BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 587—590 (1972)

The Synthesis of 2,3-Dimethyl-3-(5-bromo-2-methoxy-4-methylphenyl)-cyclohexene, a Potentially Useful Intermediate for the Syntheses of Aplysin and Related Sesquiterpenes

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(Received August 18, 1971)

As a key intermediate for the syntheses of aplysin, **1**, a bromine-containing sesquiterpene isolated from *Aplysia kurodai*, and related sesquiterpenes, 2,3-dimethyl-3-(5'-bromo-2'-methoxy-4'-methylphenyl)cyclohexene, **2**, was synthesized, starting from an anisole derivative, **6**. The reactivity of the double bond in **2** towards oxidizing reagents was examined: the cyclohexene, **2**, reacted with ozone to give an epoxide, **12**, and a cyclohexanone, **13**, an isomerization product of **12**; **2** could be converted to the diol, **15**, with osmium tetroxide in the presence of pyridine.

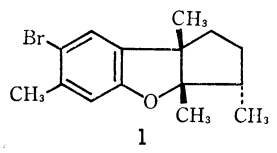
The structure of aplysin, a bromine-containing novel sesquiterpene isolated from *Aplysia kurodai*, has been established as **1**.[1] The total synthesis of aplysin, **1**, was previously achieved in our laboratory, employing cyclopentanone as the starting material.[2] A different route for the synthesis of aplysin has since been projected *via* the title compound, **2**, as an important intermediate. A keto aldehyde, **3**, which can be derived from **2**, can possibly be cyclized to a conjugated aldehyde, **4**. The aldehyde, **4**, would then be utilized as an intermediate for the syntheses of aplysin, **1**, and related sesquiterpenes (*e.g.*, laurenisol, **5**[3]). We will describe here the synthesis of the cyclohexene, **2**.

Selective metallation at the C-6 position of the anisole, **6**, was carried out with phenyllithium in ether.[2] The lithium derivative of **6** was reacted with cyclohexanone to afford a cyclohexanol, **7**, the structure of which was confirmed by a study of the NMR

1) S. Yamamura and Y. Hirata, *Tetrahedron*, **19**, 1485 (1963).

2) K. Yamada, H. Yazawa, D. Uemura, M. Toda, and Y. Hirata, *ibid.*, **25**, 3509 (1969).

3) T. Irie, A. Fukuzawa, M. Izawa, and E. Kurosawa, *Tetrahedron Lett.* **1969**, 1343.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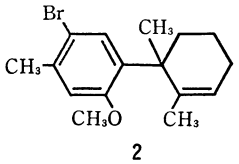
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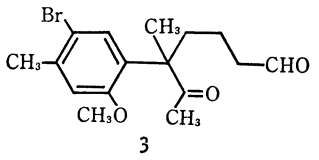
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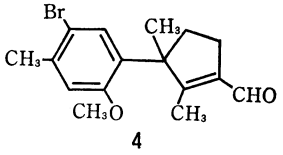
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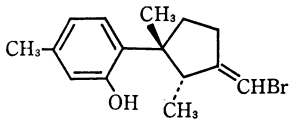
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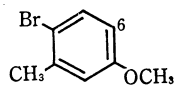
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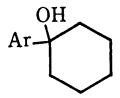
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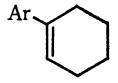
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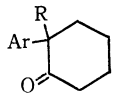
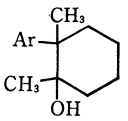

9: R=H
10: R=CH$_3$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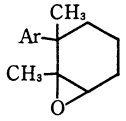
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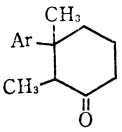
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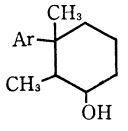
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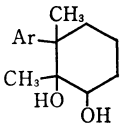
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Ar=5-bromo-2-methoxy-4-methylphenyl.

spectral evidence: two sharp singlets arising from aromatic protons were observed at δ 6.80 and 7.50, indicating that the condensation took place between the C-6 position of the anisole, **6**, and cyclohexanone. The dehydration of the cyclohexanol, **7**, was smoothly effected by heating it with oxalic acid to give a cyclohexene, **8**. Although the double bond of **8** was inert towards various peracids, the conversion of the cyclohexene, **8**, to a cyclohexanone, **9**, was effected by heating it in performic acid. Methylation at the benzylic carbon atom alpha to the carbonyl group in **9** was performed by treating the cyclohexanone, **9**, with sodium hydride in 1,2-dimethoxyethane and then with methyl iodide. The resulting cyclohexanone, **10**, was submitted to the Grignard reaction under forcing conditions to afford a cyclohexanol, **11**, (~30%) with the recovery of **10** (62%). The rather unreactive nature of the carbonyl group in **10** must be due to steric reasons: the cyclohexanone, **9**, gave the corresponding alcohol in a Grignard reaction in a good yield (~70%). The cyclohexanol, **11**, was dehydrated by heating it in benzene - 50% sulfuric acid to give the desired cyclohexene, **2**.

The double bond of the cyclohexene, **2**, was rather unreactive towards oxidizing reagents. When treated with ozone, the cyclohexene, **2**, afforded an epoxide, **12**, and a cyclohexanone, **13**, and no cleavage of the double bond of **2** occurred. The structures of the two products, **12** and **13**, were established by the spectral data and the following chemical evidence: the epoxide, **12**, was isomerized with 50% sulfuric acid at 80°C to **13**; the reduction of **13** with lithium borohydride yielded a cyclohexanol, **14**, which was then led to the starting cyclohexene, **2**, on treatment with sulfuric acid. The formation of the epoxide, **12**, from **2** suggests that the double bond of **2** is sterically hindered; there are precedents for the formation of an epoxide from a sterically-hindered olefin by ozone.[4] While the *cis*-hydroxylation of **2** with wet silver acetate - iodine[5] did not take place under any conditions, the cyclohexene, **2**, reacted slowly with osmium tetroxide, though only in the presence of pyridine, to afford a diol, **15**. This diol, **15**, was then cleaved by periodic acid to give an oily, rather unstable keto aldehyde, **3**.

Experimental

The melting points are uncorrected. The IR spectra were measured on a JASCO Model IRS spectrophotometer, and the UV spectra (methanol as solvent), on a Perkin-Elmer Model 202 spectrophotometer. The NMR spectra were recorded with a JNMC-60H spectrometer; only the prominent peaks are cited, while the chemical shifts are expressed in ppm downfield from TMS as the internal standard (δ); s, singlet; d, doublet; m, multiplet; the coupling constants are given in Hz. The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer, operating with an ionization energy of 70 eV. Thin-layer chromatography (TLC) was performed on silica gel GF_{254} (E. Merck, A. G., Germany), and column chromatography, on silicic acid (100 mesh, Millinckrodt, U.S.A.). The organic solutions were dried over anhydrous magnesium sulfate and evaporated by means of a rotary evaporator.

1-(5'-Bromo-2'-methoxy-4'-methylphenyl)cyclohexanol (7). A phenyllithium solution was prepared by stirring 16 g (2.28 mol) of metallic lithium into 176 g (1.1 mol) of bromobenzene in 900 m*l* of anhydrous ether under nitrogen. To the solution of phenyllithium, 200 g (1 mol) of the anisole, **6**, was then added, drop by drop, at room temperature. The mixture was stirred for 20 hr at room temperature and then refluxed for 10 hr. After cooling, 97 g (1 mol) of

4) K. W. Bentley, "Technique of Organic Chemistry," Vol. XI, ed. by A. Weissberger, Interscience Publishers, New York, N. Y. (1963), p. 882.

5) R. B. Woodward and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 209 (1958); *cf.* F. D. Gunstone, "Advances in Organic Chemistry, Methods and Results," Vol. I, ed. by R. A. Raphael, E. C. Taylor, and H. Wynberg, Interscience Publishers, New York, N. Y. (1960), p. 103.

cyclohexanone were added, and the mixture was stirred for 30 min and then refluxed for 5 hr. The mixture was poured into ice water, acidified with 10% hydrochloric acid, and repeatedly extracted with ether. The ethereal extracts were washed with water, dried, and evaporated to give a solid, the recrystallization of which from 95% ethanol afforded pure **7** (94.6 g, 32%); mp 118—119°C; UV 288 (ε 2000), 281 (ε 2000), 233 nm (ε 6700); IR (KBr) 3450, 1600, 1545 cm^{-1}; NMR ($CDCl_3$) 2.36 (3H, s), 3.88 (3H, s), 6.80 (1H, s), 7.50 (1H, s). Found: C, 56.40; H, 6.30; Br, 26.64%. Calcd for $C_{14}H_{19}O_2Br$: C, 56.23; H, 6.41; Br, 26.73%.

*1-(5'-Bromo-2'-methoxy-4'-methylphenyl)cyclohexene (**8**).* A solid mixture of 80 g (0.27 mol) of the cyclohexanol, **7**, and 40 g (0.44 mol) of anhydrous oxalic acid was kept at 210°C for 30 min. After cooling, water was added and the resulting mixture was repeatedly extracted with ether. The ethereal extracts were washed with a 10% sodium hydroxide solution and water, dried, and then evaporated to give a crystalline residue. Recrystallization from 95% ethanol afforded pure **8** (72 g, 96%); mp 51—53°C; UV 291 (ε 2800), 239 nm (ε 9300); IR (KBr) 1600, 1550 cm^{-1}; NMR (CCl_4) 2.35 (3H, s), 3.75 (3H, s), 5.70 (1H, m, vinyl H), 6.62 (1H, s), 7.20 (1H, s); mass, M^+ 282 and 280. Found: C, 59.90; H, 6.05; Br, 28.64%. Calcd for $C_{14}H_{17}OBr$: C, 59.84; H, 6.10; Br, 28.44%.

*2-(5'-Bromo-2'-methoxy-4'-methylphenyl)cyclohexanone (**9**).* To a stirred suspension of 18 g (0.064 mol) of the cyclohexene, **8**, in 60 m*l* of 85% formic acid, we added, drop by drop, 7.5 g of a 30% hydrogen peroxide solution under ice-bath cooling. The mixture was stirred at room temperature for 1 hr and at 90—95°C for 2 hr, and was then allowed to stand at room temperature overnight. The solid thus deposited was filtered and washed with water, a 10% sodium hydroxide solution, and water. The solid was subsequently chromatographed on silicic acid (80 g) with chloroform to give a crystalline material, the recrystallization of which from 95% ethanol afforded pure **9** (11.3 g, 60%); mp 174—175°C; IR (KBr) 1710, 1605, 1550 cm^{-1}; mass, M^+ 298 and 296. Found: C, 56.63; H, 5.55; Br, 27.01%. Calcd for $C_{14}H_{17}O_2Br$: C, 56.61; H, 5.77; Br, 26.91%.

*2-Methyl-2-(5'-bromo-2'-methoxy-4'-methylphenyl)cyclohexanone (**10**).* A mixture of 12 g (0.04 mol) of the cyclohexanone, **9**, and 1.2 g (0.05 mol) of sodium hydride in 160 m*l* of 1,2-dimethoxyethane was kept at 80°C for 2 hr with stirring under nitrogen. After the addition of 8 g (0.056 mol) of methyl iodide, the mixture was stirred at 80°C for 30 min, refluxed for 1 hr, and poured into ice water. The aqueous mixture was repeatedly extracted with benzene. The benzene extracts were washed with water, dried, and evaporated to give a residue, which was then chromatographed on silicic acid (25 g) with chloroform. The crude material thus obtained was recrystallized from 95% ethanol to afford pure **10** (4.9 g, 39%); mp 135—137°C; IR (KBr) 1700, 1602, 1550 cm^{-1}; NMR (CCl_4) 1.18 (3H, s), 2.34 (3H, s), 3.68 (3H, s), 6.64 (1H, s), 7.28 (1H, s); mass, M^+ 312 and 310. Found: C, 57.89; H, 6.08; Br, 25.73%. Calcd for $C_{15}H_{19}O_2Br$: C, 57.93; H, 6.16; Br, 25.70%.

*1,2-Dimethyl-2-(5'-bromo-2'-methoxy-4'-methylphenyl)cyclohexanol (**11**), and 2,3-Dimethyl-3-(5'-bromo-2'-methoxy-4'-methylphenyl)-cyclohexene (**2**).* A solution of methyl magnesium iodide was prepared from 1.7 g (0.07 g-atom) of metallic magnesium and 9.7 g (0.068 mol) of methyl iodide in 120 m*l* of anhydrous ether under nitrogen. The ether was then distilled off, and 120 m*l* of dried benzene were added. To the stirred Grignard solution, 8.5 g (0.027 mol) of **10** in 60 m*l* of benzene were added. The mixture was stirred at room temperature for 30 min, refluxed for 15 hr, and, after cooling, poured into a saturated ammonium chloride solution. The benzene layer was separated, washed with water, and dried. The subsequent evaporation of the benzene afforded an oily residue, which showed two spots on a TLC plate (chloroform as the solvent). The residue was chromatographed on silicic acid (120 g) with chloroform to give the starting ketone, **10** (5.3 g), and a colorless oil, **11** (2.7 g). A solution of 2.7 g of **11** in 27 m*l* of benzene was mixed with 5.5 m*l* of 50% sulfuric acid, after which the mixture was refluxed while being stirred for 3 hr. The benzene layer was separated, washed with a saturated sodium bicarbonate solution and water, and dried. The subsequent evaporation of the solvent afforded an oily product (2.2 g), which was chromatographed on silicic acid (40 g) with chloroform to give a crystalline material. Recrystallization from 95% ethanol afforded pure **2** (1.35 g, 43% from **10**: the yield was calculated from the amount of **10** actually consumed); mp 96—98°C; IR (KBr) 1600, 1550 cm^{-1}; NMR (CCl_4) 1.45 (3H, s), 1.48 (3H, d, J=2), 2.33 (3H, s), 3.76 (3H, s), 5.50 (1H, m, vinyl H), 6.64 (1H, s), 7.17 (1H, s); mass, M^+ 310 and 308. Found: C, 62.06; H, 6.72; Br, 25.89%. Calcd for $C_{16}H_{21}OBr$: C, 62.19; H, 6.85; Br, 25.86%.

*Oxidation of the Cyclohexene (**2**) with Ozone.* Ozone was passed through a solution of 150 mg of **2** in 5 m*l* of dichloromethane at −60°C. The progress of the reaction was examined by TLC. The excess ozone in the solution was flushed out with nitrogen at −60°C. The subsequent evaporation of the solvent afforded a residue, to which water was added. The mixture was allowed to stand at room temperature for 2 hr and was then extracted with benzene repeatedly. The benzene extracts were washed with water, dried, and evaporated to give a yellow oily residue (0.15 g), which showed three spots on a TLC plate. The residue was chromatographed on silicic acid (5 g) with chloroform. The starting material, **2** (35 mg), was thus obtained from the early fractions; the following fractions gave **13**, which was recrystallized from 95% ethanol to give pure **13** (22 mg, 15%); from the later fractions, the epoxide, **12**, was obtained, the recrystallization of which from ethanol afforded pure **12** (75 mg, 50%).

12: mp 116—118°C; IR ($CHCl_3$) 1640, 1600, 1490 cm^{-1}; mass, M^+ 326 and 324.

13: mp 121—122°C; IR (KBr) 1708, 1600, 1545 cm^{-1}; NMR (CCl_4) 0.65 (3H, d, J=7), 1.16 (3H, s), 2.33 (3H, s), 3.82 (3H, s), 6.66 (1H, s), 7.20 (1H, s); mass, M^+ 326 and 324. Found: C, 59.00; H, 6.71%. Calcd for $C_{16}H_{21}O_2Br$: C, 59.13; H, 6.51%.

*Conversion of the Epoxide (**12**) to the Cyclohexanone, (**13**).* A mixture of 19 mg of **12** in 1 m*l* of 50% sulfuric acid was heated at 80°C for 2 hr and then poured into ice water. After the mixture has been repeatedly extracted with benzene, the benzene extracts were washed with water, a saturated sodium bicarbonate solution, and water, dried, and evaporated to give 10 mg of crystalline **13**.

*Conversion of the Cyclohexanone (**13**) to the Cyclohexene (**2**).* A mixture of 15 mg of **13** and 5 mg of lithium borohydride in 2 m*l* of tetrahydrofuran was refluxed for 2 hr. After cooling, the mixture was diluted with water-acetic acid (9 : 1) and extracted with benzene. The benzene extracts were washed with a saturated sodium bicarbonate solution and water, dried, and evaporated to give 15 mg of the alcohol, **14**; IR (neat) 3450 cm^{-1}. A mixture of 15 mg of **14** in 2 m*l* of benzene and 0.1 m*l* of 50% sulfuric acid was refluxed for 2 hr and then poured into a saturated sodium bicarbonate solution. The benzene layer was separated, washed with water, dried, and evaporated, thus affording a crystalline residue. Recrystallization from 95% ethanol afforded 9 mg

of pure **2**.

*Oxidation of the Cyclohexene (**2**) with Osmium Tetroxide.* To a stirred solution of 633 mg (2.05 mmol) of **2** in pyridine (10 m*l*)-tetrahydrofuran (8 m*l*), we added, drop by drop, a solution of 510 mg (2.0 mmol) of osmium tetroxide in tetrahydrofuran (15 m*l*) at room temperature under nitrogen. After two weeks, the dark-red solution was concentrated under reduced pressure to give a residue, which was then taken up in 80 m*l* of 95% ethanol - chloroform (1 : 1). Hydrogen sulfide was passed through the dark-red solution for 10 min, and the resulting black precipitate was filtered. The filtrate was evaporated to afford a dark brown oil, which was chromatographed on silicic acid (60 g); fractions eluted with chloroform gave the starting material, **2** (*ca.* 70 mg), while fractions eluted with chloroform - methanol (v/v, 98 : 2) afforded the crude diol (460 mg), the recrystallization of which from hexane gave the pure diol, **15**; mp 145—146°C. Found: C, 55.88; H, 6.74%. Calcd for $C_{15}H_{23}O_3Br$: C, 56.02; H, 6.76%.

*Periodic Acid Oxidation of the Diol (**15**).* A solution of 106 mg of periodic acid dihydrate in water (1 m*l*) was added to a solution of 140 mg of **15** in tetrahydrofuran (4 m*l*)-water (2 m*l*), after which the mixture was stirred at room temperature for 4 hr. The mixture was then evaporated, neutralized with a sodium bicarbonate solution, and repeatedly extracted with ethyl acetate. The ethyl acetate extracts were washed with a saturated sodium chloride solution, dried, and evaporated to give a colorless oil, **3** (*ca.* 120 mg); IR ($CHCl_3$) 2730, 1725, 1710 cm^{-1}; NMR (CCl_4) 1.35 (3H, s), 1.78 (3H, s), 2.37 (3H, s), 3.73 (3H, s), 6.70 (1H, s), 7.30 (1H, s), 9.60 (1H, t, $J=3$); mass, M^+ 342 and 340.