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A Diversity-Oriented Approach to Diphenylalkanes by Strategic Utilization of [2+2+2] Cyclotrimerization, Cross-Enyne Metathesis and Diels–Alder Reaction

Sambasivarao Kotha*[a] and Priti Khedkar[a]

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A novel and efficient approach towards the synthesis of polysubstituted diphenylalkane derivatives have been demonstrated using a strategic combination of [2+2+2] cyclotrimerization, ethylene cross-enyne metathesis and Diels–Alder reaction as key steps. The strategy involves the stepwise functionalization of acetylenic termini of α,ω-diyne scaffold to build functionalized aromatic units.

Introduction

The diphenylalkane structural motif is present in a variety of natural products and biologically important molecules. For example, viscolin **1** (Figure 1) is a naturally occurring 1,3-diphenylpropane, isolated from the *Viscum coloratum*,[1] a hemiparasite herb used in Chinese medicine as a curative for a number of ailments such as hemorrhage, pleurisy, gout, heart disease, epilepsy, arthritis, and hypertension.[2] Also, 1,2-diphenylethane derivatives are known to possess cytotoxic activity towards genital fibroblasts.[3] Some diphenylethane derivatives (for instance **2**) are known to possess antiestrogenic activity.[4] The neuroendocrine effects of (+)-1,4-diphenylbutane-2,3-diol (**3**, DPB) which is testicular in origin has been subject of intense studies.[5] Lopinavir (ABT-378) **4** containing the 1,6-diphenylalkane backbone is an antiretroviral of the protease inhibitor class. It is marketed by Abbott as Kaletra®, a coformulation with a subtherapeutic dose of ritonavir, as a component of combination therapy to treat HIV/AIDS.[6]

Synthetic routes to prepare diphenylalkane derivatives are limited,[7,8] and most of these methods involve the use of benzenoid precursors and thereby limit the scope for incorporation of desirable substituents in the aromatic ring. Further, many of these procedures are not general in nature and they are not applicable for the preparation of diphenylalkane derivatives containing alkyl chain of varying length. However, in 1980, Japanese investigators demonstrated a general approach to diphenylalkane derivatives containing alkyl chains of varied length, although benzenoid compounds have been used as starting materials.[8] Motivated by these findings, the two acetylenic ends of untethered α,ω-diyne scaffolds (for instance 5) have been used for the assembly of aromatic units and a new approach to polysubstituted diphenylalkane derivatives via a strategic utilization of [2+2+2] cyclotrimerization reaction,[9] cross-enyne metathesis (CEM)[10] and Diels–Alder (DA) reaction[11] as key steps has been conceived. The methodology proposed here constitutes a diversity-oriented approach[12] as there are several points of diversity where structural variations can be incorporated in the target molecule.

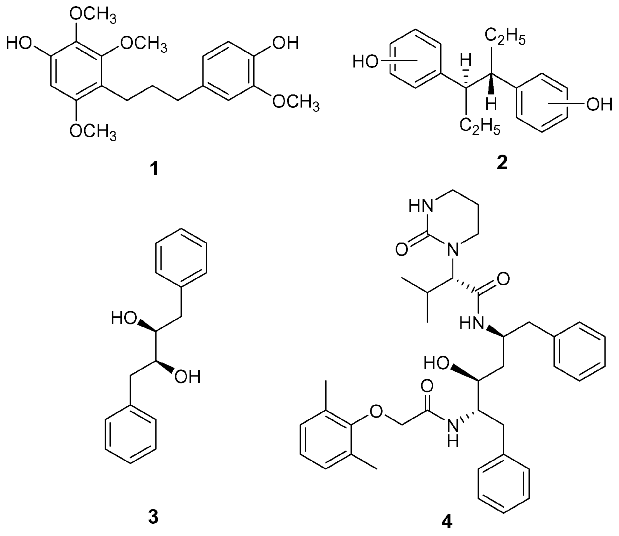

Figure 1. Various biologically active diphenylalkane derivatives.

Results and Discussion

The theme proposed here involves the generation of novel polysubstituted benzene derivatives **6**, containing terminal alkyne appendage by performing [2+2+2] cyclotrimerization of α,ω-diynes **5** and monoyne **5a**. These compounds seem to be suitable substrates for performing an-

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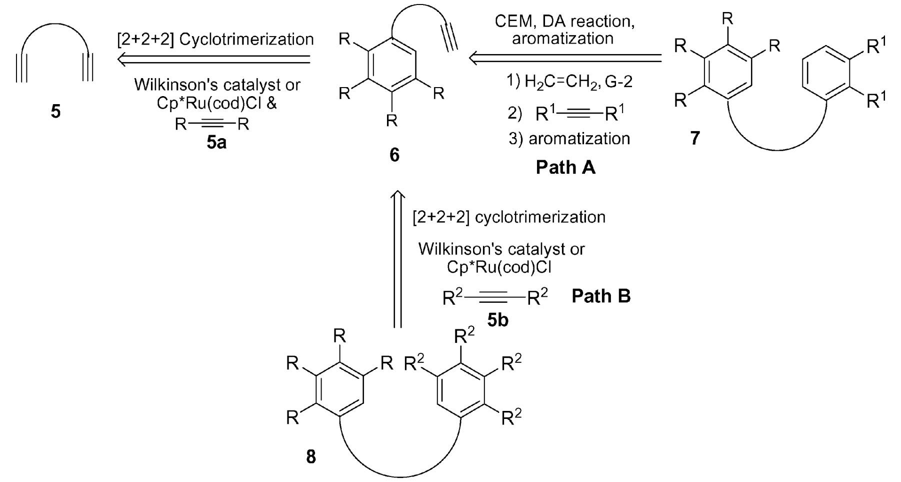
[a] Department of Chemistry, Indian Institute of Technology – Bombay,
Powai, Mumbai 400076, India
Fax: +91-22-2572-3480
E-mail: srk@chem.iitb.ac.in



Scheme 1. Strategies proposed for the synthesis of polysubstituted diphenylalkanes.

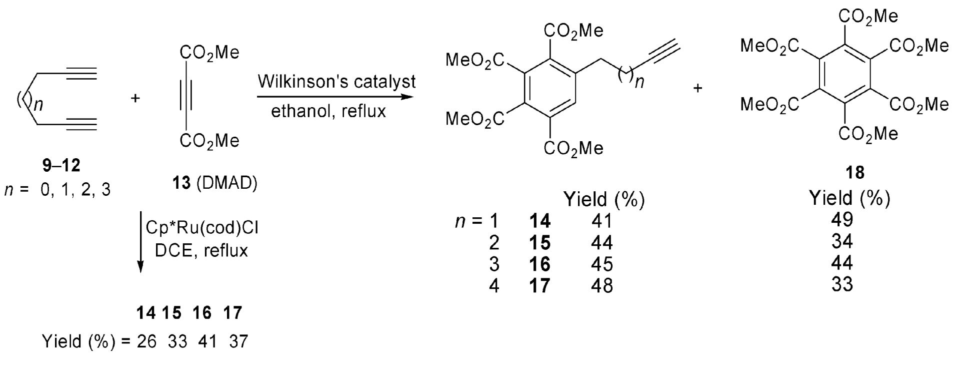
other [2+2+2] cyclotrimerization with monoyne **5b** leading to the formation of diphenylalkane derivative such as **8** (path B, Scheme 1). Moreover, compounds of type **6** appeared to be suitable candidates for the synthesis of densely functionalized diphenylalkane derivatives of type **7** via ethylene CEM followed by DA reaction (path A, Scheme 1).

Recent advances in transition metal-catalyzed [2+2+2] cyclotrimerizations has paved the way for assembling diverse molecular frames of synthetic interest.[9] In particular, rhodium-catalyzed [2+2+2] cyclotrimerization reactions[13–15] are widely used to design complex molecular arrays. Also, we have demonstrated a tactical utilization of Wilkinson's catalyst, $RhCl(PPh_3)_3$ to deliver highly functionalized compounds.[16] Although, few reports[17] deal with the usage of transition metal complexes to effect [2+2+2] cyclotrimerizations of the untethered α,ω-diynes, only limited examples demonstrate the use of rhodium complexes.[14c,14s,18]

In connection with our major program directed towards the synthesis of annulated benzocycloalkane derivatives, various α,ω-diynes such as 1,5-hexadiyne (**9**), 1,6-heptadiyne (**10**), 1,7-octadiyne (**11**) and 1,8-nonadiyne (**12**), were subjected to [2+2+2] cyclotrimerization reaction with dimethyl acetylenedicarboxylate (DMAD, **13**). We employed Wilkinson's catalyst to affect this transformation and found that the polysubstituted benzene derivatives **14**–**17** were produced. The hexamethyl mellitate was also generated in all the cases, the formation of which can be attributed to self-trimerization of DMAD (Scheme 2).

Yamamoto and co-workers have demonstrated tactical utilization of Cp*Ru(cod)Cl in cyclotrimerization reactions to assemble various polycyclic molecules.[19] When we employed, Cp*Ru(cod)Cl to achieve cyclotrimerization reaction between α,ω-diynes **9**–**12** and DMAD (**13**) various polysubstituted benzene derivatives such as **14**–**17** were obtained (Scheme 2). However, with ruthenium catalyst DMAD self-trimerization product, hexamethyl mellitate **18**, was not generated in detectable amounts. High dilution conditions, changing the molar equivalence of diyne to monoyne and varying the sequence of addition of starting materials, gave the same products. When the monoyne partner was changed to but-2-yne-1,4-diol, 1,4-diacetoxy-2-butyne, or 1,2-bis(trimethylsilyl)acetylene no such trimerization products could be isolated.

Alkyne building blocks have been used as starting materials in many processes such as Sonogashira reaction,[20] Glaser coupling,[21] Pauson–Khand reaction,[22] enyne metathesis,[23] and [2+2+2] cyclotrimerization[9] reactions. This has resulted in the emergence of various methods to generate terminal acetylenic compounds.[24] However, some of



Scheme 2. Preparation of polysubstituted benzene derivatives.

these procedures involve lengthy synthetic sequences and strong bases. Gratifyingly, we found that the [2+2+2] cyclotrimerization reaction of α,ω-diynes and DMAD can be utilized to generate terminal alkynes in a single step. Moreover, this methodology may permit the preparation of aromatic unit with a flexible substitution pattern, depending upon the monoyne employed. Thus, the strategy employed here provides a unique opportunity to assemble the aromatic core containing terminal alkyne in a single step under mild reaction conditions.

Literature precedence indicates that metallocyclopentadienes are key intermediates in transition metal-catalyzed cyclotrimerization reactions.[9,14c] Among the various mechanistically possible rhodacyclopentadiene intermediates[14c] we have considered two such intermediates which can justify the formation of products obtained in the present investigation. Various other alternative rhodacyclopentadiene intermediates[14c] might have formed under the reaction conditions employed but their involvement could not be inferred based on the products isolated. Rh^I complex probably couples oxidatively with two acetylenic moieties thereby delivering Rh^I rhodacyclopentadienes **19** and **20**. Later on, an insertion or a Diels–Alder-type process incorporates the third acetylenic partner into the rhodacyclopentadiene intermediate. Finally, reductive elimination of Rh^I is considered to complete the catalytic cycle. Reaction of **19** with one molecule of **13**, or **20** reacting with one end of diyne moiety can account the formation of polysubstituted benzene derivatives **6′**. The isolation of hexamethyl mellitate **18** can be explained on the basis of DMAD molecule reacting with rhodacyclopentadiene **20** (Figure 2).

Various polysubstituted benzene derivatives **14**, **15**, **16** and **17** (Scheme 2) obtained via [2+2+2] cyclotrimerization reaction appear to be ideal candidates for the synthesis of functionalized diphenylalkane derivatives. In principle, repetition of [2+2+2] cyclotrimerization process at the alkyne terminal of these molecular entities **14**–**17** can produce highly functionalized diphenylalkane derivatives (Scheme 1, Path B). When the terminal alkyne **14** was subjected again to cyclotrimerization in the presence of Wilkinson's catalyst using DMAD as a monoyne partner, only the starting material was recovered and most of the DMAD was found to undergo self-trimerization to deliver **18**. Even the use of the traditional cobalt catalyst $CpCo(CO)_2$ was found to be futile to effect the cotrimerization between **14** and DMAD. In a series of separate experiments, both Wilkinson's catalyst and $CpCo(CO)_2$ were found to be inefficient to catalyze the self-trimerization of **14**.

Metal-catalyzed olefin metathesis[25] undoubtedly has a profound impact on organic synthesis and is widely used for C–C bond formation. The commercial availability of Grubbs' first- and second-generation catalysts (G-I or G-II) (Figure 3)[26] has provided an easy access to a wide range of complex compounds. The literature examples[10] and our previous experience[10a,10b] suggested that ethylene CEM can be a valuable process to create 1,3-diene at the alkyne terminal of polysubstituted benzene derivatives. The DA reaction performed at diene may deliver the diphenylalkane derivative.

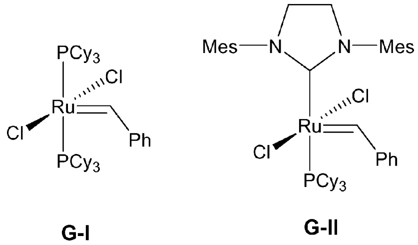


Figure 3. Commonly used ruthenium-based metathesis catalysts.

In this regard, the alkynes **14**–**17** were subjected to CEM with ethylene in presence of a G-II catalyst, using toluene as a solvent. We were pleased to obtain diene derivatives **21**–**24** in excellent yields (Scheme 3). Before the addition of catalyst, the reaction mixture was degassed by bubbling ethylene and then the reaction mixture was maintained under ethylene atmosphere. The yield of these reactions was remarkably reduced when dichloromethane was used as a solvent. When the CEM was attempted with G-I, consumption of the starting material was found to be sluggish and even high catalyst loading seems to be ineffective in accelerating the rate of the reaction. The dienes **21**–**24** were found to be stable and could be isolated and characterized by the spectroscopic methods.

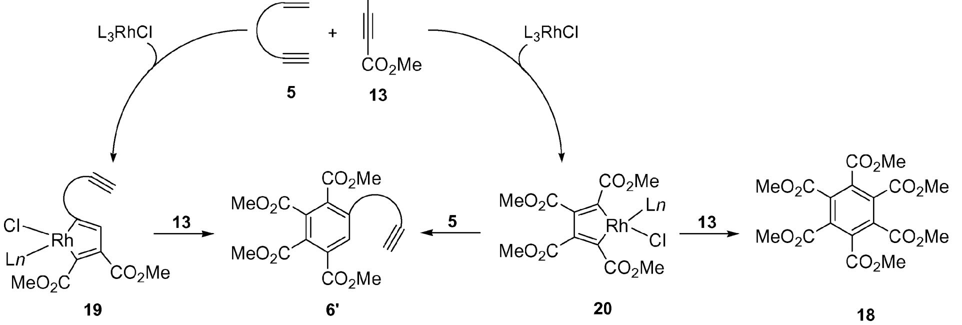
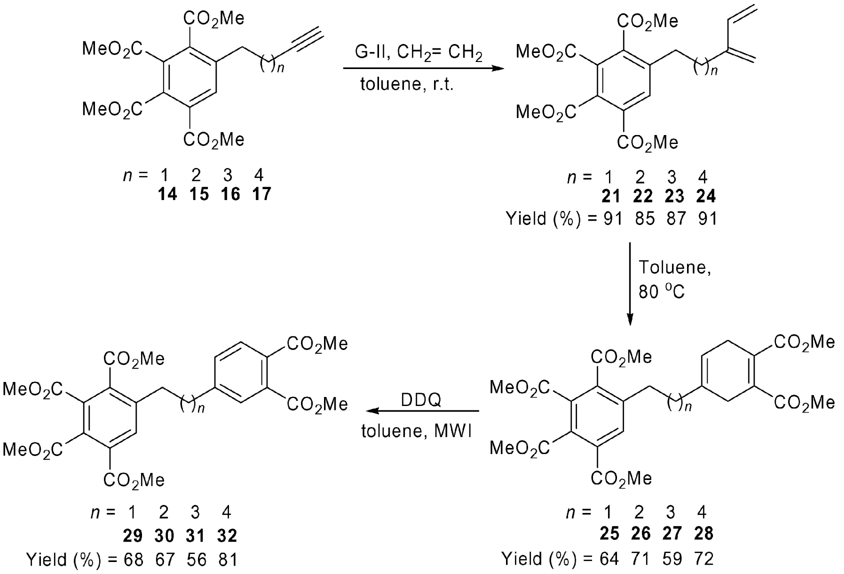


Figure 2. Probable mechanistic pathways defining the formation of terminal alkyne containing polysubstituted benzenes.



Scheme 3. Preparation of diphenylalkanes.

The DA reaction of **21**–**24** has been accomplished by heating a solution of diene and dienophile, **13** in toluene at 80 °C (Scheme 3). Partial aromatization of the DA product was observed when the reaction mixture was heated at reflux temperature in toluene. However, prolonged refluxing in toluene did not lead to complete aromatization. When the reaction was performed at room temp. or at 50 °C no formation of DA product was observed. Also, an attempt to perform the DA reaction at lower temperature using Lewis acid, such as $BF_3{\cdot}OEt_2$, as a catalyst was proved to be futile.

All the DA adducts **25**–**28** were subsequently aromatized by using 2,3-dichoro-5,6-dicyano-*p*-benzoquinone (DDQ). Although conventional conditions involving heating the DA adduct and DDQ in toluene were found to be ineffective, microwave irradiation of the reaction mixture delivered the corresponding aromatized diphenylalkane derivatives **29**–**32** in good yields (Scheme 3).

Conclusions

A simple and novel route to terminal alkyne containing aromatic compounds has been established via exclusive monofunctionalization of commercially available α,ω-diynes. A diversity oriented approach towards the synthesis of densely functionalized diphenylalkane derivatives has been established via a sequential implementation of [2+2+2] cyclotrimerization, ethylene CEM and DA reaction. The two different polysubstituted aromatic rings are built at the two ends of α,ω-diyne scaffold in a stepwise manner. This strategy offers four points of diversity. The first aspect is the commercial availability of α,ω-diynes of varying chain length. The second diversity point is the utilization of [2+2+2] cyclotrimerization where the monoyne can be altered. The third dimension is the utilization of DA reaction where different dienophiles can be used. Finally, one can use various ethylene derivatives to effect CEM sequence and introduce an additional functionality in the 1,3-diene component. Designing of unsymmetrical molecules starting with symmetrical synthons is of major concern in organic synthesis.[27] As we have created desymmetrization in highly symmetrical starting materials, α,ω-diynes, this method offers the additional value. In view of the tactical utilization of highly atom-economical processes such as [2+2+2] cyclotrimerization, CEM and DA reaction, our approach can be regarded as a "Green Route" for the synthesis of densely functionalized diphenylalkanes.

Experimental Section

General: Analytical TLC was performed on glass plates (10 × 5 cm) coated with silica gel G or GF 254 (containing 13% $CaSO_4$ as a binder). Visualization of the spots on TLC plate was achieved either by exposure to I_2 vapour or UV light. Column chromatography was performed using silica gel (100–200 mesh) and column was usually eluted with ethyl acetate and petroleum ether (boiling range 60–80 °C) mixture. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectroscopic data were recorded on a Varian VXR 300 and Varian VXR 400 spectrometers using TMS as an internal standard and $CDCl_3$ or C_6D_6 as the solvent. The coupling constants (*J*) are given in Hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from internal reference, tetramethylsilane. The standard abbreviation s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublet, and triplet of doublet respectively. Mass spectroscopic data was recorded on a Q-TOF micromass machine. Infrared (IR) spectra were recorded on a Nicolet Impact-400 FT IR spectrometer. Solid samples were recorded as KBr wafers and liquid samples were recorded as neat. Melting points were recorded on Labhosp or Veego melting point apparatus and are uncorrected.

1,5-Hexadiyne (**9**), 1,6-heptadiyne (**10**), 1,7-octadiyne (**11**), 1,8-nonadiyne (**12**), DMAD (**13**), and Wilkinson's catalyst were purchased from Alfa-Aesar-Lancaster (Whitelund, U. K.). Second-generation Grubbs' catalyst (**G-II**) was purchased from Fluka chemicals (Switzerland).

Preparation of Alkyne 14

a) Using Wilkinson's Catalyst: To a solution of 1,5-hexadiyne **9** (110 mg, 1.41 mmol) in dry degassed ethanol (12 mL) maintained under nitrogen, was added **13** (1 g, 7.04 mmol) and Wilkinson's catalyst (13 mg, 0.014 mmol, 1 mol-%). The resulting pale yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (226 mg) followed by the polysubstituted benzene derivative **14** (210 mg, 41%) as a colorless solid. Further elution of the column with 40% EtOAc/petroleum ether furnished, hexamethyl mellitate **18** (162 mg, 49%[28]) as a colorless crystalline solid. Data for compound **18**: $\boldsymbol{R}_\mathbf{f}$ = 0.19 (silica gel, 40% EtOAc/petroleum ether), m.p. 186 °C.[29]

b) Using Cp*Ru(cod)Cl Catalyst: To a solution of 1,5-hexadiyne **9** (48 mg, 0.615 mmol) in dry degassed dichloroethane (20 mL) maintained under nitrogen was added **13** (440 mg, 3.09 mmol) and Cp*Ru(cod)Cl (6 mg, 0.015 mmol, 2.5 mol-%). The resulting yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (148 mg) followed by the polysubstituted benzene derivative **14** (59 mg, 26%) as a colorless solid. Data for compound **14**: R_f = 0.43 (silica gel, 40% EtOAc/petroleum ether), m.p. 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00 (t, J = 2.4 Hz, 1 H), 2.52 (dt, J_1 = 8.8, J_2 = 2.4 Hz, 2 H), 2.94 (t, J = 7.2 Hz, 2 H), 3.86–3.92 (m, 12 H), 8.06 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 20.0, 32.3, 53.0, 53.0, 53.1, 53.3, 70.3, 82.3, 130.0, 130.1, 133.8, 134.4, 136.9, 140.3, 165.0, 165.8, 167.3, 167.6 ppm. IR (KBr): $\tilde{\nu}$ = 3304, 2954, 2305, 1736, 1440, 1158 cm^{-1}. HRMS (Q-Tof): m/z calcd. mass 385.0899 for $C_{18}H_{18}O_8Na$ [M + Na]$^+$; found 385.0898.

Preparation of Alkyne 15

a) Using Wilkinson's Catalyst: To a solution of 1,6-heptadiyne **10** (161 mg, 1.75 mmol) in dry degassed ethanol (12 mL) maintained under nitrogen, was added **13** (1.2 g, 8.45 mmol) and Wilkinson's catalyst (16 mg, 0.017 mmol, 1 mol-%). The resulting pale yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (200 mg) followed by the polysubstituted benzene derivative **15** (291 mg, 44%) as a colorless solid. Further elution of the column with 40% EtOAc/petroleum ether furnished, hexamethyl mellitate **18** (135 mg, 34%[28]) as a colorless crystalline solid.

b) Using Cp*Ru(cod)Cl Catalyst: To a solution of 1,6-heptadiyne **10** (52 mg, 0.565 mmol) in dry degassed dichloroethane (12 mL) maintained under nitrogen was added **13** (401 mg, 2.82 mmol) and Cp*Ru(cod)Cl (5 mg, 0.013 mmol, 2.4 mol-%). The resulting yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (160 mg) followed by the polysubstituted benzene derivative **15** (71 mg, 33%) as a colorless solid. Data for compound **15**: R_f = 0.47 (silica gel, 40% EtOAc/petroleum ether), m.p. 62–64 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.87 (m, 2 H), 2.02 (t, J = 2.4 Hz, 1 H), 2.23 (dt, J_1 = 6.8, J_2 = 2.8 Hz, 2 H), 2.84 (t, J = 8 Hz, 2 H), 3.91–3.92 (m, 12 H), 7.99 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 29.7, 32.3, 53.0, 53.1, 53.1, 53.3, 69.4, 83.4, 130.0, 130.2, 133.5, 134.2, 137.1, 141.8, 165.2, 165.8, 167.5, 167.7 ppm. IR (KBr): $\tilde{\nu}$ = 2955, 1966, 1728, 1651, 1440, 1155 cm^{-1}. HRMS (Q-Tof): m/z calcd. mass 399.1056 for $C_{19}H_{20}O_8Na$ [M + Na]$^+$; found 399.1043.

Preparation of Alkyne 16

a) Using Wilkinson's Catalyst: To a solution of 1,7-octadiyne **11** (160 mg, 1.5 mmol) in dry degassed ethanol (12 mL) maintained under nitrogen, was added **13** (1.0 g, 7.04 mmol) and Wilkinson's catalyst (14.2 mg, 0.015 mmol, 1 mol-%). The resulting pale yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (250 mg) followed by the polysubstituted benzene derivative **15** (263 mg, 45%) as a colorless solid. Further elution of the column with 40% EtOAc/petroleum ether furnished, hexamethyl mellitate **18** (148 mg, 44%[28]) as a colorless crystalline solid.

b) Using Cp*Ru(cod)Cl Catalyst: To a solution of 1,7-octadiyne **11** (20 mg, 0.188 mmol) in dry degassed dichloroethane (10 mL) maintained under nitrogen was added **13** (164 mg, 1.15 mmol) and Cp*Ru(cod)Cl (3.5 mg, 0.009 mmol, 5 mol-%). The resulting yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (128 mg) followed by the polysubstituted benzene derivative **16** (30 mg, 41%) as a colorless solid. Data for compound **16**: R_f = 0.39 (silica gel, 40% EtOAc/petroleum ether), m.p. 80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53–1.63 (m, 2 H), 1.70–1.77 (m, 2 H), 1.96 (t, J = 2.4, Hz, 1 H), 2.21 (dt, J_1 = 6.4, J_2 = 2.4 Hz, 2 H), 2.73 (t, J = 8 Hz, 2 H), 3.86–3.92 (m, 12 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.0, 27.9, 29.9, 32.7, 52.8, 52.9, 52.9, 53.1, 68.7, 83.8, 129.8, 130.0, 133.1, 133.8, 136.7, 142.3, 165.0, 165.7, 167.4, 167.5 ppm. IR (KBr): $\tilde{\nu}$ = 2950, 1727, 1437, 1149 cm^{-1}. HRMS (Q-Tof): m/z calcd. mass 413.1212 for $C_{20}H_{22}O_8Na$ [M + Na]$^+$; found 413.1213.

Preparation of Alkyne 17

a) Using Wilkinson's Catalyst: To a solution of 1,8-nonadiyne **12** (160 mg, 1.33 mmol) in dry degassed ethanol (12 mL) maintained under nitrogen, was added **13** (960 mg, 6.7 mmol) and Wilkinson's catalyst (8.6 mg, 0.009 mmol, 1 mol-%). The resulting pale yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (210 mg) followed by the polysubstituted benzene derivative **17** (261 mg, 48%) as a thick colorless liquid. Further elution of the column with 40% EtOAc/petroleum ether furnished, hexamethyl mellitate **18** (107 mg, 33%[28]) as a colorless crystalline solid.

b) Using Cp*Ru(cod)Cl Catalyst: To a solution of 1,8-nonadiyne **12** (160 mg, 1.33 mmol) in dry degassed dichloroethane (30 mL) maintained under nitrogen was added **13** (924 mg, 6.5 mmol) and Cp*Ru(cod)Cl (12.5 mg, 0.033 mmol, 2.5 mol-%). The resulting yellow solution was refluxed for 24 h. The reaction mixture was then cooled to room temp. and the solvent was removed under reduced pressure to obtain brown, sticky crude product which was charged on a silica gel column. Elution of the column with 20% EtOAc/petroleum ether gave the unreacted **13** (187 mg) followed by the polysubstituted benzene derivative **17** (201 mg, 37%) as a thick colorless liquid. Data for compound **17**: $R_f = 0.36$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.41$–1.62 (m, 6 H), 1.93 (t, $J = 2.4$ Hz, 1 H), 2.17 (dt, $J_1 = 7.2$, $J_2 = 2.4$ Hz, 2 H), 2.69 (t, $J = 8$ Hz, 2 H), 3.86–3.92 (m, 12 H), 7.93 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 18.3$, 28.1, 28.4, 30.6, 33.3, 52.9, 53.1, 53.3, 68.5, 84.4, 129.8, 130.1, 133.3, 134.0, 136.9, 142.7, 165.2, 165.9, 167.6, 167.8 ppm. IR (KBr): $\tilde{\nu} = 2952$, 2861, 2115, 1735, 1439, 1157 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 427.1369 for $C_{21}H_{24}O_8Na$ [M + Na]$^+$; found 427.1371.

Preparation of Diene 21: The solution of alkyne **14** (49 mg, 0.135 mmol) in dry toluene (12 mL) was degassed with ethylene gas for 10 min and Grubbs' catalyst, G-II (6 mg, 0.007 mmol, 5 mol-%) was then added to it. The reaction vessel was kept under 1 atm. ethylene pressure (using balloon pressure) and reaction mixture was stirred at room temp. At the conclusion of the reaction (4 h, TLC monitoring), pressure was released and the resulting dark brown solution was concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution of the column with 20% EtOAc/petroleum ether furnished the desired diene **21** (48 mg, 91%) as a colorless oil. $R_f = 0.62$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.51$ (t, $J = 7.6$ Hz, 2 H), 2.87–2.91 (m, 2 H), 3.87–3.92 (m, 12 H), 4.96–5.13 (m, 3 H), 5.27 (d, $J = 17.6$ Hz, 1 H), 6.37 (dd, $J_1 = 17.6$, $J_2 = 11.2$ Hz, 1 H), 7.95 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 32.5$, 33.0, 53.0, 53.1, 53.1, 53.3, 113.8, 117.1, 129.9, 130.1, 133.5, 134.2, 137.0, 138.3, 142.2, 144.7, 165.2, 165.9, 167.6, 167.8 ppm. IR (KBr): $\tilde{\nu} = 2926$, 2197, 1964, 1741, 1245 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 391.1393 for $C_{20}H_{23}O_8$ [M + H]; found 391.1384.

Preparation of Diene 22: The alkyne **15** (36 mg, 0.089 mmol) in dry toluene (12 mL) was degassed with ethylene gas for 10 min and Grubbs' catalyst, G-II (6 mg, 0.007 mmol, 7.5 mol-%) was then added to it. The reaction vessel was kept under 1 atm. ethylene pressure (using balloon pressure) and reaction mixture was stirred at room temp. At the conclusion of the reaction (4 h, TLC monitoring), pressure was released and the resulting dark brown solution was concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution of the column with 20% EtOAc/petroleum ether furnished the desired diene **22** (33 mg, 85%) as a colorless oil. $R_f = 0.62$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.78$–1.82 (m, 2 H), 2.27 (t, $J = 7.6$ Hz, 2 H), 2.73 (t, $J = 8$ Hz, 2 H), 3.84–3.92 (m, 12 H), 4.99–5.09 (m, 3 H), 5.19 (d, $J = 17.6$ Hz, 1 H), 6.37 (dd, $J_1 = 17.6$, $J_2 = 10.8$ Hz, 1 H), 7.96 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 29.5$, 31.2, 33.3, 52.9, 53.1, 53.3, 113.6, 116.4, 129.9, 130.1, 133.3, 134.0, 137.0, 138.7, 142.6, 145.4, 165.2, 165.9, 167.6, 167.8 ppm. IR (KBr): $\tilde{\nu} = 2952$, 1963, 2295, 1732, 1199, 1157 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 427.1369 for $C_{21}H_{24}O_8Na$ [M + Na]$^+$; found 427.1388.

Preparation of Diene 23: The alkyne **16** (41 mg, 0.098 mmol) in dry toluene (12 mL) was degassed with ethylene gas for 10 min and Grubbs' catalyst, G-II (5.1 mg, 0.006 mmol, 6 mol-%) was then added to it. The reaction vessel was kept under 1 atm. ethylene pressure (using balloon pressure) and reaction mixture was stirred at room temp. At the conclusion of the reaction (6 h, TLC monitoring), pressure was released and the resulting dark brown solution was concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution of the column with 20% EtOAc/petroleum ether furnished the desired diene **23** (39 mg, 87%) as a colorless oil. $R_f = 0.54$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$–1.66 (m, 4 H), 2.23 (t, $J = 7.2$ Hz, 2 H), 2.72 (t, $J = 8$ Hz, 2 H), 3.86–3.92 (m, 12 H), 4.97–5.07 (m, 3 H), 5.20 (d, $J = 18$ Hz, 1 H), 6.36 (dd, $J_1 = 18$, $J_2 = 10.8$ Hz, 1 H), 7.95 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 27.8$, 31.0, 31.0, 33.3, 52.8, 53.0, 53.2, 113.3, 116.0, 129.9, 130.1, 133.2, 133.9, 136.9, 138.9, 142.8, 145.9, 165.2, 165.9, 167.6, 167.8 ppm. IR (KBr): $\tilde{\nu} = 2952$, 1963, 2295, 1732, 1199, 1157 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 419.1706 for $C_{22}H_{28}O_8$ [M + H]$^+$; found 419.1697.

Preparation of Diene 24: The alkyne **17** (70 mg, 0.162 mmol) in dry toluene (12 mL) was degassed with ethylene gas for 10 min and Grubbs' catalyst, G-II (8 mg, 0.0094 mmol, 6 mol-%) was then added to it. The reaction vessel was kept under 1 atm. ethylene pressure (using balloon pressure) and reaction mixture was stirred at room temp. At the conclusion of the reaction (2.5 h, TLC monitoring), pressure was released and the resulting dark brown solution was concentrated under reduced pressure. The crude product was purified by flash chromatography. Elution of the column with 20% EtOAc/petroleum ether furnished the desired diene **24** (68 mg, 91%) as a colorless oil. $R_f = 0.51$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.25$–1.66 (m, 6 H), 2.20 (t, $J = 7.2$ Hz, 2 H), 2.70 (t, $J = 8$ Hz, 2 H), 3.86–3.92 (m, 12 H), 4.97–5.06 (m, 3 H), 5.21 (d, $J = 17.6$ Hz, 1 H), 6.36 (dd, $J_1 = 17.6$, $J_2 = 10.8$ Hz, 1 H), 7.95 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 27.9$, 29.3, 31.0, 31.3, 33.5, 52.9, 53.1, 53.3, 113.3, 115.8, 129.8, 130.1, 133.2, 134.0, 137.0, 139.0, 142.9, 146.4, 165.3, 166.0, 167.7, 167.8 ppm. IR (neat): $\tilde{\nu} = 2952$, 2344, 1963, 1644, 1260 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 455.1682 for $C_{23}H_{28}O_8Na$ [M + Na]$^+$; found 455.1668.

Preparation of Compound 25: To a solution of diene **21** (48 mg, 0.123 mmol) in toluene (12 mL) was added **13** (58 mg, 0.40 mmol) and the reaction mixture was heated at 80 °C. At the conclusion of the reaction (16 h, TLC monitoring), the reaction mixture was concentrated under the reduced pressure and the crude product was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired compound **25** (42 mg, 64%) as a colorless thick liquid. $R_f = 0.25$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, C_6D_6): $\delta = 1.88$ (t, $J = 7.2$ Hz, 2 H), 2.49–2.53 (m, 2 H), 2.73–2.81 (m, 3 H), 3.41–3.53 (m, 15 H), 3.68 (s, 3 H), 4.93 (br. s, 1 H), 7.61 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): $\delta = 29.2$, 31.0, 31.8, 38.3, 52.0, 52.7, 52.7, 52.9, 118.3, 131.4, 132.0, 132.6, 133.6, 134.0, 137.0, 142.6, 165.6, 166.8, 167.6, 167.7, 168.2, 168.5; ^{13}C ppm. NMR (100.6 MHz, $CDCl_3$): $\delta = 28.7$, 30.5, 31.5, 38.0, 52.4, 52.4, 53.0, 53.1, 53.1, 53.3, 118.0, 130.1, 130.2, 131.8, 132.0, 133.3, 133.5, 134.0, 136.9, 141.9, 165.1, 165.9, 167.5, 167.7, 168.3, 168.6 ppm. IR (neat): $\tilde{\nu} = 2958$, 1731, 1659, 1436, 1157 cm^{-1}. HRMS (Q-Tof): *m/z* calcd. mass 555.1478 for $C_{26}H_{28}O_{12}Na$ [M + Na]$^+$; found 555.1495.

Preparation of Compound 26: To a solution of diene **22** (28 mg, 0.069 mmol) in toluene (12 mL) was added **13** (30 mg, 0.21 mmol) and the reaction mixture was heated at 80 °C. At the conclusion of the reaction (18 h, TLC monitoring), the reaction mixture was concentrated under the reduced pressure and the crude product was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired compound **26** (27 mg, 71%) as a colorless thick liquid. $R_f = 0.25$ (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (300 MHz, C_6D_6): $\delta = 1.32$–

1.43 (m, 2 H) 1.64 (t, *J* = 7.2 Hz, 2 H), 2.40 (t, *J* = 7.2 Hz, 2 H), 2.69–2.75 (m, 2 H), 2.87–2.89 (m, 2 H), 3.42–3.53 (m, 15 H), 3.69 (s, 3 H), 5.02 (br. s, 1 H), 7.66 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, C_6D_6): δ = 28.6, 29.1, 31.0, 33.3, 36.5, 52.0, 52.6, 52.9, 52.9, 117.6, 131.4, 131.9, 133.1, 133.2, 133.2, 133.9, 134.1, 137.1, 143.0, 165.7, 166.7, 167.7, 167.7, 168.4, 168.5 ppm. IR (neat): $\tilde{\nu}$ = 3054, 1732, 1422, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 569.1635 for $C_{23}H_{28}O_8Na$ [M + Na]$^+$; found 569.1646.

Preparation of Compound 27: To a solution of diene **23** (29 mg, 0.069 mmol) in toluene (12 mL) was added **13** (35 mg, 0.246 mmol) and the reaction mixture was heated at 80 °C. At the conclusion of the reaction (18 h, TLC monitoring), the reaction mixture was concentrated under the reduced pressure and the crude product was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired compound **27** (23 mg, 59%) as a colorless thick liquid. R_f = 0.27 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42–1.62 (m, 4 H), 2.00–2.09 (m, 2 H), 2.71 (t, *J* = 8 Hz, 2 H), 2.86–2.90 (m, 2 H), 2.99–3.01 (m, 2 H), 3.77–3.92 (m, 18 H), 5.40 (br. s, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 26.8, 28.6, 30.5, 30.7, 33.3, 36.3, 52.3, 52.8, 53.0, 53.2, 116.7, 129.9, 130.1, 132.3, 133.1, 133.1, 133.3, 133.9, 136.9, 142.6, 165.2, 165.9, 167.6, 167.7, 168.5, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 2953, 1966, 1735, 1650, 1440, 1265 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 583.1791 for $C_{28}H_{32}O_{12}Na$ [M + Na]$^+$; found 583.1764.

Preparation of Compound 28: To a solution of diene **24** (48 mg, 0.11 mmol) in toluene (12 mL) was added **13** (70 mg, 0.49 mmol) and the reaction mixture was heated at 80 °C. At the conclusion of the reaction (15 h, TLC monitoring), the reaction mixture was concentrated under the reduced pressure and the crude product was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired compound **28** (46 mg, 72%) as a colorless thick liquid. R_f = 0.29 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.62 (m, 6 H), 1.97–1.99 (m, 2 H), 2.69 (t, *J* = 8 Hz, 2 H), 2.89–3.01 (m, 4 H), 3.78–3.92 (m, 18 H), 5.40 (br. s, 1 H), 7.95 (s, 1 H) ppm. NMR (100.6 MHz, $CDCl_3$): δ = 26.9, 28.6, 29.0, 30.5, 31.0, 33.4, 36.4, 52.3, 52.9, 53.0, 53.2, 116.4, 130.1, 132.5, 133.0, 133.2, 133.4, 134.0, 136.9, 142.8, 165.2, 165.9, 167.7, 168.7 ppm. IR (neat): $\tilde{\nu}$ = 2954, 1965, 1727, 1650, 1438, 1264 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 597.1954 for $C_{29}H_{34}O_{12}Na$ [M + Na]$^+$; found 597.1954.

Preparation of Diphenylalkane Derivative 29: Compound **25** (28 mg, 0.05 mmol) was taken in anhydrous toluene (3 mL) and DDQ (23 mg, 0.01 mmol) was added and the resulting yellow solution was irradiated in microwave oven for 8 min. The dark orange reaction mixture was then concentrated under reduced pressure and the crude product obtained was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired diphenylalkane derivative **29** (19 mg, 68%) as a colorless liquid. R_f = 0.25 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (br. s, 4 H), 3.87–3.93 (m, 18 H), 7.30 (dd, *J* = 7.8, *J* = 1.5 Hz, 1 H), 7.48 (d, *J* = 1.5 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.86 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 35.2, 37.2, 52.7, 52.8, 53.1, 53.3, 128.9, 129.6, 129.8, 130.3, 130.4, 131.1, 132.9, 133.8, 134.2, 136.9, 141.0, 144.4, 165.0, 165.8, 167.4, 167.6, 167.8, 168.3 ppm. IR (neat): $\tilde{\nu}$ = 2923, 1733, 1643, 1440, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 553.1322 for $C_{26}H_{26}O_{12}Na$ [M + Na]$^+$; found 553.1335.

Preparation of Diphenylalkane Derivative 30: Compound **26** (21 mg, 0.038 mmol) was taken in anhydrous toluene (3 mL) and DDQ (16 mg, 0.070 mmol) was added and the resulting yellow solution was irradiated in microwave oven for 8 min. The dark orange reaction mixture was then concentrated under reduced pressure and the crude product obtained was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired diphenylalkane derivative **30** (14 mg, 67%) as a colorless liquid. R_f = 0.25 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.96 (quint, *J* = 8 Hz, 2 H), 2.72 (t, *J* = 8 Hz, 4 H), 3.83–3.92 (m, 18 H), 7.34 (dd, *J* = 7.6, *J* = 1.6 Hz, 1 H), 7.49 (d, *J* = 1.2 Hz, 1 H), 7.70 (d, *J* = 8 Hz, 1 H), 7.92 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 32.1, 33.0, 35.3, 52.7, 52.8, 52.9, 53.1, 53.3, 128.8, 129.4, 129.5, 130.1, 130.3, 131.0, 132.9, 133.5, 133.9, 137.0, 141.9, 145.5, 165.1, 165.9, 167.5, 167.7, 167.8, 168.5 ppm. IR (neat): $\tilde{\nu}$ = 2117, 1644, 1264, 1108 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 567.1478 for $C_{27}H_{28}O_{12}Na$ [M + Na]$^+$; found 567.1502.

Preparation of Diphenylalkane Derivative 31: Compound **27** (18 mg, 0.032 mmol) was taken in anhydrous toluene (3 mL) and DDQ (12 mg, 0.052 mmol) was added and the resulting yellow solution was irradiated in microwave oven for 8 min. The dark orange reaction mixture was then concentrated under reduced pressure and the crude product obtained was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired diphenylalkane derivative **31** (10 mg, 56%) as a colorless liquid. R_f = 0.27 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.64–1.66 (m, 4 H), 2.68–2.72 (m, 4 H), 3.85–3.92 (m, 18 H), 7.32 (dd, *J* = 7.8, *J* = 1.5 Hz, 1 H), 7.47 (d, *J* = 1.5 Hz, 1 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.92 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 29.8, 30.6, 30.6, 33.3, 35.4, 52.6, 52.7, 52.9, 53.1, 53.2, 128.7, 129.2, 129.4, 130.2, 131.0, 132.8, 133.9, 136.9, 142.4, 146.2, 165.2, 165.9, 167.6, 167.7, 167.9, 168.6 ppm. IR (neat): $\tilde{\nu}$ = 2923, 1642, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 581.1656 for $C_{28}H_{30}O_{12}Na$ [M + Na]$^+$; found 581.1656.

Preparation of Diphenylalkane Derivative 32: Compound **28** (21 mg, 0.036 mmol) was taken in anhydrous toluene (2 mL) and DDQ (15 mg, 0.066 mmmol) was added and the resulting yellow solution was irradiated in microwave oven for 8 min. The dark orange reaction mixture was then concentrated under reduced pressure and the crude product was purified by column chromatography. Elution of the column with 30% EtOAc/petroleum ether furnished the desired diphenylalkane derivative **32** (17 mg, 81%) as a colorless liquid. R_f = 0.29 (silica gel, 40% EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.40 (m, 2 H), 1.59–1.68 (m, 4 H), 2.64–2.71 (m, 4 H), 3.86–3.92 (m, 18 H), 7.32 (dd, *J* = 8, *J* = 1.6 Hz, 1 H), 7.48 (d, *J* = 1.2 Hz, 1 H), 7.68 (d, *J* = 8 Hz, 1 H), 7.94 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.9, 30.7, 30.9, 33.3, 35.5, 52.6, 52.7, 52.8, 53.0, 53.2, 128.7, 129.0, 129.4, 130.0, 130.2, 130.9, 132.8, 133.2, 133.9, 136.8, 142.7, 146.6, 165.2, 165.9, 167.6, 167.7, 167.9, 168.6 ppm. IR (neat): $\tilde{\nu}$ = 2923, 1734, 1638, 1265, 1438 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd. mass 573.1960 for $C_{29}H_{33}O_{12}$ [M + H]$^+$; found 573.1960.

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