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A Novel *o*-Quinodimethane Tandem Diels−Alder Reaction

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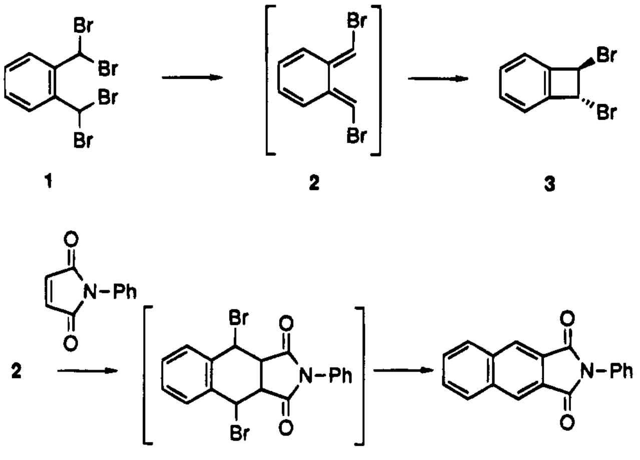
In recent decades, *o*-quinodimethanes have generated considerable interest as reactive synthetic intermediates. When generated in the presence of a dienophile, they can provide elegant synthons for the formation of [4 + 2] cycloadducts. Various methods for the generation of these highly reactive dienes have been developed and their high reactivity has been exploited to give both inter- and intramolecular Diels−Alder products.[1] In 1957, we first suggested the participation of *o*-quinodimethane **2** as a reaction intermediate in the conversion of α,α,α′,α′-tetrabromo-*o*-xylene (**1**) to *trans*-1,2-dibromobenzocyclobutene **3**[2] (Scheme 1), and this was later proven by trapping experiments with a number of cyclic dienophiles. The initial adducts were not isolated, since they underwent facile elimination of two molecules of hydrogen bromide with the formation of a new aromatic ring, as illustrated in Scheme 1 in the case of *N*-phenylmaleimide.[3]

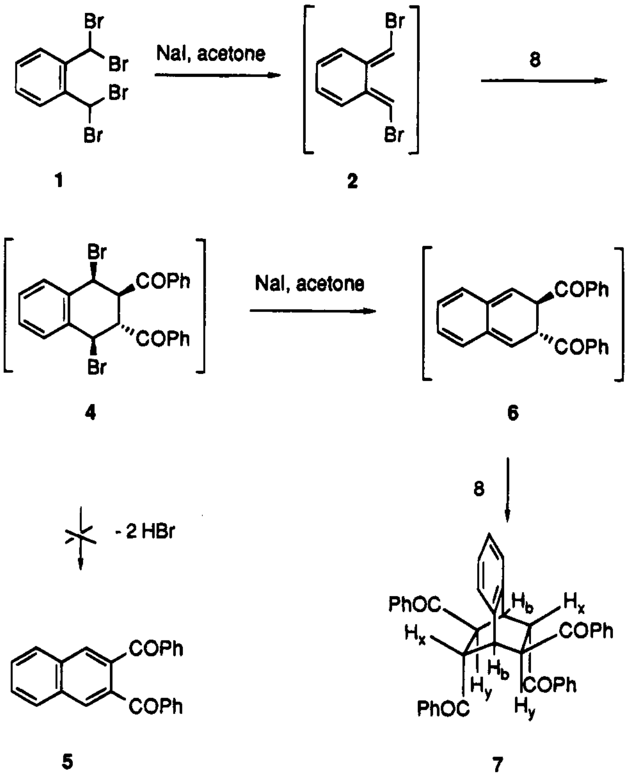
In the course of a search for a convenient route to 1,2-dibenzoylnaphthalene (**5**), we attempted its synthesis *via* the *o*-quinonoid dibromide **2**, using *trans*-1,4-diphenyl-2-butene-1,4-dione (**8**) as the dienophile. However, when **1** was refluxed with excess **8** in acetone in the presence of excess sodium iodide, the reaction took an unusual course and afforded only a new product (**7**), the structure of which was confirmed by spectroscopic measurements.

The *o*-quinonoid intermediate **2** generated from **1** apparently undergoes the expected [4 + 2] cycloaddition with one molecule of the dienophile **8** to form an adduct which, instead of eliminating two molecules of hydrogen bromide to form **5**, eliminates a second bromide to give the second *o*-quinodimethane intermediate **6**. The latter now readily undergoes a second [4 + 2] cycloaddition with dienophile **8** to form the product **7**. Compound **7** was also obtained by carrying out the reaction with equimolar amounts of **1** and the dienophile **8**, showing that the generation of the second quinodimethane **6** from adduct **4** is considerably faster than its aromatization to **5**. This preference must be attributed to stereochemical differences in adducts of **2** with a transoid dienophile as compared to adducts of **2** with a cisoid dienophile. Indeed, a molecular model of intermediate **4** shows the two bromines to be coplanar with the adjacent aromatic ring. The formation of **7** is outlined in Scheme 2.

Scheme 1



Scheme 2



The proton NMR spectrum of **7** showed a pair of doublet of doublets at δ 4.31 (J = 6.0 and 2.4 Hz) and δ 4.74 (J = 6.0 and 1.7 Hz), each integrating to two protons. These can be assigned to protons H_x (endo to the benzo ring) and H_y (exo to the benzo ring), respectively. Proton H_x is shifted downfield relative to H_y on account of the deshielding influence exerted by the benzo ring. A broad triplet at δ 3.86 (J = 2.0 Hz) can be attributed to the bridgehead protons H_b. The stereochemistry of these protons is assigned by relating the dihedral angle and the coupling constants of the vicinal protons. The aromatic region ranging from δ 6.90− to 8.00 integrated to a total of 24 protons. The ^{13}C-NMR spectrum of the compound showed 16 resonances, including two downfield resonances at δ 198.9 and 200.9 corresponding to the two different carbonyl carbons and the resonances at δ 42.0, 42.7, and 47.1 corresponding to the three aliphatic carbons. The presence of the carbonyl functionality was also confirmed by the IR absorption at 1680 cm^{-1}. Additional evidence for structure **7** was obtained by a molecular ion peak of 574 in the mass spectrum and by satisfactory C, H, and N analysis.

The structure of the adduct **7** has been further confirmed by its conversion into the novel heterocycles **9**, **10**, and **11** as shown in (Scheme 3).

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[1] (a) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873. (b) Funk, R. L.; Vollhardt, K. P. C. *Chem. Soc. Rev.* **1980**, *9*, 41. (c) Oppolzer, W. *Synthesis* **1978**, 793.

[2] Cava, M. P.; Napier, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 1701.

[3] Cava, M. P.; Deana, A. A.; Muth, K. *J. Am. Chem. Soc.* **1959**, *81*, 6458.

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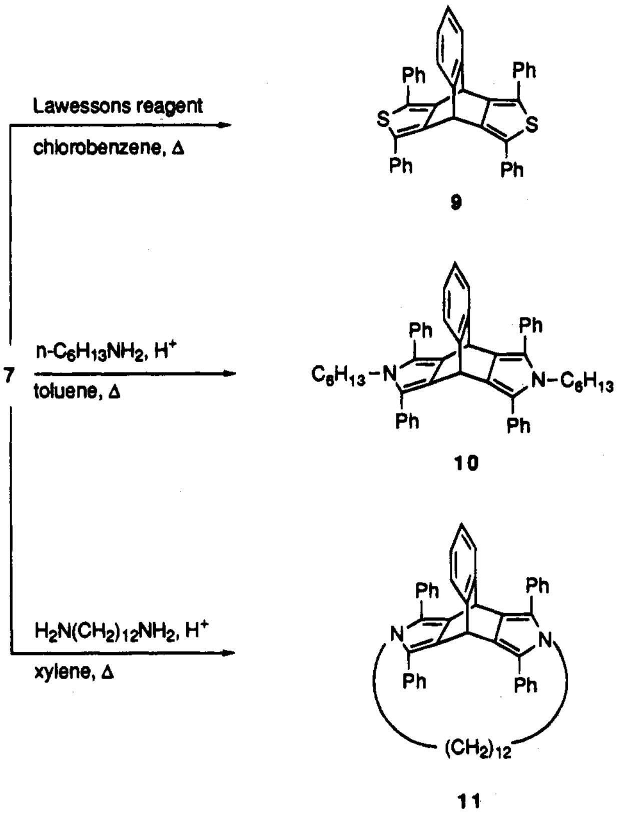
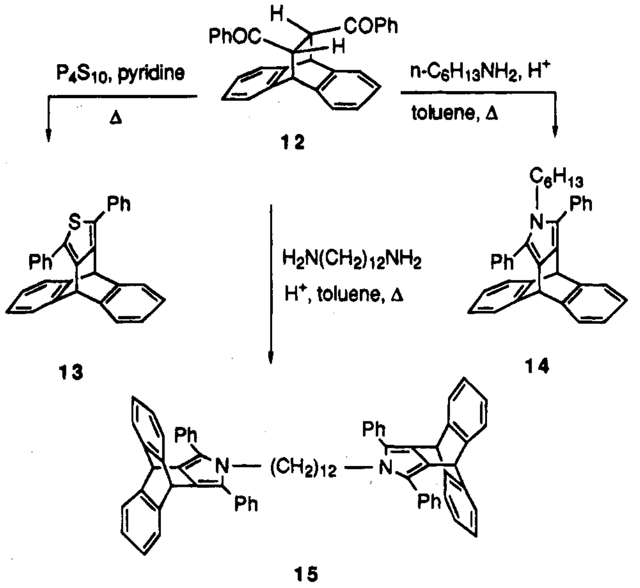
Scheme 3



Scheme 4



Treatment of **7** with Lawesson's reagent[4] in refluxing chlorobenzene gave, in fair yield, the bisthiophene derivative **9**. Paal–Knorr condensation of **7** with *n*-hexylamine in refluxing toluene yielded the bispyrrole derivative **10**. Performing a double Paal–Knorr condensation on the adduct **7** using the bifunctional amine 1,12-diaminododecane afforded, in low yield, the novel bridged bispyrrole derivative **11**. The poor yield obtained for this product can be attributed to its highly hindered structure. To explore the extent of proximity of the bis-heterocyclic rings and its effect on the electronic conjugation by π-electron interaction between the rings, a comparative study of the electronic absorptions of the bis-heterocycles with a series of corresponding monoheterocycles was required. This warranted the preparation of the compounds **13**, **14**, and **15** (Scheme 4) from the known Diels–Alder adduct **12**, which was obtained by the literature procedure.[5]

The proton NMR spectrum of **12** was interesting in that it showed the presence of two singlets at δ 4.57 and 4.61, corresponding to the two vicinal alicyclic protons. The absence of any splitting by the adjacent protons can be explained by a structural twist caused by the bulky benzoyl groups, leading to a dihedral angle of around 90°, corresponding to a coupling constant of zero. Attempts to obtain the monothiophene derivative **13** by refluxing **12** in toluene with Lawesson's reagent gave predominantly retro Diels–Alder products. Furthermore, no reaction took place with benzene as the solvent. A different approach, namely treatment of **12** with phosphorus pentasulfide and pyridine at 100 °C for 3 days, gave some of the desired product **13** along with a substantial amount of anthracene. Paal–Knorr condensation of **12** with *n*-hexylamine and 1,12-diaminododecane afforded the pyrrole derivatives **14** and **15**, respectively. A comparison of the UV–vis spectra of the bis-heterocycles **9**, **10**, and **11**, and the corresponding monoheterocycles **13**, **14**, and **15**, revealed no significant differences in their absorption maxima, indicating that the rings of the bis-heterocycles are not close enough to exert a bathochromic shift.

In conclusion, the reaction of *trans*-1,4-diphenyl-2-butene-1,4-dione (**8**) with $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene and sodium iodide leads to the formation of the tetrabenzoylbenzobicyclo[2.2.2]octane **7** in a process which involves the tandem generation of two *o*-quinodimethane intermediates. The tetraketone **7** served as an intermediate for the preparation of several novel thiophene and pyrrole analogs of trypticene.

Experimental Section

Melting point determinations are uncorrected. Chromatography was performed with silica gel 60 (E. Merck, Darmstadt) 230–400 mesh, with the indicated solvents. ^{1}H- and ^{13}C-NMR spectra were run in $CDCl_3$ at 360 and 90.6 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Low- and high-resolution mass spectra were recorded at an ionizing voltage of 70 eV by electron impact.

Tetraketone 7. To a mixture of NaI (255 g, 1.7 mol) and *trans*-1,4-diphenyl-2-butene-1,4-dione (**8**) (75 g, 320 mmol) in acetone (1 L) was added $\alpha,\alpha,\alpha',\alpha'$-tetrabromo-*o*-xylene (**1**) (105 g, 250 mmol), and the solution was refluxed for 3 d. The reaction mixture was cooled to room temperature and the solid product separated was removed by filtration. After being washed with acetone, the product was suspended in water to remove the inorganic materials. This was again filtered, dried, and crystallized from CH_3CN to give white crystals of **7** (70 g, 49%). Recrystallization from a C_6H_6:CH_3CN mixture afforded an analytically pure sample: mp 252 °C; IR (KBr) 1680–1700 cm^{-1}; ^{1}H NMR δ 3.86 (br t, 2H, J = 2.0 Hz), 4.31 (dd, 2H, J_1 = 6.0 Hz, J_2 = 2.4 Hz), 4.74 (dd, 2H, J_1 = 6.0 Hz, J_2 = 1.7 Hz), 6.92 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.3 Hz), 7.20 (dd, 2H, J_1 = 5.4 Hz, J_2 = 3.2 Hz), 7.26 (t, 4H, J = 8.0 Hz), 7.46 (t, 6H, J = 7.5 Hz), 7.56 (t, 2H, J = 7.3 Hz), 7.73 (d, 4H, J_1 = 7.8 Hz), 7.98 (d, 4H, J = 7.8 Hz); ^{13}C NMR δ 42.0, 42.7, 47.1, 124.5, 127.7, 128.3, 128.5, 128.6, 128.9, 133.0, 133.1, 135.6, 136.9, 137.9, 198.9, 200.9; MS *m/z* (relative intensity) 574 (0.3, M$^+$), 556 (3), 538 (2), 469 (6), 337 (17), 320 (32), 259 (100), 233 (88), 202 (34), 155 (13), 128 (20). Anal. Calcd for $C_{40}H_{30}O_4$: C, 83.60; H, 5.26. Found: C, 83.49; H, 5.32.

Thionation of 7. A mixture of **7** (1 g, 1.74 mmol) and Lawesson's reagent (1.1 g, 2.61 mmol) in chlorobenzene (40 mL)

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(4) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
(5) Hurd, C. D.; Tockman, A. *J. Am. Chem. Soc.* **1959**, *81*, 116.

was refluxed under nitrogen for 36 h. The solvent was evaporated and to the residue was added a cold aqueous 10% NaOH solution (30 mL). Extraction with CH_2Cl_2 (3 × 30 mL), washing of the organic layer with water (3 × 20 mL), and removal of solvent from the dried (Na_2SO_4) extract afforded the crude product which was purified by flash chromatography using hexanes:CH_2Cl_2 (5:1) as eluent, yielding a creamy white crystalline product (**9**) (0.68 g, 69%). An analytical sample was obtained by recrystallization in a hexanes:1,2-dichloroethane mixture: mp 289 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 295.5 (4.62); ^1H NMR δ 5.75 (s, 2H), 7.13 (dd, 2H, J_1 = 5.3 Hz, J_2 = 3.2 Hz), 7.32–7.38 (m, 20H), 7.43 (dd, 2H, J_1 = 5.3 Hz, J_2 = 3.2 Hz); ^{13}C NMR δ 44.3, 124.4, 126.2, 127.6, 128.5, 128.9, 132.9, 133.5, 142.9, 144.3; MS *m/z* (relative intensity) 570 (100, M^+), 537 (15), 449 (58), 372 (14), 187 (18), 121 (33). Anal. Calcd for $C_{40}H_{26}S_2$: C, 84.17; H, 4.59. Found: C, 84.29; H, 4.60.

Bispyrrole Derivative 10. A mixture of **7** (1 g, 1.74 mmol), *n*-hexylamine (0.69 mL, 5.33 mmol), and propionic acid (3 mL) in toluene (50 mL) was refluxed under nitrogen with a Dean–Stark trap for 3 d. The solvent was evaporated and the residue on neutralization by careful addition of cold saturated aqueous $NaHCO_3$ gave a gummy solid which was extracted with C_6H_6 (3 × 30 mL). The organic layer was washed with water, dried over Na_2SO_4, evaporated, and purified by flash chromatography, eluting with hexanes:CH_2Cl_2 (5:1) to afford 0.63 g (51%) of spectroscopically pure **10** as white crystals. An analytical sample was obtained by recrystallization in a hexanes:1,2-dichloroethane mixture: mp 197 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 307.2 (4.51); ^1H NMR δ 0.62–1.09 (m, 22H), 3.77 (t, 4H, J = 7.5 Hz), 5.13 (s, 2H), 6.91 (dd, 2H, J_1 = 5.3 Hz, J_2 = 3.2 Hz), 7.17 (dd, 2H, J_1 = 5.3 Hz, J_2 = 3.2 Hz), 7.27–7.39 (m, 20H); ^{13}C NMR δ 13.8, 22.2, 25.8, 30.5, 30.8, 40.0, 45.0, 123.0, 124.4, 126.4, 127.3, 128.3, 129.4, 131.6, 133.2, 148.5; MS *m/z* (relative intensity) 704 (100, M^+), 647 (10), 634 (19), 620 (20), 516 (11), 457 (7), 432 (8), 352 (9), 188 (21). Anal. Calcd for $C_{52}H_{52}N_2$: C, 88.59; H, 7.43; N, 3.97. Found: C, 88.55; H, 7.47; N, 3.95.

Bispyrrole Derivative 11. A mixture of **7** (1 g, 1.74 mmol), 1,12-diaminododecane (0.36 g, 1.8 mmol), and propionic acid (5 mL) in xylene (50 mL) was refluxed under nitrogen with a Dean–Stark trap for 3 d. The solvent was evaporated and the residue was neutralized with cold saturated aqueous $NaHCO_3$. This was extracted with $CHCl_3$ (3 × 30 mL), washed with water, and dried (Na_2SO_4). After removal of solvent the crude product obtained was purified by chromatography using hexanes:CH_2Cl_2 as eluent to afford white crystals of **11** (0.18 g, 15%). An analytical sample of **11** was obtained by recrystallization in a hexanes:1,2-dichloroethane mixture: mp 355–357 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 307.2 (4.58); ^1H NMR δ 0.60–0.69 (m, 4H), 0.80–0.91(m, 4H), 0.96–1.11 (m, 12H), 3.93 (t, 4H, J = 5.77 Hz), 5.17 (s, 2H), 6.64 (dd, 4H, J_1 = 5.3 Hz, J_2 = 3.3 Hz), 6.78 (dd, 4H, J_1 = 5.3 Hz, J_2 = 3.3 Hz), 7.33–7.62 (m, 20H); ^{13}C NMR δ 25.5, 26.4, 27.3, 27.4, 30.0, 40.2, 45.4, 122.8, 123.8, 126.5, 128.5, 128.6, 129.5, 131.5, 133.6, 148.8; MS *m/z* (relative intensity) 702 (100, M^+), 599 (5), 549 (6), 351 (23), 332 (13), 318 (5); HRMS calcd for $C_{52}H_{50}N_2$ 702.3974, found 702.3983.

Thionation of 12. To a mixture of phosphorus pentasulfide (3.76 g, 8.45 mmol) and pyridine (60 mL) was added **12** (0.7 g, 1.69 mmol), and the solution was heated on a steam bath for 3 d. It was then neutralized by adding ice-cold 10% HCl and extracted with CH_2Cl_2 (3 × 30 mL), followed by washing with water (3 × 30 mL). Removal of solvent from the dried (Na_2SO_4) extract gave a pale yellow solid which after purification by flash chromatography eluting with hexanes:CH_2Cl_2 (7:1) yielded crystals of **13** (0.32 g, 46%) and anthracene (0.1 g, 33%). Recrystallization of **13** from a hexanes:1,2-dichloroethane mixture gave an analytically pure sample: mp 230 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 303.0 (4.37); ^1H NMR δ 5.57 (s, 2H), 7.06 (dd, 4H, J_1 = 5.2 Hz, J_2 = 3.2 Hz), 7.36–7.41 (m, 6H), 7.48 (t, 4H, J = 7.5 Hz), 7.54 (d, 4H, J = 7.2 Hz); ^{13}C NMR δ 49.1, 123.9, 125.6, 127.5, 128.4, 128.9, 132.4, 133.9, 143.4, 145.0; MS *m/z* (relative intensity) 412 (100, M^+), 379 (36), 334 (22), 302 (26), 291 (27), 189 (13), 178 (6), 167 (11), 121 (78). Anal. Calcd for $C_{30}H_{20}S$: C, 87.34; H, 4.89. Found C, 87.36; H, 4.93.

Pyrrole Derivative 14. A mixture of **12** (0.7 g, 1.69 mmol), *n*-hexylamine (0.67 mL, 5.07 mmol), and propionic acid (2.5 mL) in toluene (30 mL) was refluxed under nitrogen with a Dean–Stark trap for 24 h. The solvent was completely removed and the residue was neutralized with cold saturated aqueous $NaHCO_3$, extracted with C_6H_6 (3 × 30 mL), and washed with water (3 × 30 mL). Removal of solvent from the dried (Na_2SO_4) extract followed by purification by flash chromatography using hexanes:CH_2Cl_2 (6:1) as eluent furnished **14** as a pale yellow crystalline solid (0.68 g, 84%). An analytical sample was obtained by recrystallization in a hexanes:C_6H_6 mixture: mp 94 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 310.2 (4.39); ^1H NMR δ 0.62 (t, 3H, J = 7.2 Hz), 0.68–1.06 (m, 8H), 3.78 (t, 2H, J =7.6 Hz), 5.28 (s, 2H), 6.98 (dd, 4H, J_1 = 5.2 Hz, J_2 = 3.2 Hz), 7.32 (dd, 4H, J_1 = 5.2 Hz, J_2 = 3.2 Hz), 7.36–7.52 (m, 10H); ^{13}C NMR δ 13.7, 22.1, 25.8, 30.4, 30.7, 44.9, 47.1, 123.3, 124.7, 126.7, 127.4, 128.5, 129.5, 129.9, 133.0, 147.1; MS *m/z* (relative intensity) 479 (100, M^+), 422 (9), 408 (28), 394 (14), 289 (32), 276 (7), 231 (5), 188 (7). Anal. Calcd for $C_{36}H_{33}N$: C, 90.15; H, 6.93. Found: C, 90.03; H, 6.97.

Pyrrole Derivative 15. A mixture of **12** (0.5 g, 1.21 mmol), 1,12-diaminododecane (0.13 g, 0.66 mmol), and propionic acid (3 mL) in toluene (30 mL) was refluxed under nitrogen with a Dean–Stark trap for 2 d. Evaporation of toluene and neutralization of the residue with cold saturated aqueous $NaHCO_3$ gave a gummy solid which was extracted with C_6H_6 (3 × 30 mL). Washing of the organic layer with water (3 × 30 mL) and removal of solvent from the dried (Na_2SO_4) extract afforded the crude product which was further purified by flash chromatography using hexanes:CH_2Cl_2 (7:1) as eluent, yielding pale yellow crystals of **15** (0.16 g, 14%). An analytical sample was obtained by recrystallization in a hexanes:C_6H_6 mixture: mp 216–218 °C; UV ($CHCl_3$) λ_{max} (log ϵ) 309.9 (4.74); ^1H NMR δ 0.65–0.90 (m, 20H), 3.73 (t, 4H, J = 7.6 Hz), 5.24 (s, 4H), 6.96 (dd, 8H, J_1 = 5.2 Hz, J_2 = 3.2 Hz), 7.30 (dd, 8H, J_1 = 5.2 Hz, J_2 = 3.2 Hz), 7.30–7.47 (m, 20H); ^{13}C NMR δ 26.1, 28.5, 29.0, 29.1, 30.4, 44.4, 47.1, 123.3, 124.7, 126.7, 127.3, 128.5, 129.5, 133.0, 147.1; MS *m/z* (relative intensity) 957 (100, M^+), 562 (23), 478 (11), 408 (57), 291 (30), 231 (14). Anal. Calcd for $C_{72}H_{84}N_2$: C, 90.34; H, 6.74. Found: C, 90.15; H, 6.79.

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