

© Springer-Verlag 1996

Synthesis of Halogenated 4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones[§]

Xiao-Pei Guan^{†,*}, Zhuang Su[‡], Jian-Guang Sun[†], Yong-Zhong Yu

College of Chemical Engineering and Materials Science, Beijing Institute of Technology, 100081 Beijing, P.R.China

[†] Present address: Department of Chemistry, The City College of the City University of New York, New York, NY 10031, USA. Tel.: +1-212-650-6068; Fax: +1-212-650-6107 (jgsum@scisun.sci.cuny.cuny.edu)

[‡] Present address: Center for Cancer Research, E17-133, Department of Biology and Chemistry, MIT, 40 Ames Street, Cambridge, MA 02139-4307, USA. Tel.: +1-617-258-6172 (szhuang@mit.edu)

Received: 10 June 1996 / Accepted: 12 July 1996 / Published: 13 September 1996

Abstract

The Diels-Alder cycloadditions of 6,6-dimethylfulvene **2** with halogenated benzoquinones **3a-e** were investigated and *endo*-dominated cycloadducts were obtained. Subsequent intramolecular photocycloadditions of **4a-e** afforded the desired halogenated 4-isopropylidenetrishomocubane-8,11-diones **5a-e**.

Keywords: Diels-Alder cycloaddition, photocycloaddition, 6,6-dimethylfulvene, halogenated benzoquinones, TS-trishomocubanes

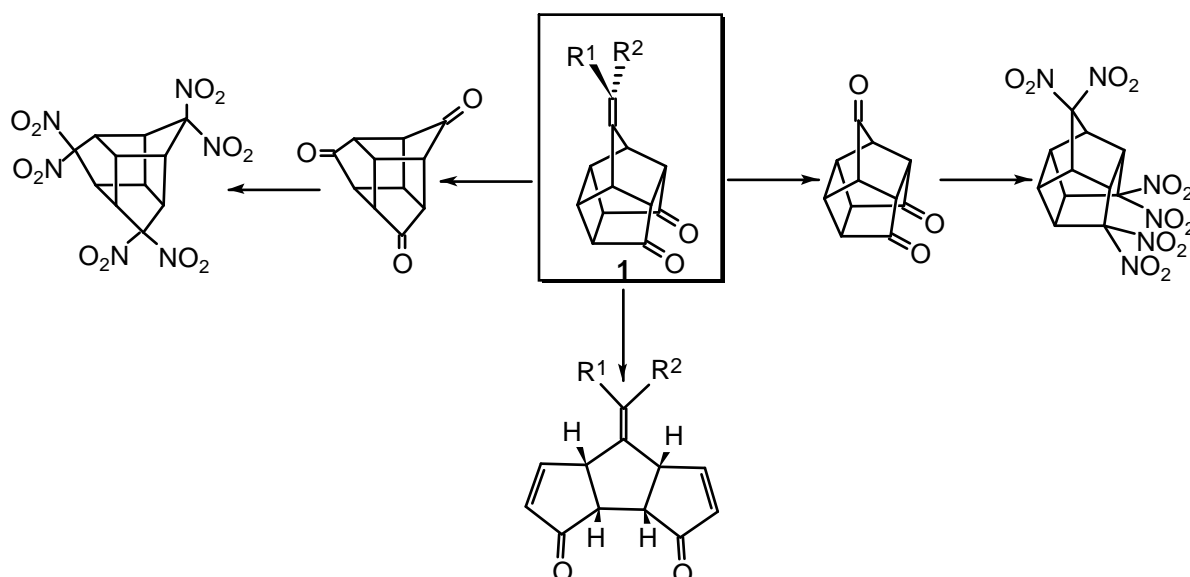
Introduction

There is currently considerable interest in 4-alkylidene-pentacyclo-[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-diones (**1**) as intermediates in the synthesis of linearly fused triquinanes [1] and polynitro-trishomocubanes [2] (Scheme 1). Here we wish to report the synthesis of the halogenated derivatives of **1** (Scheme 2). The Favorskii ring contraction of these α -halo ketones might also afford polyfunctionalized 1,3-bishomocubanes and homocubanes, which are potential precursors to polynitro cage molecules [3].

Results and Discussion

The Diels-Alder cycloaddition of 6,6-dimethylfulvene (**2**) with benzoquinone (1 equivalent) was reported to proceed slowly to give a ~1:1 *endo/exo* mixture in polar solvents such as ethanol [4], but to proceed with high *endo*-stereoselectivity when water was used as solvent [1]. The *endo*-adduct is kinetically preferred, so the addition of excess fulvene **2** would increase the *endo* ratio. We found that the cycloaddition of benzoquinone with 4 equivalents of fulvene **2** in EtOH in an ice-water bath afforded a 3:1 *endo/exo* mixture (based on ¹H-NMR spectra). Under the same conditions, the reaction of **2** with **3a** and **3b** gave complex mixtures; presumably, the cycloaddition occurred

* To whom correspondence should be addressed



Scheme 1

at both C2=C3 and C5=C6. In contrast to this, similar treatment of **3c**, **3d** and **3e** gave the pure *endo* cyclo-adducts **4c**, **4d** and **4e** respectively.

To our surprise, the Diels-Alder cycloaddition of **2** with **3b** carried out in water afforded a 1:10 *endo/exo* mixture, if **2** was added in one portion at room temperature. On the other hand, when the reactions were carried out at 0 °C and **2** was added dropwise, *endo*-dominated mixtures were obtained: ~20:1 *endo/exo* for **4a** and **4b**; ~6:1 *endo/exo* for **4c**, **4d** and **4e**. It is worthy noting that although the Diels-Alder cycloaddition of **3c**, **3d** and **3e** resulted in a lower *endo* ratio in water than in EtOH, the yields were greatly increased (96 %, 98 % and 71 % vis-à-vis 64 %, 72 % and 56 %, respectively).

The Diels-Alder cycloadducts **4a-e** readily undergo cycloreversion in organic solvents at room temperature. Even in the solid state they show slow retro cleavage. This is due to the angle-deformation [5] at the sp²-hybridized C11 atom [6], which is engendered by the abnormally small C1-C11-C8 bond angle [7]. In organic solvents, the initial cycloreversion was followed by further complex reactions, including polymerization of dimethylfulvene [8] and unclear oxidation-reduction (halogenated hydroquinones were isolated after several days). Lowering the temperature to ~0 °C did reduce the decomposition rate. Upon ultraviolet irradiation, the dissociation of **4a-e** was much more rapid and complex, resulting in the production of unidentified tars. The stability toward irradiation decreased in the following order: **4a**, **4b** > **4c** > **4d**, **4e**.

The instability of the Diels-Alder cycloadducts **4a-e** caused the failure of the subsequent intra-molecular [2+2]

photocycloadditions on a large scale. To obtain reasonable yields of products **5** (employing a 400W high pressure mercury vapor lamp, Pyrex glass filter and 80 mL EtOAc as solvent), only ~2 g of **4a** or **4b**, ~400 mg of **4c** and ~200 mg of **4d** or **4e** could be irradiated in a single run.

Experimental Section

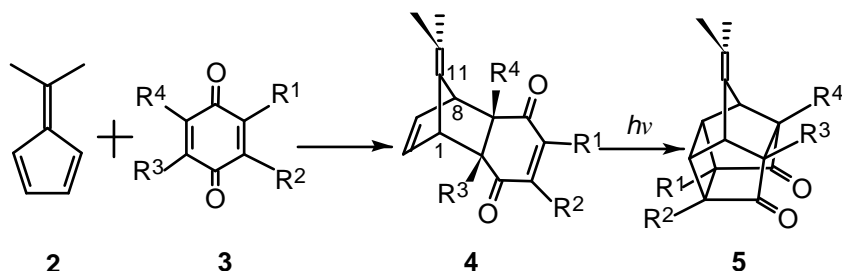
Melting points are uncorrected. IR spectra were recorded on a Shimadzu IR-408 spectrometer. ¹H-NMR spectra were recorded on a Varian EM-360L spectrometer and ¹³C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. MS were measured with a Finnigan-Mat TSQ-45B instrument and HRMS were measured with a Kratos AEI-MS50 instrument.

Diels-Alder cycloadditions of 6,6-dimethylfulvene (**2**) with halogenated benzoquinones (**3a-e**).

Method A. A suspension of halogenated benzoquinone (1 mmol) in EtOH (2.5 mL) was cooled to ~5 °C in an ice-water bath. To this suspension was added dropwise with stirring 6,6-dimethylfulvene (4 mmol). The resulting mixture was stirred at ~5 °C for one to two days. The resulting microcrystalline solid was collected by suction filtration and washed with cold EtOH.

Method B. A suspension of halogenated benzoquinone (10 mmol) in H₂O (6.5 mL) was cooled to ~5 °C in an ice-water bath. To this suspension was added dropwise with vigorous stirring 6,6-dimethylfulvene (10 mmol). A reddish-brown oil was formed quickly and the stirred reac-

Scheme 2



- a:** R¹=Br, R²=R³=R⁴=H; **b:** R¹=Cl, R²=R³=R⁴=H;
c: R¹=R²=Cl, R³=R⁴=H; **d:** R¹=R³=Br, R²=R⁴=H;
e: R¹=R³=Cl, R²=R⁴=H.

tion mixture was allowed to warm gradually to rt. The reaction mixture was stirred for one to two days and the mixture solidified gradually. The crude solid was collected by suction filtration and washed with cold EtOH.

endo-4-Bromo-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione (**4a**)

Recrystallization of the crude solid from EtOH (<40 °C) afforded the pure **4a** as a light yellow microcrystalline solid (62 %, method B): m.p. 62–64 °C; IR (KBr) 3030(w), 2910(w), 1685(s), 1664(s), 1587(m), 1249(m), 965(m) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.61(s, 6H), 3.26(m, 2H), 3.91(m, 2H), 6.13(m, 2H), 7.05(s, 1H); MS (CI/CH₄) m/z (relative intensity) 295(93 %), 293(100) (M⁺+1). Anal. Calcd for C₁₄H₁₃O₂Br: C 57.36; H 4.47. Found: C 57.39; H 4.52.

endo-4-chloro-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione (**4b**)

Recrystallization of the crude solid from EtOH (<40 °C) afforded pure **4b** as a light yellow microcrystalline solid (61 %, method B): m.p. 74–75 °C; IR (KBr) 3040(w), 2920(w), 1690(s), 1661(s), 1590(m), 1252(m), 983(m) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.62(s, 6H), 3.31(m, 2H), 3.98(m, 2H), 6.25(m, 2H), 6.91(s, 1H); MS (CI/CH₄) m/z (relative intensity) 251(75 %), 249(100) (M⁺+1). Anal. Calcd for C₁₄H₁₃O₂Cl: C 67.61; H 5.27. Found: C 67.59; H 5.44.

exo-4-Chloro-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione

To a suspension of chlorobenzoquinone **3b** (1.426 g, 10 mmol) in H₂O (6.5 mL) was added with vigorous stirring 6,6-dimethylfulvene (1.5 mL, 12 mmol) in one portion. After stirring for two days, the reaction mixture was cooled

to ~5 °C to give a solid. Recrystallization of the crude solid from EtOH (<40 °C) afforded the pure *exo* isomer of **4b** (690 mg, 28 %) as light yellow crystals: m.p. 82–83 °C; IR (KBr) 3030(w), 2970(w), 2910(w), 1693(s), 1663(s), 1598(m), 1233(m), 991(m), 733(m) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.47(s, 6H), 2.72(m, 2H), 3.71(m, 2H), 6.50(m, 2H), 7.00(s, 1H); MS (CI/CH₄) m/z (relative intensity) 251(15 %), 249(40) (M⁺+1). Anal. Calcd for C₁₄H₁₃O₂Cl: C 67.61; H 5.27. Found: C 67.57; H 5.27.

endo-4,5-Dichloro-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione (**4c**)

Creamy yellow microcrystalline solid (64 %, method A; 96 %, method B): m.p. >80 °C (dec.); IR (KBr): 3002(w), 2910(w), 1683(s), 1564(m), 1222(s), 1029(m) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.61(s, 6H), 3.37(m, 2H), 3.98(m, 2H), 6.21(m, 2H); MS (CI/CH₄) m/z (relative intensity) 287(5 %), 285(35), 283(62) (M⁺+1). Anal. Calcd for C₁₄H₁₂O₂Cl₂: C 59.39; H 4.27. Found: C 59.43; H 4.00.

endo-2,5-Dibromo-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione (**4d**)

Yellow microcrystalline solid (72 %, method A; 98 %, method B): m.p. >80 °C (dec.); IR (KBr) 3030(w), 2920(w), 1690(s), 1672(s), 1587(m), 1237(s) cm⁻¹; ¹H-NMR (CDCl₃) δ 1.72(s, 6H), 3.66 (d, *J* = 4.2 Hz, 1H), 4.10(m, 2H), 6.27(m, 2H), 7.28(s, 1H); MS (CI/CH₄) m/z (relative intensity) 375 (30 %), 373(55), 371(27) (M⁺+1). Anal. Calcd for C₁₄H₁₂O₂Br₂: C 45.20; H 3.25. Found: C 45.23; H 3.05.

endo-2,5-Dichloro-11-Isopropylidenetricyclo[6.2.1.0^{2,7}]-undeca-4,9-diene-3,6-dione (**4e**)

Creamy yellow microcrystalline solid (56 %, method A; 71 %, method B): m.p. 80–83 °C (dec.); IR (KBr) 2980(w), 2930(w), 1682(s), 1590(m), 1310(m), 1240(m),

743(m) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.72(s, 6H), 3.51(d, $J = 4.0$ Hz, 1H), 3.98(m, 2H), 6.27(m, 2H), 7.01(s, 1H); MS (CI/CH_4) m/z (relative intensity) 287(2 %), 285(47), 283(49) ($\text{M}^+ + 1$). Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{Cl}_2$: C 59.39; H 4.27. Found: C 59.24; H 4.29.

General Procedure for Photocycloaddition of the Diels-Alder Cycloadducts.

A cold EtOAc solution of the Diels-Alder adduct ($\sim 5^\circ\text{C}$) was carefully purged with dry N_2 for ~ 5 min. The solution was then irradiated with a 400 W high pressure mercury vapor lamp (Pyrex filter) at $10\sim 15^\circ\text{C}$ for 10–15 min. Removal of the solvent in vacuo and recrystallization of the crude products afforded the pure product.

1-Bromo-4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (**5a**)

Irradiation of **4a** (1.743 g, 5.946 mmol) and recrystallization of the crude solid from EtOAc/heptane (charcoal) afforded pure **5a** as colorless crystals (1.290 g, 74 %): m.p. $190\sim 191^\circ\text{C}$; IR (KBr) 2990(w), 1768(s), 1740(s) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.79(s, 6H), 2.83(m, 2H), 3.06(m, 1H), 3.35(m, 4H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.2(q), 37.0(d), 42.3(d), 42.8(d), 49.5(d), 49.7(d), 53.2(d), 55.6(d), 55.9(s), 123.5(s), 138.9(s), 203.3(s), 207.3(s); MS (CI/CH_4) m/z (relative intensity) 294(89 %), 292(100) (M^+); HRMS (EI) m/z 292.0092, calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2^{79}\text{Br}$ 292.0099. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{Br}$: C 57.36; H 4.47; Found: C 57.26; H 4.35.

1-Chloro-4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (**5b**)

Irradiation of **4b** (1.697 g, 6.823 mmol) and recrystallization of the crude solid from EtOAc/heptane (charcoal) afforded pure **5b** as colorless crystals (1.409 g, 83 %): m.p. $202\sim 203^\circ\text{C}$; IR (KBr) 2990(w), 1768(s), 1739(s) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.80(s, 6H), 2.7–3.1(m, 3H), 3.34(m, 4H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.2(q), 36.3(d), 42.1(d), 42.5(d), 48.7(d), 50.1(d), 53.3(d), 54.9(d), 64.8(s), 123.5(s), 139.1(s), 203.7(s), 207.5(s); MS (CI/CH_4) m/z (relative intensity) 251(30 %), 249(100) ($\text{M}^+ + 1$); HRMS (EI) m/z 248.0616, calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2^{35}\text{Cl}$ 248.0604. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{O}_2\text{Cl}$: C 67.61; H 5.27. Found: C 67.56; H 5.20.

1,7-Dichloro-4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (**5c**)

Irradiation of **4c** (358 mg, 1.27 mmol) and recrystallization of the crude solid from EtOAc/heptane (charcoal) afforded pure **5c** as colorless needles (213 mg, 59 %): m.p. $245\sim 247^\circ\text{C}$; IR (KBr) 2980(w), 1779(s), 1758(s) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.77(s, 6H), 2.97(m, 2H), 3.38(m, 4H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.4(q), 41.9(d), 48.3(d), 50.6(d), 70.3(s), 125.1(s), 138.6(s), 201.2(s); MS (CI/CH_4) m/z (relative in-

tensity) 286(8 %), 284(60), 282 (100) (M^+); HRMS (EI) m/z 282.0224, calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2^{35}\text{Cl}_2$ 282.0215. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{Cl}_2$: C 59.39; H 4.27. Found: C 59.14; H 4.19.

1,9-Dibromo-4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (**5d**)

4d (204 mg, 0.548 mmol) was irradiated. The crude solid was digested with hot heptane (charcoal). Evaporation of heptane and recrystallization of the residue from heptane afforded pure **5d** as a colorless microcrystalline solid (123 mg, 60 %): m.p. $187\sim 188^\circ\text{C}$; IR (KBr) 2910(w), 1758(s) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.85(s, 6H), 3.0–3.6(m, 6H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.3(q), 21.6(q), 36.6(d), 43.9(d), 48.4(d), 51.0(d), 51.6(d), 55.2(s), 61.6(d), 67.0(s), 127.6(s), 136.2(s), 199.7(s), 199.8(s). MS (CI/CH_4) m/z (relative intensity) 374(49 %), 372(95), 370(51) (M^+); HRMS (EI) m/z 371.9165, calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2^{79}\text{Br}^{81}\text{Br}$ 371.9185. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{Br}_2$: C 45.20; H 3.25. Found: C 45.03; H 3.03.

1,9-Dichloro-4-Isopropylidenepentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]-undecane-8,11-dione (**5e**)

4e (151 mg, 0.534 mmol) was irradiated. The crude solid was digested with hot heptane (charcoal). Evaporation of heptane and recrystallization of the residue from heptane afforded pure **5e** as a colorless microcrystalline solid (98 mg, 65 %): m.p. $170\sim 171^\circ\text{C}$; IR (KBr) 2990(w), 2920(w), 1758(s) cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 1.83(s, 6H), 2.9–3.7(m, 6H); $^{13}\text{C-NMR}$ (CDCl_3) δ 21.2(q), 21.4(q), 34.6(d), 43.3(d), 47.4(d), 50.3(d), 50.4(d), 61.5(d), 64.5(s), 75.2(s), 127.4(s), 136.2(s), 200.0(s), 200.3(s); MS (CI/CH_4) m/z (relative intensity) 287(41 %), 285(76), 283(100) ($\text{M}^+ + 1$); HRMS (EI) m/z 282.0211, calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2^{35}\text{Cl}_2$ 282.0215. Anal. Calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2\text{Cl}_2$: C 59.39; H 4.27. Found: C 59.19; H 4.09.

References and Notes

- § Synthesis of Polyfunctionalized C_5 -Trishomocubanes. Part 2. For part 1, see: Guan, X.-P.; Yu, Y.-Z. *Youji Huaxue* **1995**, *15*, 263.
1. Griesbeck, A. G. *J. prakt. Chem.* **1992**, *334*, 558.
2. (a) Sun, J.-G. Ph. D. Dissertation, Beijing Institute of Technology, Beijing, **1993**.
(b) Sun, J.-G.; Guan, X.-P.; Yu, Y.-Z. *Proceedings of The 3rd Beijing International Symposium on Pyrotechnics and Explosives* **1995**, p263.
(c) Sun, J.-G.; Su, Z.; Yu, Y.-Z. *Chin. Chem. Lett.* **1995**, *8*, 645.
3. For review, see: Marchand, A. P. *Tetrahedron* **1988**, *44*, 2377.

4. Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S.; Sakai, R. *Tetrahedron* **1979**, *35*, 2861.
5. Halford, J. O. *J. Chem. Phys.* **1956**, *24*, 830.
6. Guan, X.-P.; Sun, J.-G.; Yu, Y.-Z. *Chin. Chem. Lett.* **1995**, *6*, 931.
7. Woods, W. G.; Carboni, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1956**, *78*, 5653.
8. Uebersax, B.; Neuenschwander, M.; Kellerhals, H.-P. *Helv. Chim. Acta* **1982**, *65*, 74.