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Sequence of bromination of (*E*)-4,4-dimethyl-6-isobutylidenecyclohex-2-en-1-one

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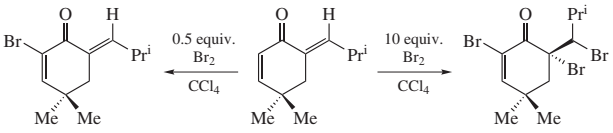
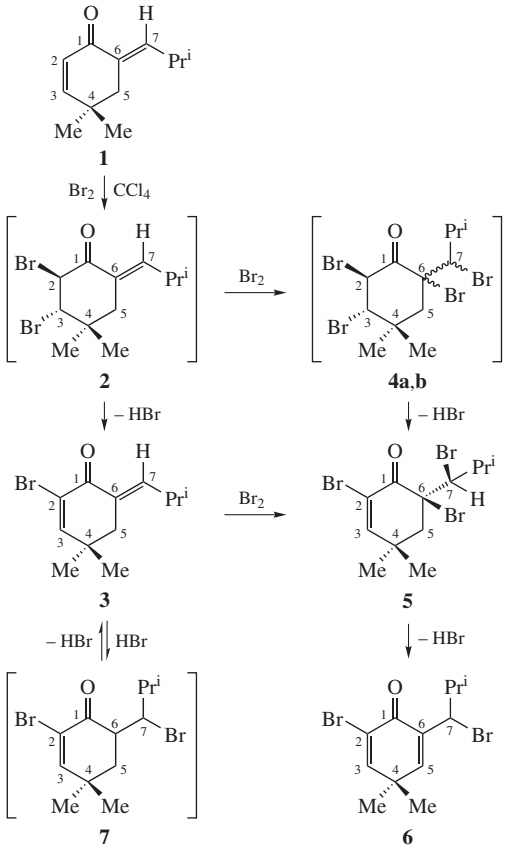
The bromination of (*E*)-4,4-dimethyl-6-isobutylidenecyclohex-2-en-1-one with molecular bromine occurs first at endocyclic double bond and next at the exocyclic one.



The 6-methylidenecyclohex-2-ene moiety is a structural fragment of a number of natural compounds[1–14] which exhibit various biological activities.[1,4,8,12–17] *exo*,*endo*-Cross-conjugated dienones are also important as synthetic intermediates in the preparation of biologically active natural products.[14,18–21]

Michael addition is one of the most powerful and frequently used methods for the construction of new compounds to increase molecular complexity. This method, however, is usually applied to simple unsaturated carbonyl substrates and only rarely to more complex Michael acceptors. In this respect, conjugated dienone **1** (Scheme 1) is a particularly interesting starting material, as there is the possibility of sequential 1,4-addition reactions of two nucleophiles to the endocyclic and exocyclic acceptor systems. To our knowledge, there is only one report[22] on the Michael addition to this diene. A rhodium-catalyzed enantioselective 1,4-addition of arylboronic acids to compound **1** in the presence of phosphoramidites proceeded regioselectively at the endocyclic C=C double bond, while the reasons for such a selectivity were not discussed. In the present study, we examined the bromination of dienone **1** with bromine as a limiting factor or with bromine in excess. Previously, we showed that the bromination of 4,4-dimethylcyclohexa-2,5- and 6,6-dimethylcyclohexa-2,4-dienones initially occurred at the C(2)=C(3) bond followed by dehydrobromination.[23–25]

We monitored the bromination reaction mixtures by ^{1}H and ^{13}C NMR spectroscopy after 30 min, preparative separation of the products being performed after 24 h. Preparative yields of the bromination products of dienone **1** with deficiency or with a large excess of bromine (Scheme 1) depend on the ratio of the initial reactants (Table 1). Bromides **3**, **5** and **6** were isolated by column chromatography† and characterized by IR, UV, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Bromides **2**, **4**, **6**, **7** were detected by ^{1}H and ^{13}C NMR in the reaction mixtures and in the mixed fractions of chromatographic separations (see Figures S2–S7, Online Supplementary Materials). Determination of the structures was carried out using NMR criteria established previously.[23,25]



Scheme 1

† A solution of bromine (for the amount, see Table 1) in CCl_4 (5–6 ml) was added to a solution of compound **1** (0.36 g, 2 mmol) in CCl_4 (4 ml) and the reaction mixture was left at room temperature for one day. The volatiles were removed *in vacuo*. The residue, a steaming red oil, was dissolved in diethyl ether, washed with 15% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, the ether was distilled off *in vacuo* and the resulting light yellow oil was chromatographed on SiO_2 (eluent, chloroform–hexane, 4:1) to afford products **3**–**6** in yields depending on the reactant ratio.

To isolate product **6**, compound **5** was triturated in a pasty mass with a small amount of diethyl ether and Al_2O_3. After 15 days the products were extracted with Et_2O and chromatographed on SiO_2 (eluent, chloroform–hexane, 4:1).

Table 1 Yields of compounds **3**, **5** and **6** in the bromination reaction of dienone **1** with different reagent ratios.

1:Br_2	Yields (%)[a]			**1**:Br_2	Yields (%)[a]		
	3	**5**	**6**		**3**	**5**	**6**
1:0.5	42	–	–	1:2.5	trace	68	trace
1:1.0	33	10	6	1:10.0	–	73	–
1:1.25	33	27	3				

[a]Yields were determined after separation by column chromatography. The reaction time was 24 h.

With a deficiency of bromine (**1**:Br_2 = 1:0.5), its molecule adds initially to the *endo*-C=C bond to form *trans*-dibromide **2**, whose formation was confirmed by ^{1}H and ^{13}C NMR data: a mixture of compounds **1** and **2** in a 1:1 ratio was detected 30 min after mixing the reactants in $CDCl_3$. Compound **2** was easily dehydrobrominated giving monobromide **3** (Figure S3, Online Supplementary Materials).

With an excess of bromine (**1**:Br_2 = 1:10), two stereoisomeric tetrabromo derivatives **4a**,**b** were detected in the mixture as the main reaction products after 24 h. Both isomers gave similar sets of signals in the ^{1}H and ^{13}C NMR spectra. For the signal assignments, COSY45 and DEPT analyses were performed together with a coupled ^{13}C spectrum (see Figure S4, Online Supplementary Materials). Tetrabromides **4a**,**b** completely converted into tribromide **5** upon chromatography of the reaction products on silica gel or on contact of the reaction mixture with alkaline alumina for 24 h.

The HBr elimination in compounds **4a**,**b**, affording tribromide **5**, also occurs simultaneously at room temperature, however, the reaction is slow. According to X-ray data of **5**, one of the methyl groups at C(4) and the bromine atom at C(6) occupy axial positions (Figure 1).‡ In turn, the bromine atom is in a near *trans* position to the Br atom of the alkyl substituent [the dihedral angle Br(2)–C(6)–C(9)–Br(3) is 170.30(12)°; numbering is given in accordance with that in Figure 1]. The C(6)–C(9)–C(10) angle is 119.5(2)°; the other angles at C(9) atom are close to a tetrahedral confirmation.

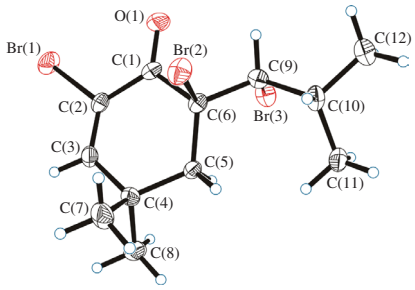


Figure 1 Molecular structure of compound **5**. Displacement ellipsoids are shown at the 50% probability level.

On keeping compound **5** over alkaline Al_2O_3 for 15 days, the second HBr molecule can be eliminated to produce dibromide **6** with two cross-conjugated double bonds (Figure S6).

Monitoring the reaction of dienone **1** with Br_2 (1:1) in $CDCl_3$ reveals the presence of dibromide **7** (~5% in 2 h). The amount of compound **7** after 4 h becomes comparable with that of **3**, however, after one day compound **7** diappears. The reaction of the individual compound **3** with dry HBr in $CDCl_3$ led to dibromide **7** as the main reaction product (Figure S7). Thus, compound **3** is apparently able to reversibly add HBr at the exocyclic double bond; however, the addition product is unstable.

To rationalize the bromination regioselectivity, one should take into account that dienone **1** contains two C=C double bonds differing in the character of conjugation with the carbonyl group. The UV spectrum of dienone **1** (see Figure S8) shows two absorption bands with λ_{max} = 240 nm (lgε = 4.01) and λ_{max} = = 269 nm (lgε = 3.87) which belong accordingly to conjugated and unconjugated with the carbonyl group C=C bonds. DFT calculations [B3LYP/6-31G(d,p)]§ indicate a non-coplanar arrangement of the C(6)=C(7) bond and carbonyl group [with a dihedral angle O=C(1)–C(6)=C(7) of 14.45°]. At the same time, the endocyclic double bond C(2)=C(3) is almost in conjugation with

2,3-Dibromo-6-isobutylidene-4,4-dimethylcyclohexanone **2** (in the reaction mixture in $CDCl_3$; 30 min after the start of the reaction; starting ratio **1**:Br_2 = 1:0.5, the observed ratio **2**:**1** ~ 1:1). ^{1}H NMR, δ: 1.05 (br. d, 6H, CH*Me*$_2$, ^3J 6 Hz, overlaps with CH*Me*$_2$ of **1**), 1.19 and 1.30 (2 s, 3H, 4-Me), 2.37 and 2.78 (2d, 1H, CH_2, ^2J 16.1 Hz), 2.6 (m, 1H, C*H*Me$_2$, overlaps with C*H*Me$_2$ of **1**), 4.34 and 4.69 (2d, 1H, 2,3-H, ^3J 9.6 Hz), 6.68 (d, 1H, 7-H, ^3J 10.0 Hz). ^{13}C{^{1}H} NMR, δ: 20.59, 21.50, 21.78, 30.73 (CH*Me*$_2$, 4-Me), 27.55 (*C*HMe$_2$), 37.74 (CH_2), 56.69, 66.94 (C^{2,3}), 129.56 (C^6), 151.77 (C^7), 190.88 (C=O). C^4 signal could not be identified due to the presence of signals of minor reaction products in the area of 32–37 ppm.

2,3,6-Tribromo-6-(1-bromo-2-methylpropyl)-4,4-dimethylcyclohexanone, a ~1.6:1 mixture of **4a** and **4b** isomers. ^{1}H NMR, δ: 1.02 and 1.30 [2 s, 4-Me (**4a**)], 1.04 and 1.12 [2d, CH*Me*$_2$ (**4b**), ^3J 6.6 Hz], 1.08 and 1.11 [2d, CH*Me*$_2$ (**4b**), ^3J 6.6 Hz], 1.28 and 1.46 [2 s, 4-Me (**4b**)], 2.57 and 2.90 [2d, CH_2 (**4b**), ^2J 16.3 Hz], 2.64 [m, C*H*Me$_2$ (**4a**,**b**)], 2.68 and 3.14 [2d, CH_2 (**4a**), ^2J 16.1 Hz], 4.23 and 5.04 [2d, 2,3-H (**4b**), ^3J 12.1 Hz], 4.50 and 4.90 [2d, 2,3-H (**4a**), ^3J 10.8 Hz], 4.74 [d, 7-H (**4b**), ^3J 1.8 Hz], 4.82 [d, 7-H (**4a**), ^3J 2.1 Hz]. ^{13}C{^{1}H} NMR, δ: 18.30, 21.38, 23.64, 32.24 [CH*Me*$_2$ (**4a**), 4-Me (**4a**)], 19.87, 21.65, 23.88, 32.91 [CH*Me*$_2$ (**4b**), 4-Me (**4b**)], 29.62 [*C*HMe$_2$ (**4b**)], 30.37 [*C*HMe$_2$ (**4a**)], 36.41 [C^4 (**4a**)], 37.50 [C^4 (**4b**)], 45.37 [CH_2 (**4b**)], 47.64 [CH_2 (**4a**)], 49.35, 62.27, 63.41 [CHBr (**4a**)], 55.94, 65.13, 67.11 [CHBr (**4b**)], 65.19 [C^6 (**4b**)], 65.37 [C^6 (**4a**)], 192.65 [C=O (**4a**)], 193.36 [C=O (**4b**)].

2-Bromo-6-(1-bromo-2-methylpropyl)-4,4-dimethylcyclohex-2-en-1-one **7** was detected in the reaction mixtures based on ^{1}H, ^{13}C NMR data. The sample for spectral comparison was synthesized by bubbling gaseous HBr into solution of compound **3** in $CDCl_3$. ^{1}H NMR, δ: 0.99 and 1.08 (2d, 3H, CH*Me*$_2$, ^3J 6.6 Hz), 1.27 (s, 6H, 4-Me), 1.86 (ddd, 1H, 5-H, ^2J 13.6 Hz, ^3J 4.6 Hz, ^4J 2.0 Hz), 2.00 (d sept., 1H, C*H*Me$_2$, ^3J 9.8 and 6.6 Hz), 2.29 (dd, 1H, 5-H, ^2J 13.6 Hz, ^3J 13.4 Hz), 2.96 (ddd, 1H, 6-H, ^3J 13.4, 4.6 and 2.5 Hz), 4.57 dd (1H, 7-H, ^3J 9.8 and 2.5 Hz), 7.13 (d, 1H, 3-H, ^4J 2.0 Hz). ^{13}C{^{1}H} NMR, δ: 19.98, 22.31 (CH*Me*$_2$), 25.90, 30.35 (4-Me), 33.05 (*C*HMe$_2$), 36.17 (C^4), 37.12 (CH_2), 46.52 (C^6), 61.96 (C^7), 121.83 (C^2), 158.95 (C^3), 189.37 (C=O).

For characteristics of compounds **1**, **3**, **5** and **6**, see Online Supplementary Materials.

‡ *Crystal data*. Intensity data for **5** were collected with a Bruker SMART APEX II diffractometer at 150 K [graphite monochromator, λ(MoKα) = = 0.71073 Å]. Crystals of **5** ($C_{12}H_{17}Br_3O$, M = 416.99) are orthorhombic, space group *Pbca*, a = 13.160(5), b = 12.455(4) and c = 17.417(6) Å, V = = 2854.8(17) Å^3, Z = 8, d_{calc} = 1.940 g cm^{-3}, μ(MoKα) = 8.458 mm^{-1}, F(000) = 1616. The intensity of 18327 reflections (2805 unique reflections, R_{int} = 0.0494) were measured in the range of 2.34° < θ <25.99° (–16 ⩽ h ⩽ 16, –11 ⩽ k ⩽ 15, –21 ⩽ l ⩽ 21) using ω-scan mode. Absorption correction was made by measurements of equivalent reflection.[27] The structure was solved by direct method and refined by full-matrix least squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms.[28] All hydrogen atoms were placed in calculated positions and refined using a riding model. The final R-values were: R_1 = = 0.0243 for 2267 reflections with $I > 2\sigma(I)$ and wR_2 = 0.0599 for all data and 149 parameters. GOF = 1.015, $\Delta\rho_{min/max}$ = –0.331/0.499 e Å^{-3}.

CCDC 1511901 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

§ Conformational analysis was carried out by a series of one-dimensional scans using the B3LYP/6-31G(d,p) density functional level. Potential energy surface scans were performed in steps of 10° for the internal rotations about the single C–C bonds. The geometry of all minima detected on the potential surface was optimized at B3LYP/cc-pVTZ level of theory. The Gaussian 03 package of programs[29] was used for all quantum chemical calculations.

the carbonyl group [with a dihedral angle O=C(1)–C(2)=C(3) of 5.35°]. Therefore, nucleophilic Michael addition of the first bromine molecule should occur regioselectively at the endocyclic C=C bond that is nearly coplanar with the carbonyl group.

During the formation of dibromide **2**, the dihedral angle of O=C(1)–C(6)=C(7) slightly decreases (to 12.20°) according to the DFT calculations, *i.e.*, the efficiency of conjugation between the carbonyl group and endocyclic C(6)=C(7) bond increases. As a result, the bromination of the exocyclic double C=C bond in dibromide **2** is facilitated as compared with that of the starting dienone **1**, and tetrabromides **4** are accumulated in the reaction mixture; HBr elimination from **4** leads to conjugated vinylic bromide **5**.

Similarly, in the vinylic bromide **3**, conjugation in the O=C(1)–C(6)=C(7) system is more effective than in the original dienone **1** [the dihedral angle O=C(1)–C(6)=C(7) is 13.63° according to our calculations]. This is also confirmed by UV spectroscopy; the UV spectrum of compound **3** exhibits two absorption bands with λ_{max} of 263 nm ($\lg\varepsilon$ = 4.05) and 284 nm ($\lg\varepsilon$ = 3.97), corresponding to conjugated and unconjugated carbonyl C=C fragments, respectively (Figure S8). For compound **1**, $\Delta\lambda_{max}$ = 27 nm, $\Delta\lg\varepsilon$ = 0.14. For compound **3** these valuse are reduced to $\Delta\lambda_{max}$ = 21 nm, $\Delta\lg\varepsilon$ = 0.08, which is indicative of a better conjugation between the carbonyl group and the C(6)=C(7) fragment. As a result, the nucleophilic addition of the second bromine molecule at the C(6)=C(7) bond of dienone **3** is also facilitated, which leads to compound **5**. Thus, compound **5** can be formed by two pathways: either by bromination of monobromide **2** or by dehydrobromination of tetrabromide **4**.

In conclusion, initial bromination of bifunctional Michael acceptor, 4,4-dimethyl-6-isobutylidenecyclohex-2-en-1-one, proceeds regioselectively at the endocyclic C=C double bond to form a *trans*-dibromide **2** as a result of the nucleophilic Michael addition to the double bond which is in conjugation with a carbonyl group. Furthermore, the elimination of HBr to form the vinylic bromide **3** as the final product occurs with a lack of bromine. In case of excess of bromine, the final product is tribromide **5**, resulting from two alternative pathways: bromination of the exocyclic double bond of the vinylic bromide **3** or the initial formation of tetrabromide **4** followed by HBr elimination from C(2)–C(3) moiety.

This work was carried out using equipment acquired at the expense of the Program of M. V. Lomonosov Moscow State University development. X-ray diffraction studies were performed at the Centre of Shared Equipment of N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.09.022.

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