

Triple self-condensation of fused cycloalkanonylparacyclophanes promoted by titanium tetrachloride and triethylamine

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Abstract—The triple self-condensation of [2](4,7)indano[2]paracyclophan-5-one and 5-oxo-4,5,6,7-tetrahydro[2]paracyclo[2]-(1,4)naphthalenophane, as representative examples of fused cycloalkanonylparacyclophanes, promoted by titanium tetrachloride and triethylamine is here reported.

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1. Introduction

[2_n] Cyclophanes have binding sites, which enable them to participate in specific aromatic binding interactions and serve as points of attachment for functional groups, complexation and catalysis.^{1,2} The synthesis of macrocycles from acyclic precursors has gained great importance, especially because of the development of host–guest chemistry in which polycyclic cyclophanes play a central role.^{1–3} Polycyclic cyclophanes are also fundamentally interesting compounds relevant to many areas of supramolecular and materials chemistry.^{1–3} An important application of polycyclic [2_n]cyclophanes is their use as precursors of topologically novel compounds such as circulenes, propellicenes, paddlanes, and helicene-derived cyclophanes, to name but a few.³ We previously prepared several phenanthrenoparacyclophanes and phenanthrenophanes by the reactions of benzyne with various divinyl[2.2]paracyclophanes.⁴ Our synthetic program uses efficient and facile methods for the preparation of novel heterophanes and polycyclic cyclophanes,^{4,5} which do not suffer from low yields due to multiple steps as described in other procedures.⁶

The use of titanium tetrachloride (TiCl₄) in selective C–C bond forming reactions has been extensively explored, especially in Grignard, and Michael additions, and for substitution reactions,⁷ and as a catalyst in the synthesis

of polyolefins.⁸ It was also reported that TiCl₄ can be used as a mediator in the promotion of the self-condensation of acetophenones.⁹ Sun and co-workers¹⁰ reported the triple self-condensation of several ketones, which was carried out by refluxing with 2 equiv of TiCl₄ in toluene. In this context, we report the effectiveness of TiCl₄ as a mediator for the direct triple-self condensation of fused cycloalkanonylparacyclophanes.

2. General procedure

The procedure was carried out by stirring the ketone (**1** or **5**) with 2 equiv of TiCl₄ and 1 equiv of Et₃N in dichloromethane under an N₂ atmosphere in an ice bath (–15 °C). In a typical example, 2 equiv of TiCl₄ (8 mmol, 0.88 mL) were added dropwise at –15 °C to a solution of **1** or **5** (4 mmol) in dichloromethane (800 mL) together with Et₃N (4 mmol, 0.40 g). After stirring for 4–8 h at –15 °C (the reaction progress was followed by TLC analysis), the reaction mixture was further stirred at room temp for 2 h. The resulting black solution was poured into ice water (500 mL). The product was extracted with chloroform (300 mL) and washed with water and brine, then dried over MgSO₄. After evaporation of the solvent in vacuo, the residue was purified by column chromatography (silica gel, dichloromethane/petroleum ether = 5:1). Ketone **1** gave predominately **4** as the fastest migrating zone. The indenonylparacyclophane **2** and indenylindenone **3** separated as the slowest migrating zones, respectively. In the case of **5**, only **6** was obtained using the same eluent for separation.

Keywords: Cycloalkanonylparacyclophanes; Titanium tetrachloride; Triethylamine; Triple self-condensation.

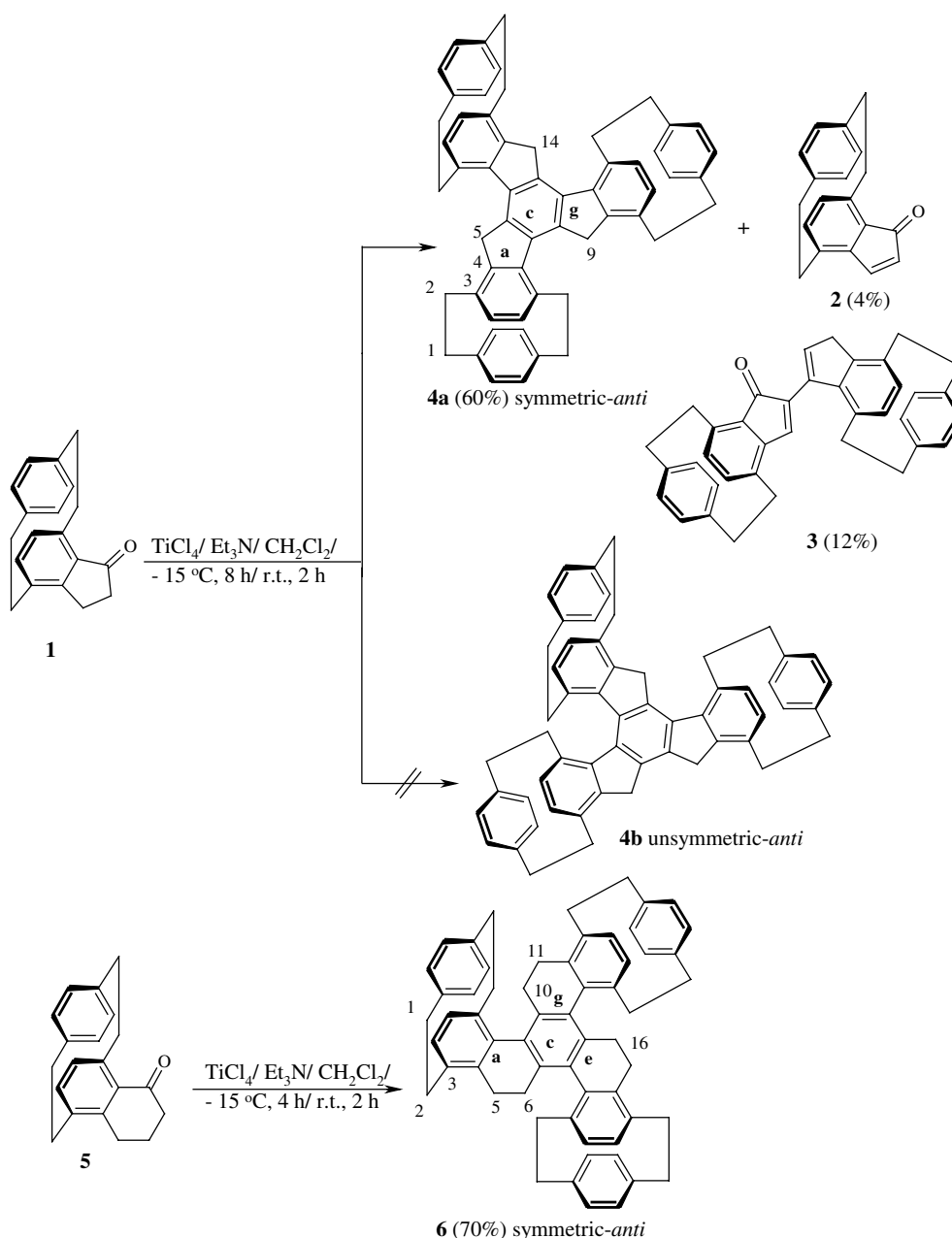
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3. Results and discussion

We applied Sun's methodology to racemic [2](4,7)-indano[2]paracyclophan-5-one (**1**)¹¹ and racemic 5-oxo-4,5,6,7-tetrahydro[2]paracyclo[2](1,4)naphthalenophane (**5**).¹² Unfortunately, the reaction failed to give any of the desired product and only polymeric products were obtained. TiCl_4 has been used to mediate direct acylation of hydroxyparacyclophanes¹³ but the reaction conditions, 1.3 equiv TiCl_4 , RCOCl , -15°C to room temp in dichloromethane as a solvent, were useful only for paracyclophane itself.

For the preparation of triple condensed-benzene products from paracyclophanes, we applied a modified methodology previously reported using TiCl_4 as a catalyst

together with triethylamine (Et_3N) at -15°C . It was observed that 2 equiv of TiCl_4 were necessary for the indanone **1**¹¹ and tetralone **5**¹² to undergo the triple self-condensation reaction. In the case of **1**, the reaction, after column separation, gave predominately the target 5,9,14-trihydrotri[2]paracyclophanyl[2](4,7)indanyl[*c,e,g*]benzene (**4a**),¹⁴ in 60% yield, together with compounds **2**¹⁵ and **3**¹⁶ (Scheme 1). On the other hand, **5** underwent trimerization to yield 5,6,10,11,16,17-hexahydrotri[2]paracyclophanyl[2](4,7)naphthalenophanyl[*c,e,g*]benzene (**6**)¹⁷ in 70% yield (Scheme 1). On applying this procedure with equimolar equivalents of **1**, TiCl_4 and Et_3N in dichloromethane, **4a** was isolated in only 30% yield. In principle, the Et_3N initiates the removal of HCl and thus is expected to increase the progress of the reaction toward product formation.



Scheme 1. Trimerization of cycloalkanonylparacyclophanes.

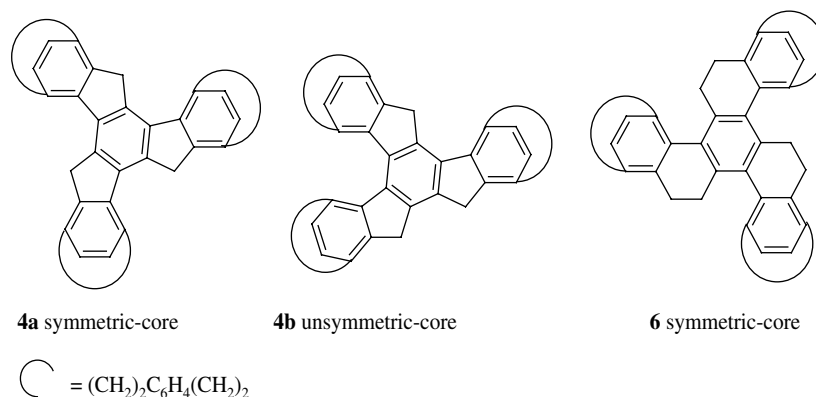


Figure 1. The structures of the two possible regioisomers **4a** and **4b** and triple-condensed product **6**.

Interestingly, the reaction of **1** with TiCl_4 in the absence of Et_3N gave **4a** as the major product in relatively low yield (50%).

Ligands such as **4a** are related to helicenes, which have been investigated thoroughly by Katz and co-workers, who have also been successful in converting these into chiral metallocenes.¹⁸ The main difference between the structures discussed here and those described by Katz is that our helicenes contain an additional 'layer' provided by the [2.2]paracyclophane molecule; the annelation is continued at a 'higher level'.

The elemental analysis and mass spectra confirmed the molecular formula of **6** as $\text{C}_{60}\text{H}_{54}$, that is, with the same number of carbons as C_{60} . Therefore, the synthesis of **6** constitutes a new class in the field of polycyclic cyclophanes.

Scheme 1 illustrates the reaction conditions required for the trimerization reactions of **1** and **5** to yield **4a** and **6**, respectively. NMR spectra and elemental analyses were used to confirm the structures of the products obtained. Moreover, COSY C–H and H–H spectra helped in establishing the structures of the products. Conclusive evidence for the proposed structures was obtained from NOE experiments. The product formation, as depicted in Scheme 1, depends upon the fact that TiCl_4 is a strong Lewis acid with a high affinity for oxygenated organic molecules as well as having a powerful dehydrating ability.^{9,19}

Regioisomeric and stereoisomeric forms of the trimeric products can be envisaged. The PM3 program²⁰ suggests that the trimer derived from **1** is symmetric with respect to the central aromatic ring, that is, core structure **4a** rather than **4b** (Scheme 1), steric energy = 103.3 kcal/mol for the symmetric isomer **4a** compared with 455.8 kcal/mol for the unsymmetric isomer **4b**.²⁰ Moreover, it was reported that the trimerization of indanone and tetralone derivatives, prompted by TiCl_4 , is a regioselective process and only produces the symmetrical structural isomers.²¹ It should be noted that the regioisomers of either **4a** or **6** also have two possible stereoisomers. Further calculations based on the PM3 program²⁰ indicated that the stereoisomer **4a** symmetric-*anti* with one paracyclophane on

the opposite face to the other two is the most stable (Fig. 1). Therefore, the structures suggested for compounds **4a** and **6** are their symmetric-*anti* forms (Fig. 1). The NMR spectral data of **4a** and **6** confirmed the presence of only one isomer in each case.

In conclusion the triple self-condensation of fused cycloalkanonylparacyclophanes promoted by TiCl_4 and Et_3N has been described.

References and notes

- Brown, C. J.; Farthing, A. C. *Nature* **1949**, 164, 915.
- (a) Vögtle, F. *Cyclophane Chemistry—Synthesis, Structure and Reactions*; John Wiley: New York, 1993; (b) Vögtle, F. *Supramolecular Chemistry*; John Wiley: New York, 1991; (c) Diederich, F. *Cyclophanes*; The Royal Society of Chemistry: Thomas Graham House, Science Park, Cambridge, 1991; (d) Review on Cyclophane Chemistry see: Bodwell, G. J. *Angew. Chem.* **1996**, 108, 2221; *Angew. Chem., Int. Ed.* **1996**, 35, 2085; (e) Meijere, A. de.; König, B. *Synlett* **1997**, 1221.
- Keehn, P. M.; Rosenfeld, S. M. *Cyclophanes I and II*; Academic: New York, 1983; Chapter 7, p 443.
- Aly, A. A.; Hopf, H.; Ernst, L. *Eur. J. Org. Chem.* **2000**, 3021.
- (a) Aly, A. A. Ph.D. Thesis, Chemistry Department, Faculty of Science, El-Minia University, El-Minia, Egypt, 1994; (b) Aly, A. A.; Hassan, A. A.; Mourad, A. E. *Can. J. Chem.* **1993**, 71, 1845; (c) Aly, A. A.; Hassan, A. A.; Mourad, A. E.; Hopf, H. *Arch. Pharm.* **1992**, 325, 625; (d) Aly, A. A.; Hassan, A. A.; Mourad, A. E. *Bull. Chem. Fr.* **1994**, 131, 45; (e) Aly, A. A.; Mourad, A. E. *Tetrahedron* **1993**, 49, 7325; (f) Aly, A. A. *Org. Biomol. Chem.* **2003**, 1, 756; (g) Aly, A. A. *Tetrahedron* **2003**, 59, 1739; (h) Hopf, H.; Aly, A. A.; Swaminathan, V. N.; Ernst, L.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.*, in press.
- Hopf, H.; Rozenberg, L.; Sergeeva, E. In *Modern Cyclophane Chemistry*; Hopf, H., Gleiter, R., Eds.; Wiley-VCH: Weinheim, 2004.
- For overviews, see: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer: New York, 1986; (b) Reetz, M. T. *Organotitanium Chemistry*. In *Organometallics in Synthesis*; Schlosser, M., Ed., 2nd ed.; Wiley: New York, 2002.
- Galli, P.; Cecchin, G.; Chadwick, J. C.; Del Duca, D.; Vecellio, G. In *Metalorganic Catalysts for Synthesis and Polymerization*; Kaminsky, W., Ed.; Springer: Berlin, 1999; p 14.

9. Mazza, L. J.; Guarna, A. *Synthesis* **1980**, 41.
10. Li, Z.; Sun, W.-H.; Jin, X.; Shaoa, C. *Synlett* **2001**, 1947.
11. Hopf, H.; Raulfs, F.-W. *Isr. J. Chem.* **1985**, 25, 210.
12. (a) Minuti, L.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E.; Galeazzi, E. *Eur. J. Org. Chem.* **1999**, 3155; (b) Minuti, E.; Taticchi, A.; Gacs-Baitz, E.; Marrocchi, A. *Tetrahedron* **1995**, 51, 8953; (c) Gacs-Baitz, E.; Minuti, L.; Taticchi, A. *Tetrahedron* **1994**, 50, 10359; (d) Minuti, A.; Taticchi, A.; Marrocchi, A.; Gacs-Baitz, E. *Synth. Commun.* **1998**, 28, 2181.
13. Rozenberg, V.; Danilova, T.; Sergeeva, E.; Vorontsov, E.; Starikova, Z.; Lysenko, K.; Belokon, Y. *Eur. J. Org. Chem.* **2000**, 3295.
14. 5,9,14-Trihydrotri[2]paracyclophanyl[2](4,7)indanyl-[c,e,g]benzene (**4**) was obtained as yellow crystals (1.74 g, 60%), mp 272 °C (ethanol), (R_f 0.7, CH_2Cl_2); [Found: C, 93.55; H, 6.60%. $\text{C}_{57}\text{H}_{48}$ requires C, 93.40; H, 6.60%]; ν_{max} (KBr) 3060–3010 (Ar-CH), 2895–2850 cm^{-1} (Aliph.-CH), 1582 (C=C); λ_{max} (CH_3CN , log ϵ) 440 nm (4.30); δ_{H} (400 MHz, CDCl_3) 7.74–7.68 (m, 2H), 7.53–7.46 (m, 2H), 7.34 (d, 2H, $J = 7.8$ Hz), 7.20 (d, 2H, $J = 7.8$ Hz), 6.92–6.75 (m, 6H), 6.70–6.52 (m, 4H), 4.34–4.20 (m, 6H, CH_2), 3.80–3.60 (m, 2H, CH_2), 3.40–2.80 (m, 16H, CH_2), 2.54–2.48 (m, 2H, CH_2), 2.44–2.40 (m, 2H, CH_2), 2.40–2.30 (m, 2H, CH_2); δ_{C} (100.6 MHz, CDCl_3) 140.00, 139.60, 138.40, 138.20, 138.00, 137.80, 137.60, 137.00, 136.90, 136.80, 136.60, 136.40, 136.20, 136.00, 135.80, 135.60, 135.40, 135.00, 134.82, 134.60, 134.40 (PC-C), 134.00, 133.80, 133.60 (PC-CH), 133.40, 133.20, 133.00 (PC-C), 132.80, 132.60, 132.40, 132.00, 130.80, 130.40, 130.20, 130.00, 128.00, 127.80, 127.60, 126.80, 126.60, 126.40, 126.20 (PC-CH), 36.80, 36.40, 35.00, 34.80, 34.64, 33.40, 33.20, 33.00, 32.80, 32.60, 32.20, 32.00, 30.60, 30.60, 30.00 (CH_2); m/z (EI) 732 [M^+] (100), 696 (18), 628 [$\text{M}^+ - 104$] (52), 524 (34), 420 (26), 405 (22), 389 (20), 104 (38), 91 (20).
15. [2]Paracyclophanyl[2](4,7)inda-6-en-5-one (**2**) was obtained as pale yellow crystals (0.04 g, 4%), mp 80 °C (acetonitrile), (R_f 0.3, CH_2Cl_2); [Found: C, 87.50; H, 6.15%. $\text{C}_{19}\text{H}_{16}\text{O}$ requires C, 87.66; H, 6.19%]; ν_{max} (KBr) 3010–2996 cm^{-1} (Ar-CH), 2888–2790 (Aliph.-CH), 1715 (C=O), 1570 (C=C); λ_{max} (CH_3CN , log ϵ) 380 nm (3.60); δ_{H} (400 MHz, CDCl_3) 7.44 (d, 1H, $J = 8.4$ Hz, H-7), 6.80 (d, 1H, $J = 7.8$ Hz, PC-H), 6.64 (dd, 2H, $J = 8.0$, 1.2 Hz, PC-H), 6.42 (dd, 2H, $J = 8.2$, 1.2 Hz, PC-H), 6.32 (d, 1H, $J = 7.8$ Hz, PC-H), 5.82 (d, 1H, $J = 8.2$ Hz, H-6), 4.04–3.94 (m, 1H, $\text{CH}_2\text{-CH}_2$), 3.15–2.80 (m, 6H, $\text{CH}_2\text{-CH}_2$), 2.72–2.64 (m, 1H, $\text{CH}_2\text{-CH}_2$); NOEs: 6-H \rightarrow 7-H, 7-H \rightarrow 6-H; δ_{C} (100.6 MHz, CDCl_3) 198.90 (C=O), 148.90 (CH-7), 145.30, 141.80, 140.90 (PC-C), 138.20, 136.00 (PC-H), 136.03, 135.40 (PC-C), 132.80, 132.56 (PC-CH), 130.80 (PC-C), 128.90, 128.68 (PC-CH), 125.40 (CH-6), 35.90, 35.40, 32.90, 31.50; m/z (EI) 260 [M^+] (64), 156 [$\text{M}^+ - 104$] (56), 128 (24), 104 (100), 78 (16).
16. Di[2]paracyclophanyl-5',6-di[2](4,7)-indene-5-one (**3**) was obtained as pale yellow crystals (0.24 g, 12%), mp 140 °C (acetonitrile), (R_f 0.4, CH_2Cl_2); [Found: C, 90.60; H, 6.30%. $\text{C}_{38}\text{H}_{32}\text{O}$ requires C, 90.44; H, 6.39%]; ν_{max} (KBr) 3060–3000 cm^{-1} (Ar-CH), 2890–2820 (Aliph.-CH), 1710 (C=O), 1580 (C=C); λ_{max} (CH_3CN , log ϵ) 360 nm (3.4); δ_{H} (400 MHz, CDCl_3) 7.38 (s, 1H, indenone-H-7), 7.25 (dd, 1H, $J = 7.8$, 1.2 Hz), 6.85 (dd, 1H, $J = 7.8$, 1.2 Hz), 6.78–7.74 (m, 2H), 6.66 (dd, 2H, $J = 7.5$, 1.2 Hz), 6.60 (d, 1H, $J = 7.6$ Hz), 6.57–6.52 (m, 2H), 6.44–6.40 (m, 2H), 6.32 (dd, 1H, $J = 7.6$, 1.2 Hz), 6.00 (t, 1H, $J = 8.0$ Hz, vinylic-H), 4.10–4.06 (m, 1H, CH_2), 3.52–3.46 (m, 1H, CH_2), 3.37–2.92 (m, 14H, CH_2), 2.85–2.80 (m, 1H, CH_2), 2.64–2.58 (m, 1H, CH_2); NOEs: 7-H \rightarrow PC- CH_2 ; δ_{C} (100.6 MHz, CDCl_3) 197.60 (C=O), 140.80 (vinylic-C), 140.00 (indenone- α -C-6), 136.20, 135.80, 135.60 (PC-C), 135.00 (indenone- β -CH-7), 134.90, 133.20, 133.00 (PC-CH), 132.80, 132.60, 132.40, 132.10, 131.40 (PC-C), 130.90, 130.60, 130.40, 130.20, 129.20, 129.00 (PC-CH), 128.80, 128.60, 128.30, 128.00 (PC-C), 127.00, 126.90, 126.00 (PC-CH), 120.00 (vinylic-CH), 38.20, 35.80, 35.60, 34.40, 34.20, 32.00, 31.40, 30.60, 29.40 (CH_2); m/z (EI) 505 [M^+] (44), 504 [M^+] (100), 401 (12), [$\text{M}^+ - 104$] (32), 296 (36), 267 (24), 253 (30), 252 (50), 104 (34), 57 (14).
17. 5,6,10,11,16,17-Hexahydrotri[2]paracyclophanyl[2](4,7)-naphthalenophanyl[c,e,g]benzene (**6**) was obtained as yellow crystals (2.17 g, 70%), mp 290–292 °C (ethanol), (R_f 0.4, CH_2Cl_2); [Found: C, 92.80; H, 7.00%. $\text{C}_{60}\text{H}_{54}$ requires C, 92.98; H, 7.02%]; ν_{max} (KBr) 3075–3000 cm^{-1} (Ar-CH), 2985–2830 (Aliph.-CH), 1580 (C=C); λ_{max} (CH_3CN , log ϵ) 420 nm (4.00); δ_{H} (400 MHz, CDCl_3) 7.60–7.56 (m, 2H), 7.42–7.36 (m, 2H), 7.28 (d, 2H, $J = 7.8$ Hz), 7.16 (d, 2H, $J = 7.8$ Hz), 6.80–6.55 (m, 6H), 6.50–6.36 (m, 4H), 4.40–4.20 (m, 8H, CH_2), 3.80–3.40 (m, 6H, CH_2), 3.20–2.60 (m, 16H, CH_2), 2.20–2.00 (m, 2H, CH_2), 1.80–1.40 (m, 4H, CH_2); δ_{C} (100.6 MHz, CDCl_3) 140.20, 138.40, 138.20, 138.10, 138.00, 137.60, 137.40, 137.00, 136.80, 136.56, 136.48, 136.28, 136.10, 135.90, 135.80, 135.64, 135.30, 135.20, 134.88, 134.40, 134.20 (PC-C), 133.90, 133.64, 133.42 (PC-CH), 133.26, 133.18, 133.00 (PC-C), 132.50, 132.20, 132.10, 131.80, 130.60, 130.44, 130.18, 130.06, 128.20, 128.00, 127.90, 127.00, 126.80, 126.20, 126.00 (PC-CH), 35.40, 35.24, 35.18, 35.00, 34.80, 34.60, 34.20, 34.00, 32.80, 32.60, 32.40, 32.00, 26.00, 24.30, 24.00, 22.60, 22.40, 22.00 (CH_2); m/z (EI) 775 [M^+] (100), 696 (20), 670 [$\text{M}^+ - 104$] (60), 642 (20), 614 (18), 592 (24), 586 (18), 420 (26), 405 (22), 389 (20), 104 (38), 90 (20), 78 (20).
18. (a) Sudhakar, A.; Katz, T. J. *J. Am. Chem. Soc.* **1986**, 108, 179; (b) Sudhakar, A.; Katz, T. J.; Yang, B.-W. *J. Am. Chem. Soc.* **1986**, 108, 2790.
19. Lehnert, W. *Tetrahedron* **1973**, 29, 635.
20. Allinger, N. L. PM3 (91) force field Program, obtained from Quantum Chemistry Program, Indiana University; Molecular Mechanics PM3 Program (ACD/3D), Advanced Chemical Development, Toronto, Canada, 1988.
21. Boorum, M.; Scott, L. In *Modern Arene Chemistry: Concept, Synthesis, and Applications*; Astruc, D., Ed.; Wiley-VCH: Weinheim, 2002.