature was allowed to rise to room temperature and stirring continued for 30 min. The reaction mixture was poured into ice cold water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4. The excess solvent was removed under reduced pressure and column was purified (silica gel, 20% ethyl acetate in hexane) to furnish **2a**.(**2Z**)-2-(Bromomethyl)-3-(4-methylphenyl)-2-propenoic acid (**2d**): White solid. Mp 188 °C. IR (KBr): 1422, 1651, 1673, 2835 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 2.27 (s, 3H), 4.16 (s, 2H), 7.18 (d, J = 8 Hz, 2H), 7.47 (d, J = 8 Hz, 2H), 7.59 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 21.47, 55.87, 129.67, 130.40, 132.14, 132.47, 139.45, 141.62, 169.43. MS *m/z* 254 (M^+), 256 (M^++2) Anal Calcd for $C_{11}H_{11}BrO_2$: C, 51.79; H, 4.35. Found: C, 51.84; H, 4.32.
17. (a) Choudhury, P. K.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 3581; (b) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376.
18. Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 186.
19. Detailed X-ray crystallographic data are available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK for compound **3b** (CCDC No. 698943) and **3c** (CCDC No. 698945).
20. *Typical procedure for the syntheses of compounds* **3a**: Cesium carbonate (1.35 g, 4.2 mmol) was added to 2-(bromomethyl)-3-phenyl-2-propenoic acid **2a** (1 g, 4.2 mmol) in DMF (100 mL) and the reaction mixture was stirred for 1 h. After completion of the reaction as indicated by TLC, the reaction mixture was poured into water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. The excess solvent was removed under reduced pressure and column was purified (silica gel, 10% ethyl acetate in hexane) to furnish **3a**.(**3E,7E,11E**)-3,7,11-Tris(2-methylbenzylidene)-1,5,9-trioxacyclododecane-4,8,12-trione(**3c**): White solid. Mp 126 °C. IR (KBr) :1630, 1171, 2934 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 9H), 5.08 (s, 6H), 7.18–7.30 (m, 12H), 7.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.08, 61.11, 125.98, 128.39, 128.98, 129.37, 130.42, 133.50, 137.35, 143.49, 166.63. MS *m/z* 523 (M^+). Anal Calcd for $C_{33}H_{30}O_6$: C, 75.84; H, 5.79. Found: C, 75.90; H, 5.77.