



A Diels–Alder approach to *trans*-trisbicyclo[2.2.1]heptabenzene derivative

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ABSTRACT

A new route to the synthesis of a *trans*-tris(bicyclo[2.2.1]hexeno)benzene derivative, using Diels–Alder reaction as critical step, was investigated. The compound with six methoxycarbonyl groups was successfully synthesized in good yield without any organometallic reagents. Some useful by-products from dimethyl but-2-ynedioate were also isolated from the last step. Perhaps due to stereo-hindrance or electrostatic repulsion in the *cis*-isomer, *trans*-isomer was found to be the only isomer in the crystal and its structure was proved by X-ray diffraction.

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In the recent years, much attention has been focused on the synthesis of the compounds that possess cyclohexatriene motif, which could potentially lead to new materials to broaden the scope of molecular recognition and supramolecular chemistry.¹ These compounds have also been used as precursors of subunits of fullerene² and trindane structures.³ In addition, there exists a phenomenon of bond alternation (or localization) in benzenoid structures of these compounds, which is associated with the Mills–Nixon effect,⁴ and this has been the subject of considerable theoretical investigations.⁵

Such compounds are generally synthesized through the cyclo-trimerization of trimethylstannylalkenes, using different metal catalysts.⁶ For example, F. Fabris developed an original reaction involving trimerization of vicinal bromotrimethylstannyl olefins with a copper promoter.^{6b} The reaction of polycyclic bromotrimethylstannyl olefins with alkenes in the presence of copper(II) nitrate in THF was reported to produce a mixture of *syn* and *anti* isomers.^{6a} The antiselective synthesis of the cyclo-trimer has been achieved efficiently, using a Pd(0) catalyst.^{6c} However, the synthesis still faces great challenges as it involves hypersensitive organometallic precursors, which are difficult to be prepared. Therefore, the search for a better synthetic strategy to prepare these compounds is highly desirable.

Recently, we designed a four-step route to synthesize tris(bicyclo[2.2.1]hexeno)benzene derivative from cyclopentanone (Scheme 1). This method may lead to the synthesis of a large variety of new compounds.

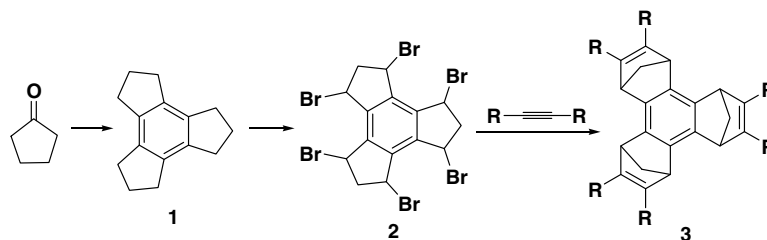
Trindane **1** was obtained in a yield of 31% from cyclopentanone and ZrCl₄ according to the literature,⁷ but under microwave irradiation.⁸ 1,3,4,6,7,9-hexabromotrindane **2** is produced by the bromination reaction of **1** with Br₂ in 82% yield, according to the method we reported previously.⁹

The most critical step of this route is the Diels–Alder reaction of 1,3,4,6,7,9-hexabromotrindanes **2** with a dienophile, such as dimethyl but-2-ynedioate, in which compound **2** eliminates six bromine atoms to generate a tri-diene intermediate. Dimethyl but-2-ynedioate was selected as the dienophile due to its high reactivity in Diels–Alder reaction and simplicity of the expected products. The target compound **3**¹⁰ was obtained in 32% yield by reacting 1 equiv of compound **2** with 8 equiv of zinc powder, and a large excess of ca. 20 equiv of dimethyl but-2-ynedioate in DMF under ultrasonic irradiation (Scheme 2). The use of ultrasonic irradiation in the reaction improved the yield of compound **3**. The control experiment showed that a lower yield of 20% of the desired product was obtained without ultrasonic irradiation. An explanation for this improvement could be the impact and cavitation effects of ultrasonic irradiation to keep the surface of Zn metal fresh.

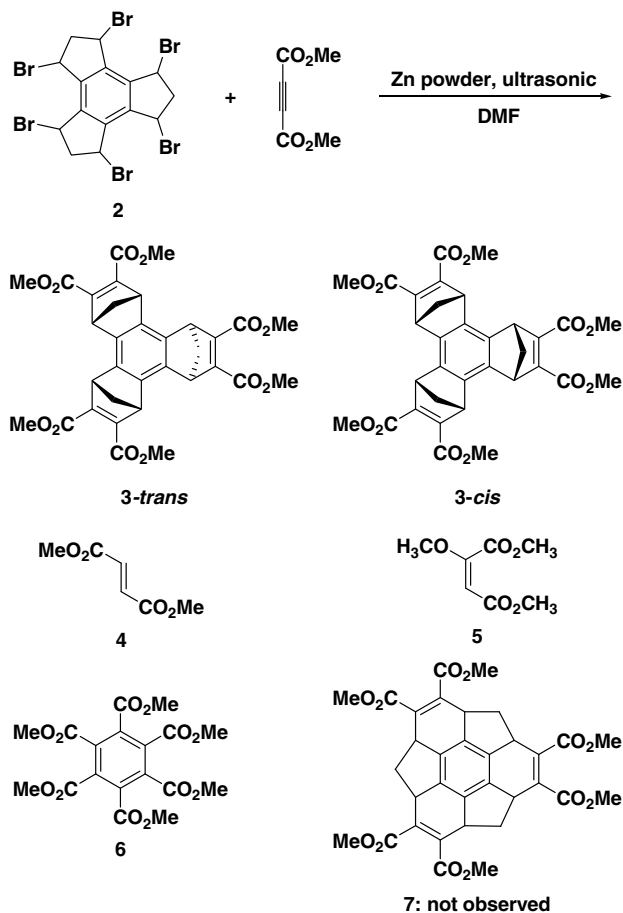
The excessive but-2-ynedioate is necessary in the reaction, since the tri-diene intermediate might be formed firstly in the debromination of compound **2** by Zn powders and carried out the Diels–Alder reaction with but-2-ynedioate to give the desired product. Since the intermediate is highly active, the side reactions, including polymerization and [1,5] σ -migration, are easy to take place. Accordingly, the excessive but-2-ynedioate can improve the yield of the desired Diels–Alder reaction.

The structure of compound **3** was confirmed by IR, ¹H NMR, ¹³C NMR spectroscopy, and elemental analyses. The absorption around

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Scheme 1.



Scheme 2.

1737 cm^{-1} demonstrated the existence of C=O. The chemical shifts of CH, CH_2 , and CH_3 groups of compound **3** appeared at 2.12–2.15 (d, 3H), 2.46–2.51 (m, 3H), 3.74 (s, 18H), and 4.30–4.35 (d, 6H), respectively. Compounds **4–6**, derived from dimethyl but-2-yne-dioate,¹¹ were also isolated from the reaction mixture in the yields of 5.2%, 3.1%, and 7.8%. Compound **6** is an important compound that can be used in the study of a novel dual fluorescence phenomenon.¹² Compound **7**, the precursor of sumanene derivatives, however, was not isolated from the reaction mixture, presumably due to the large size of the bay regions or the possible severe strain that exists in the structure.

The X-ray crystal structural analysis of **3** revealed that only the **3-trans** isomer can be found in the crystal (Fig. 1),¹³ while **3-cis** is absent. For **3-cis**, all the methoxycarbonyl groups have to be on one side of the central six-membered ring, which would possibly introduce strong steric hindrance as well as electrostatic repulsion.

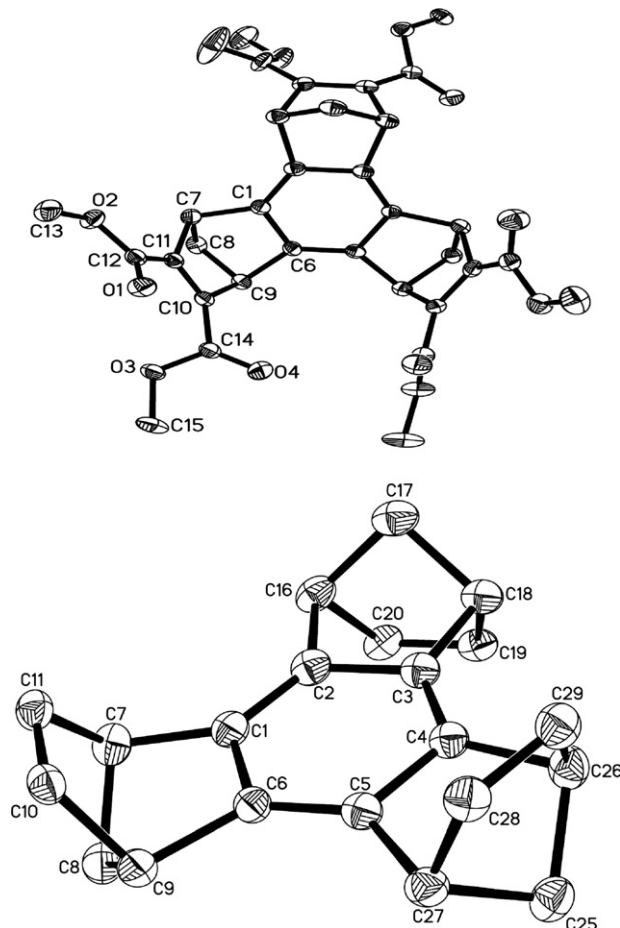


Figure 1. Top: overall perspective drawing of **3-trans**; bottom: clarified drawing of **3-trans** (all methoxycarbonyls are omitted for clarity); selected bond lengths (Å), angles (°): C1–C2 = 1.364(5), C2–C3 = 1.432(5), C1–C6 = 1.429(5), C1–C7 = 1.519(5), C3–C4 = 1.351(5), C4–C5 = 1.423(5), C5–C6 = 1.357(5), C11–C12 = 1.484(6), O1–C12 = 1.207(5), C10–C14 = 1.483(5), O3–C14 = 1.319(5), O3–C15 = 1.448(5); C2–C1–C6 = 119.5(3), C2–C1–C7 = 134.4(4), C1–C2–C3 = 120.0(4), C4–C3–C2 = 119.7(3), C9–C8–C7 = 94.0(3), C10–C11–C7 = 107.4(3), O1–C12–C11 = 124.0(4), C12–O2–C13 = 116.7(4).

Recently, the phenomenon of bond alternation (or localization) in benzene, which is associated with the Mills–Nixon effect, has become the renewed attention.¹⁴ Siegel et al. have reported the synthesis of tris(bicyclo[2.1.1]hexeno) benzene, as the first example of mononuclear benzenoid hydrocarbon with a cyclohexatriene-like geometry ($\Delta R = R_{\text{endo}} - R_{\text{exo}} = 0.089 \text{ \AA}$).¹⁵ Obviously, compound **3** presents a useful model to study the Mills–Nixon effect. As expected, the central six-membered ring is planar, and all internal bond angles of the ring are almost 120. The bond lengths are alternately shorter (average 1.357 Å) and longer

(average 1.428 Å) with the shorter bonds exocyclic to bicycloannulation. The ΔR in **3-trans** is ca. 0.071 Å.

In summary, we have developed a new protocol to prepare tris(bicyclo[2.2.1]hexeno)benzene derivatives using Diels–Alder reaction as the critical step. Compared to the previous routes, our protocol neither needs toxic organometallic compounds nor expensive catalysts. Further studies aimed at the preparation of *cis* isomers by changing the dienophile are in progress.

Acknowledgments

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- Compound 1**: To a flask containing 9 mL (0.1 mol) of cyclopentanone, ZrCl₄ (0.94 g, 4.03 mmol) was added. After the reaction mixture was stirred and refluxed under microwave irradiation for about 4 h, sodium hydroxide solution was added until the pH 7. The reaction mixture was extracted by CHCl₃ (15 mL × 4). The organic phase was dried over MgSO₄, and the crude product was purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 5:1) to afford compound **1** as white needle crystals. Yield: 31%. Mp 96.1–97.2 °C; ¹H NMR (CHCl₃, 300 MHz, δ ppm): 2.70–2.80 (t, 12H, *J* = 7.20 Hz), 2.00–2.10 (m, 6H). Anal. Calcd for C₁₅H₁₈: C, 90.85; H, 9.15. Found: C, 89.95; H, 9.06. IR (KBr disk, ν cm⁻¹): 2948, 2835, 1438, 1269.
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- Compound 3**: A mixture of zinc powder (0.46 g, 7.0 mmol), dimethyl but-2-ynedioate (1.79 g, 9.0 mmol) and DMF (10 mL) was sonicated for 15–30 min, and 0.672 g (1.0 mmol) of **2** was added to the mixture. After sonication for 3–4 h, the mixture was stirred at 40–50 °C for 5 h, then poured into water (200 mL), which was extracted with CHCl₃ (30 mL × 3). The combined organic phases were dried over MgSO₄, and then purified by column chromatography on silica gel (petroleum ether–ethyl acetate = 5:1) to afford compound **3**: Yield: 32%. Mp 249.2–251.0 °C; ¹H NMR (CHCl₃, 300 MHz, δ ppm): 4.30–4.35 (d, 6H), 3.74 (s, 18H), 2.46–2.51 (m, 3H), 2.12–2.15 (d, 3H). Anal. Calcd for C₃₃H₃₀O₁₂: C, 64.08; H, 4.76. Found: C, 63.97; H, 4.92. IR (KBr disk, ν cm⁻¹): 3011, 2959, 2849, 1736, 1447, 1233, 983, 852.
- Compound 4**: Yield: 5.2%. Mp 106–107 °C; ¹H NMR (CHCl₃, 300 MHz, δ ppm): 6.87 (s, 2H), 3.81 (s, 6H); ¹³C NMR (CHCl₃, 300 MHz, δ ppm): 52.26, 133.38, 165.35; **Compound 5**: Yield: 3.1%. M.p. 40 °C; ¹H NMR (CHCl₃, 300 MHz, δ ppm): 5.21 (s, 1H), 3.71–3.88 (m, 9H); ¹³C NMR (CHCl₃, 300 MHz, δ ppm): 51.5, 52.8, 56.9, 93.1, 93.1, 162.4, 166.2. Anal. Calcd for C₇H₁₀O₅: C, 48.21; H, 5.75. Found: C, 48.15; H, 5.57. **Compound 6**: Yield: 7.8%. Mp 186–187 °C; ¹H NMR (CHCl₃, 300 MHz, δ ppm): 3.88 (s, 18H); ¹³C NMR (CHCl₃, 300 MHz, δ ppm): 53.2, 133.9, 164.9; Anal. Calcd for C₁₈H₁₈O₁₂: C, 50.70; H, 4.23. Found: C, 50.93; H, 3.88. IR (KBr disk, ν cm⁻¹): 3013, 2960, 2904, 1738, 1446, 1365, 1233, 984.
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- Single crystals of compound **3** suitable for X-ray diffraction were obtained from hexane/dichloromethane solution for two weeks. A colorless single crystal with dimensions 0.28 × 0.23 × 0.18 mm was used for the data collection at 296(2) K on a Bruker Smart 1000 X-ray diffractometer. The crystal belongs to the triclinic crystal system of *P1* space group with unit cell parameters of *a* = 10.0810(11) Å, *b* = 10.9031(12) Å, *c* = 14.4099(16) Å; α = 73.788°, β = 84.057°, γ = 83.049° (CCDC reference: 696277).
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