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One-Step Synthesis of 5a,11a-Janusene Imide Employing 2,3-Dibromo-*N*-methylmaleimide as Acetylene Equivalent †

Petar Štrbac and Davor Margetić

Laboratory for Physical Organic Chemistry, Division of Chemistry and Biochemistry, Ruđer Bošković Institute, HR-10000 Zagreb, Croatia; Petar.Strbac@irb.hr

* Correspondence: margetid@irb.hr; Tel.: +385-1-4561008

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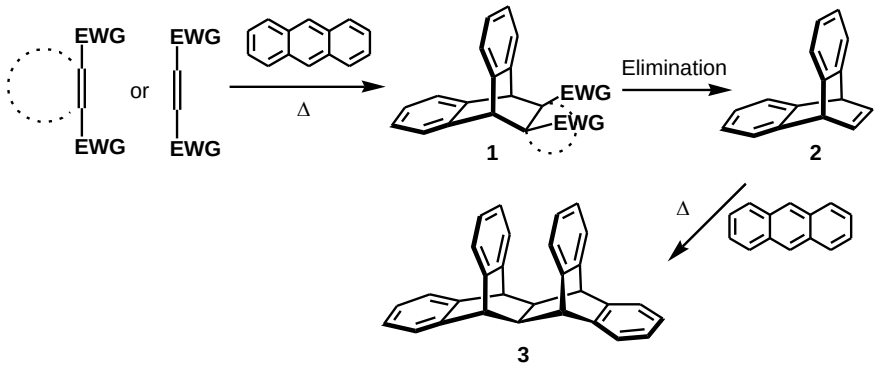
Abstract: Synthesis of janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene) requires several reaction steps starting from anthracene. In this account, one-pot, three steps synthesis of janusene *N*-methyl-5a,11a-dicarboximide employing 2,3-dibromo-*N*-methylmaleimide as acetylene equivalent is described. This thermal reaction is simple synthetic procedure in comparison to sequential-multi step [4+2] cycloaddition routes. Here 2,3-dibromo-*N*-methylmaleimide acts effectively as 'molecular glue' bridging two anthracene molecules together.

Keywords: cycloaddition; anthracene; microwave assisted organic reactions; Diels-Alder reaction; cycloreversion

1. Introduction

Diels-Alder reaction is one of the most important organic reactions for synthesis of complex polycyclic molecules [1–3] Synthesis of janusene (5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-o-benzenonaphthacene) is one example of molecules prepared by DA method which requires several reaction steps including multiple anthracene Diels-Alder reaction. The first synthesis of janusene derivative (anthracene 5a,11a-janusenedicarboxylic anhydride **23**) was reported by Diels[4] and employs three reaction steps: [4+2] cycloaddition of anthracene with 1,2-dibromomaleic anhydride, followed by 1,2-debromination[5] to alkene **22** and another [4+2] cycloaddition of anthracene. It is evident from the literature that synthesis of dibenzobarrelene is the limiting synthetic step which in the second reaction includes [4+2] cycloaddition of dibenzobarrelene to anthracene. This approach was employed in janusene synthesis by Cristol [6] from dibenzobarrelene and anthracene in thermal conditions. Later on, several synthetic routes to dibenzobarrelene employed acetylene equivalents—various dienophiles possessing activating electron-acceptor groups. After addition, dienophile activation groups are removed to obtain dibenzobarrelene (Scheme 1).



Scheme 1. Synthetic approaches to janusenes by cycloaddition strategies.

Among acetylene equivalents used for dibenzobarrelene preparation are (*E*)-1-phenylsulfonyl-2-trimethylsilylethylene devised by Paquette [7], 1-benzenesulfonyl-2-trimethylsilylacetylene developed by Williams [8], (*Z*) and (*E*)-1,2-bis(phenylsulfonyl)ethylene used by Künzer [9] and De Lucchi [10], 1,4-benzodithiin-1,1,4,4-tetraoxide, in fact cyclic variant of (Z)-1,2-bis(phenylsulfonyl)ethylene reported by Wenkert [11] and maleic anhydride used by Warrener [12]. Synthetically more elegant is intramolecular acetylene transfer via addition-reversion route from tetrafluorobenzobarrelene (one-pot) was reported by Filler [13].

2. Materials and Methods

Chemicals were purchased from Sigma and solvents (dichloromethane, ethyl acetate and light petroleum b.p. 40–60 °C) were used as purchased. The reaction products were identified by one-dimensional ^{1}H and ^{13}C spectroscopy, using Bruker Avance 300 MHz and Bruker Avance 600 MHz spectrometers.

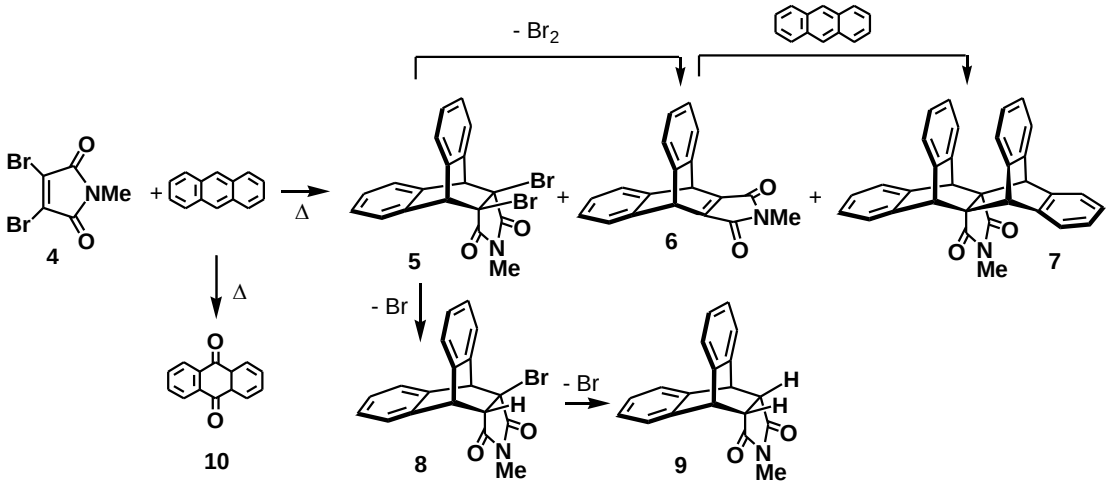
Microwave assisted heating was performed using 100 W of initial microwave power.

Thermal conditions: (Method A) Flash-vacuum pyrolysis experiments were conducted under vacuo (0.01–0.001 mbar) in an 600 × 6 mm Pyrex tube heated by a horizontally-mounted 'Thermolyne' model 21100 tube furnace using 100–200 mg of reaction mixture. Products were collected at the end of furnace on cooler part of the tube. Volatile products (furan and acetylene were condensed in liquid nitrogen trap). No experiments were conducted using silica thermolysis tubes.

Thermal conditions: (Method B) Thermolyses were conducted at atmospheric pressure in an 600 × 6 mm Pyrex tube heated by a horizontally-mounted 'Thermolyne' model 21100 tube furnace using 100–200 mg of reaction mixture. Products were collected by washing of the tube.

3. Results and Discussion

In our ongoing interest in cycloaddition reactions [14,15] we observed that cycloaddition of anthracene with 2,3-dibromo-*N*-methylmaleimide **4** when conducted by the microwave irradiation at high temperature (180 °C, DMF, 2 h) afforded several products **5–10** (Scheme 2). Minor amount of anthraquinone was also detected. Surprisingly, amongst them was small amount of janusene *N*-methyl-5a,11a-dicarboximide **7**, which could arise only from tandem Diels-Alder addition of anthracene onto imide **4**. In this transformation, with 2,3-dibromo-*N*-methylmaleimide **4** acted as acetylene equivalent in similar manner as tetrafluorobenzobarrelene earlier reported by Filler. Also, our reaction is one-pot equivalent of three-step Diels' methodology to 5a,11a-janusene derivatives. Scheme 2 depicts products and the mechanistic rationale for the formation of janusene 7. The key step is thermal 1,2-debromination which generates 2π-component required for the second [4+2] cycloaddition. The change of reaction conditions (MW irradiation for shorter time, 15 min, or without solvent, for 2 h) influences the reaction outcome. After 15 min in MW reactor in DMF solution, relatively larger ratios **6** and **7** in comparison to product **5** were obtained, whereas MW heating without the solvent provided cycloadduct **5** almost exclusively.



Scheme 2. Thermolysis of 2,3-dibromo-*N*-methylmaleimide **4** with anthracene.

The influence of the reaction conditions was further studied by reactions in flash vacuum pyrolysis (FVP) furnace and the obtained results are illustrated in Figure 1. The FVP heating under vacuum was less successful than simple heating at elevated temperatures (180–350 °C) of neat reaction mixtures in an Pyrex glass tube for short time (10–15 min). Notably, these reactions were much cleaner than MW promoted, and at 180 °C clean 1:1 cycloadduct **5** was formed exclusively, whereas thermolysis at 350 °C provided janusene 7 as the single product. Simple sublimation was employed to remove anthracene excess from products. In variance with MW reactions, imide **6** was never detected in reaction mixtures. This finding emphasizes the compatibility of different synthetic methods (conventional and MW heating). ^{1}H NMR spectroscopy was used to elucidate the structures of products and the formation of **7** was established by the characteristic up-field NMR shift of facial aromatic protons [16] (multiplets at δ 6.69 and 6.90). The structural assignment of other products was obtained by their symmetry, relative position in NMR spectra and integration of protons.

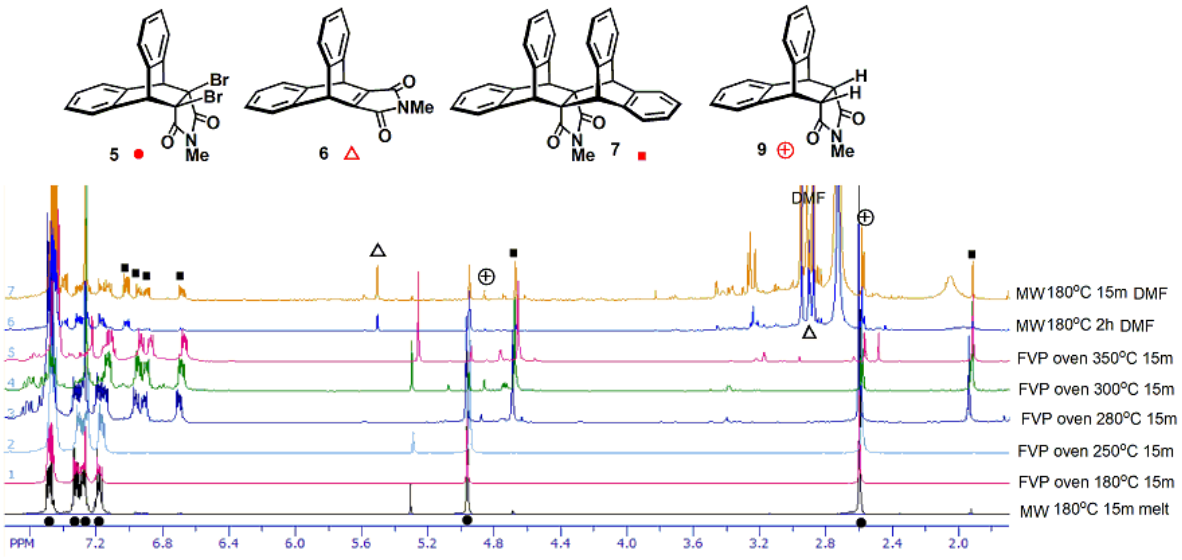


Figure 1. Temperature control of reactivity of *N*-methyl-1,2-dibromomaleimide **4** with anthracene (^{1}H NMR, $CDCl_3$).

The structure of newly synthetized janusene **7** was visualized by quantum-chemical calculations (Figure 2). Molecular modelling (B3LYP/6-31G* calculations) has shown that there is almost no difference in structures of imide **7** and parent janusene. Geometrical parameters, in particular the C-C distance between two aromatic rings in janusene **3** (3.149 Å,) does not change by the imide substitution in **7** (3.083 Å) and it is illustrated by the overlay of two optimized structures.

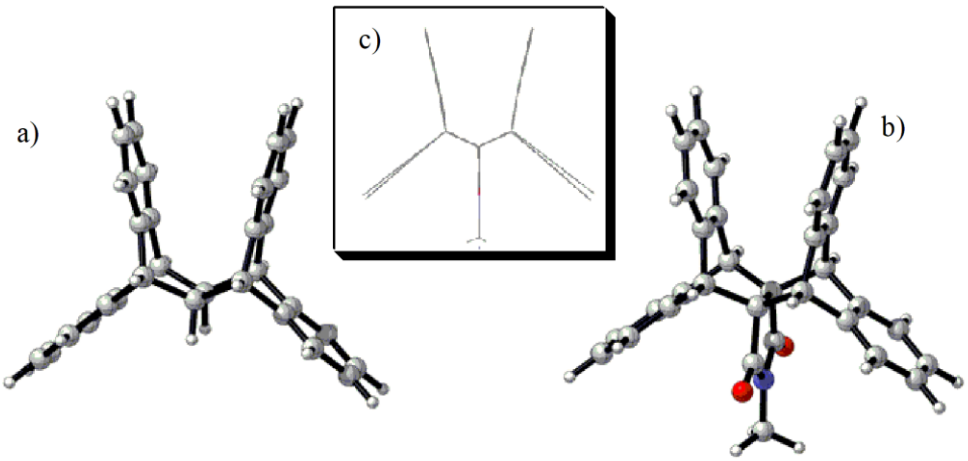
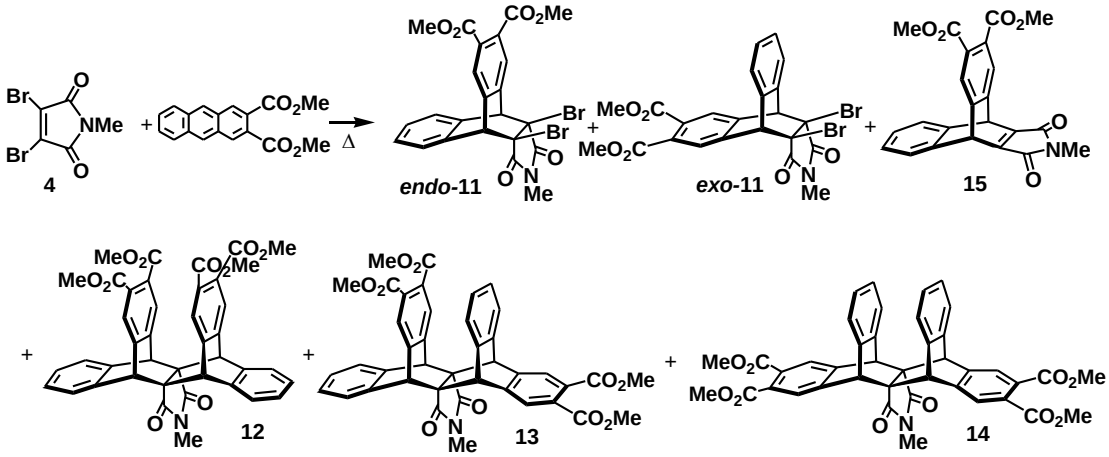


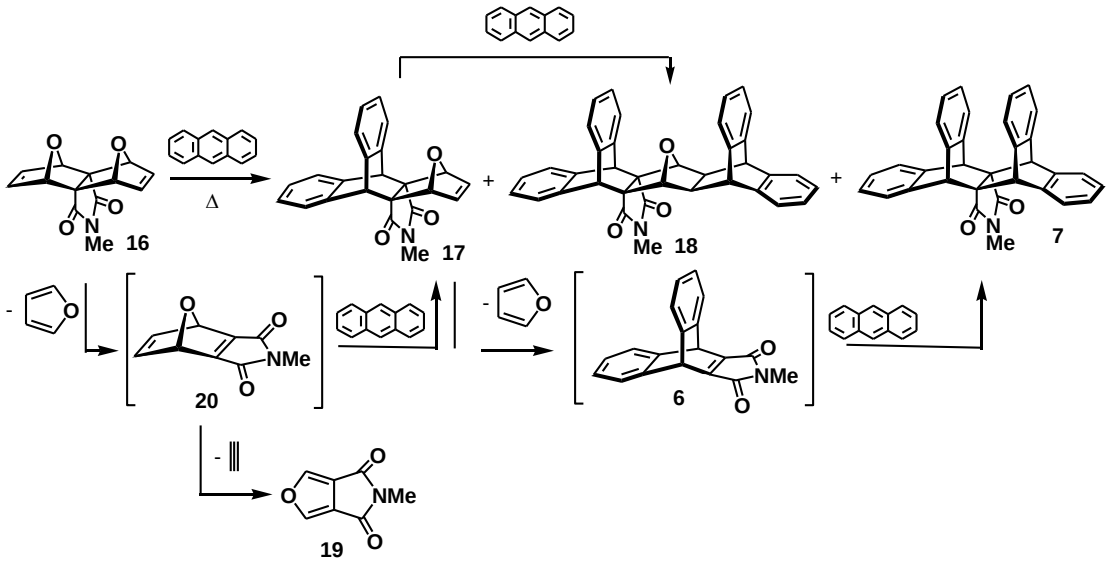
Figure 2. Optimized structures (B3LYP/6-31G*) of janusenes (**a**) **3** and (**b**) **7**; inset (**c**) the overlay of two structures.

Similar thermal reactions of 2,3-dibromo-*N*-methylmaleimide **4** with 2,3-dicarbmethoxyanthracene conducted at 180, 280 and 350 °C (15 min, pyrex glass tube in FVP furnace) resulted in inseparable mixtures of two 1:1 adducts **11** (*endo*- and *exo*-, 1:0.9 ratio) and three 2:1 adducts **12–14** (janusene derivatives) (Scheme 3). In these reactions, again, intermediate alkene **15** was not detected.



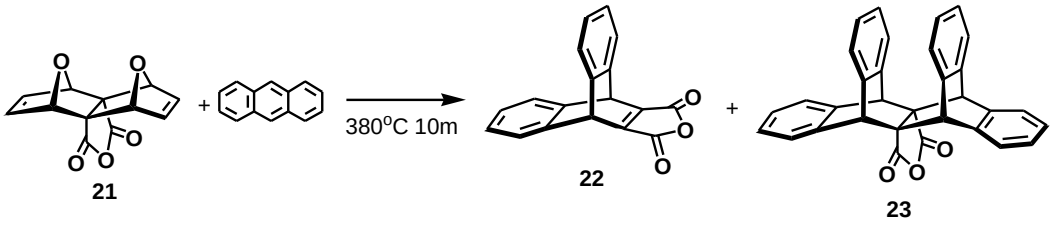
Scheme 3. Thermolysis of 2,3-dibromo-*N*-methylmaleimide **4** with 2,3-dicarbmethoxyanthracene.

The same products could be obtained by the employment of dioxaimide **16** as the acetylene equivalent (Scheme 4). Different products dominate, depending on the temperature applied and the cycloaddition adduct **18** was also obtained. As the higher thermolysis temperatures were applied, the amount of furanimide **19** [17] increases, due to complete decomposition of **16**.



Scheme 4. Thermolysis of imide **16** with anthracene.

The present cycloaddition methodology could be further extended on the anhydride functionality. When the anhydride **21** [18] was pyrolised instead of imide **16** at 380 °C for 10 min, different outcome in comparison to **16** was achieved. With the anhydride substrate, a mixture of alkene **22** and janusene anhydride **23** (previously published by Diels) [**Error! Bookmark not defined.**] in 2:1.6 ratio was obtained (Scheme 5). The structures of two products were identified by ^{1}H NMR spectroscopy: janusene **23** was determined by characteristic up-field shift of facing aromatic rings (shift up to δ 6.73), while the ^{1}H NMR spectrum of alkene **22** [19] features the characteristic bicyclo[2.2.2] proton singlet at δ 5.54, which is in full correspondence to literature value. Hence, anhydride **21** acts as acetylene equivalent in analogous manner to imide **16**. In contrast to thermal behavior of the imide **16** and our expectation that thermal decarboxylation of the alkene anhydride **22** could take place giving dibenzobarrelene [**Error! Bookmark not defined.**], product **21** could be obtained as a stable species in identical reaction conditions.



Scheme 5. Thermolysis of anhydride **21** with anthracene.

4. Conclusions

ffTandem [4+2] cycloaddition reactions were carried thermally employing 2,3-dibromo-*N*-methylmaleimide **4**, imide **16** and anhydride **21** to produce janusene derivatives. This one-pot simple methodology employs these reagents as acetylene equivalents and intramolecular acetylene transfer via addition-debromination or addition-reversion route.

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Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

References

1. Dyan, O.T.; Borodkin, G. I.; Zaikin, P.A. The Diels–Alder Reaction for the Synthesis of Polycyclic Aromatic Compounds. *Eur. J. Org. Chem.* **2019**, *44*, 7271–7306, doi:10.1002/ejoc.201901254.
2. Nicolaou, K.C.; Scott, A.; Snyder, S.A.; Montagnon, T.; Vassilikogiannakis, G. The Diels–Alder Reaction in Total Synthesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698, doi:10.1002/1521-3773(20020517)41:10<1668::AID-ANIE1668>3.0.CO;2-Z.
3. Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction: Selected Practical Methods*; Wiley: Chichester, UK, 2002; ISBN: 978-0-471-80343-0.
4. Diels, O.; Friedrichsen, W. Synthesen in der hydroaromatische Reihe. XXII. Über die Athracen-C_4O_3-Adukte, ihre Eignung zu Dien-Synthesen und ein neues Prinzip zur Synthese von Phtalsäuren und Dihydrophtalsäuren. *Ann. Chem.* **1934**, *513*, 145–155, doi:10.1002/jlac.19345130109.
5. Diels, O.; Alder, K. Synthesen in der hydroaromatischen Reihe. VIII. Mitteilung: Dien-Synthesen des Anthracens. Anthracen-Formel. *Ann. Chem.* **1931**, *486*, 191–202, doi:10.1002/jlac.19314860110C.
6. Cristol, S.J.; Lewis, D.C. Bridged polycyclic compounds. XLV. Synthesis and some properties of 5,5a,6,11,11a,12-hexahydro-5,12:6,11-di-*o*-benzenonaphthacene (Janusene). *J. Am. Chem. Soc.* **1967**, *89*, 1476–1483, doi:10.1021/ja00982a035.
7. Paquette, L.A.; Moerck, R.E.; Harirchian, B.; Magnus, P.D. Use of Phenyl Vinyl Sulfoxide as an Acetylene Equivalent in Diels-Alder Cycloadditions. *J. Am. Chem. Soc.* **1978**, *100*, 1597–1599, doi:10.1021/ja00473a044.
8. Williams, R.V.; Chauhan, K.; Gadgil, V.R. 1-Benzenesulfonyl-2-trimethylsilylacetylene: A new acetylene equivalent for the Diels-Alder reaction. *J. Chem. Soc. Chem. Commun.* **1994**, 1739-1740, doi:10.1039/C39940001739.
9. Künzer, H.; Stahnke, M.; Sauer, G.; Wiechert, R. Reductive desulfonylation of phenyl sulfones by samarium(II) iodide-hexamethylphosphoric triamide. *Tetrahedron Lett.* **1991**, *32*, 1949–1952, doi:10.1016/0040-4039(91)85009-T.
10. De Lucchi, O.; Lucchini, V.; Pasquato, L.; Modena, G. The (*Z*)- and (*E*)-1,2-bis(phenylsulfonyl)ethylenes as synthetic equivalents to acetylene as dienophile. *J. Org. Chem.* **1984**, *49*, 596–604, doi:10.1021/jo00178a004.
11. Wenkert, E.; Broka, C.A. Diels-Alder reactions with two-carbon sulfur dienophiles. *Finnish Chem. Lett.* **1984**, *4-5*, 126-129.
12. Golić, M.; Butler, D.N.; Warrener, R.N.; Margetić, D. New routes to dibenzobarrelene and pyrimidinobenzobarrelenes: A synthetic and computational study. In Proceedings of the ECSOC-3 and Proceedings of ECSOC-4, 1–30 September 1999 and 2000; Edited by Pombo-Villar, E.; 2000; pp. 1638–1650.
13. Cantrell, G.L.; Filler, R. An intramolecular acetylene transfer between anthracene and 5,6,7,8-tetrafluorobenzobarrelene. A novel synthesis of janusene and dibenzobarrelene. *J. Org. Chem.* **1984**, *49*, 3406–3407, doi:10.1021/jo00192a038.
14. Margetić, D. (ed.) *Cycloaddition Reactions: Advances in Research and Applications*; Nova Science Publishers: Hauppauge, New York, USA, 2019; ISBN:; 978-1-53615-420-7.
15. Golić, M.; Johnston, M.R.; Margetić, D.; Schultz, A.C.; Warrener, R.N. Use of a 9,10-dihydrofulvalene pincer cycloadduct as a cornerstone for molecular architecture. *Aust. J. Chem.* **2006**, *59*, 899–914, doi:10.1071/CH06286.
16. Cristol, S.J.; Imhoff, M.A. Bridged polycyclic compounds. LXVII. Carbonium ion rearrangements among janusene, hemiisojanusene, and isojanusene derivatives. *J. Org. Chem.* **1971**, *36*, 1861–1865, doi:10.1021/jo00813a002.
17. Margetić, D.; Butler, D.N.; Warrener, R.N.; Murata, Y. Domino Diels-Alder reactions of 7-oxanorbornadiene-2,3-dicarboximide: An elusive, highly reactive dienophile. *Tetrahedron* **2011**, *67*, 1580–1588, doi:10.1016/j.tet.2010.12.032.
18. Butler, D.N.; Margetić, D.; O'Neill, P.J.C.; Warrener, R.N. Parity reversal: A new Diels-Alder approach to the synthesis of sesquinorbornadienes including those of unusal geometry. *Synlett* **2000**, *1*, 98–100, doi:10.1055/s-2000-6445.
19. Smet, M.; Corens, D.; Van Meervelt, L.; Dehaen, W. Synthesis of the Formal Diels-Alder Adducts of *N*-substituted Dehydromaleimides and Anthracene. *Molecules* **2000**, *5*, 179–188, doi:10.3390/50200179.

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