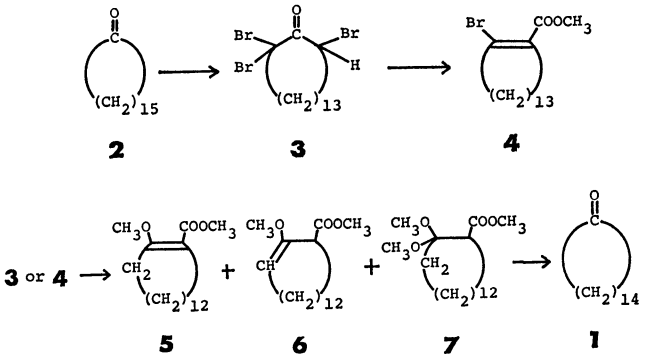
Synthesis of Cyclopentadecanone by Ring Contraction of Cyclohexadecanone

Tetsuya KATO,* Hisao KONDO, and Akihisa MIYAKE
Basic Research Laboratries, Toray Industries, Inc., Tebiro, Kamakura 248
(Received August 10, 1979)

Synopsis. Cyclopentadecanone has been synthesized from cyclohexadecanone. 2,2,15-Tribromocyclohexadecanone, upon treatment with sodium methoxide, underwent the Favorskii rearrangement *via* methyl 2-bromo-1-cyclopentadecene-1-carboxylate to produce a mixture of methyl 2-methoxy-1-cyclopentadecene-1-carboxylate, methyl 2-methoxy-2-cyclopentadecene-1-carboxylate, and methyl 2,2-dimethoxycyclopentadecane-1-carboxylate which was converted into cyclopentadecanone.

Cyclopentadecanone **1** occurs naturally as a secretion of the musk rat[1] and has attracted considerable interest due to its usefulness as a valuable perfume base. Many synthetic routes have been developed for the synthesis of cyclopentadecanone **1** from various starting materials.[2] In relation to our own interest in devising simplified approaches to the synthesis of cyclopentadecanone **1**, we have investigated the ring contraction of cyclohexadecanone **2** by applying the Favorskii rearrangement of trihalogenated ketones.[3] Our synthetic route is outlined in the following scheme.



Cyclohexadecanone **2** was easily prepared according to the method developed by Nishino *et al.*[4] Bromination of the ketone **2** with 3.5 molar equiv of bromine in dichloromethane at 25—30 °C for 20 h gave 2,2,15-tribromocyclohexadecanone **3** as colorless crystals in 92% yield.

The Favorskii rearrangement of the tribromo ketone **3** was carried out by using 2.2 molar equiv of sodium methoxide in methanol at 20 °C to afford methyl 2-bromo-1-cyclopentadecene-1-carboxylate **4** as a mixture of *cis*- and *trans*-isomer in 83% yield. The distinction between the *cis*- and *trans*-isomer has been made on the basis of a comparison of the difference in the NMR chemical shifts of the allylic methylene protons.[5] The allylic methylene protons of the *cis*-isomer resonate at 2.16—2.60 ppm whereas those of the *trans*-isomer resonate at 2.20—3.30 ppm. Bases such as magnesium methoxide, triethylamine, or calcium hydroxide also gave satisfactory results.[6] Further treatment of the bromo ester **4** with 3.3 molar equiv of sodium methoxide in methanol afforded three major compounds **5**, **6**, and **7** in 88% yield (**5**+**6**, 71%; **7**, 17%). The reaction proceeded smoothly under reflux. In preparative runs the tribromo ketone **3** was directly converted into a mixture of the methoxy esters **5**, **6**, and **7**, without any separation of the bromo ester **4**, by using 5.2 molar equiv of sodium methoxide in methanol. Each methoxy ester was isolated by chromatographic purification on silica gel. The mixture of **5**, **6**, and **7** was then saponified with sodium hydroxide in refluxing aqueous methanol for 7 h to give the corresponding enol ether carboxylic acid and ketal carboxylic acid derivatives. Acid-catalyzed hydrolysis and subsequent decarboxylation of the resulting carboxylic acids with hydrochloric acid in methanol afforded cyclopentadecanone **1** in 80% yield.

Experimental

Melting and boiling points are uncorrected. Gas-liquid chromatography (GLPC) analyses were preformed on a Shimadzu 3BT instrument using 2% silicone SE-52 coated on Chromosorb GHP (80—100 mesh) packed in glass columns (3 mm × 1.2 m). The following spectrometers were used: IR, Hitachi EPI-S-2; NMR, Varian XL-100 and HA-100 (TMS as internal standard); mass spectra, Hitachi RMU-7M and RMS-4. Silica gel (Merck, 70—230 mesh) was used for column chromatography.

2,2,15-Tribromocyclohexadecanone (3). Bromine (320 g 2.00 mol) was added dropwise over a period of 1.5 h to a cold (0—5 °C) stirred solution of cyclohexadecanone **2** (136 g. 0.571 mol) in dichloromethane (300 ml). After the addition was completed, stirring was continued at 25—30 °C for 20 h. The reaction mixture was poured into water and extracted with dichloromethane. The dichloromethane extracts were washed succesively with aqueous sodium hydrogensulfite solution and water and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave 273 g of yellow oil which was crystallized from methanol (−30 °C) to afford 250 g of tribromo ketone **3** (92%): mp 41—42 °C; IR (KBr) 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.5—2.5 (m, 26H with a s at 0.77), 4.73 (dd, J=6 and 7.5 Hz, 1H). Found: C, 40.41; H, 5.50; Br, 50.68%. Calcd for $C_{16}H_{27}OBr_3$: C, 40.45; H, 5.73; Br, 50.48%.

Methyl 2-Bromo-1-cyclopentadecene-1-carboxylate (4). To a solution of tribromo ketone **3** (39.2 g, 82.5 mmol) in anhydrous methanol (220 ml) was added dropwise a solution of sodium methoxide in methanol (0.88 mol/l, 207 ml, 182 mmol) over a period of 1.5 h at 20 °C. After the addition was completed, stirring was continued at 20 °C for an additional 1 h. The reaction mixture was poured into cold water and extracted with hexane. The hexane extracts were washed with water and dried over anhydrous magnesium sulfate. After the solvent had been removed the residue was distilled (oil bath 180 °C/0.5 Torr) to give 26.3 g of yellow oil. GLPC analysis (165 °C) showed two major peaks due to *cis*- (50.1%) and *trans*-bromo ester **4** (39.8%). The yield was 83%. Each isomer was isolated by silica gel chromatography (benzene/hexane, 1/3—1/5).

4 (*trans*-isomer): bp 155—156 °C/0.8 Torr; $n_D^{20}=1.5120$; IR (neat) 1724, 1614 cm^{-1}; NMR ($CDCl_3$) δ 1.1—1.9 (s, 22H), 2.20—3.30 (m, 4H), 3.76 (s, 3H); *m/e* 346, 344 (M^+). Found: C, 59.14; H, 8.35; Br, 23.21%. Cacld for $C_{17}H_{29}O_2Br$: C, 59.13; H, 8.47; Br, 23.14%. **4** (*cis*-isomer): bp 159—160 °C/0.6 Torr; $n_D^{20}=1.5127$; IR (neat) 1727, 1641 cm^{-1}; NMR ($CDCl_3$) δ 1.1—1.8 (s, 22H) 2.16—2.60 (m, 4H), 3.77 (s, 3H); *m/e* 346, 344 (M^+). Found: C, 59.12; H, 8.24; Br, 23.23%. Calcd for $C_{17}H_{29}O_2Br$: C, 59.13; H, 8.47; Br, 23.14%.

*Methoxy Esters (**5**, **6**, and **7**).* A solution of sodium methoxide in methanol (3.0 mol/l, 50 ml, 150 mmol) was added to bromo ester **4** (17.25 g, purity 89.9%, 150 mmol) at 20 °C. The mixture was refluxed for 5 h, cooled, poured into cold water and dried over anhydrous sodium sulfate. After the solvent had been removed the residue was distilled (oil bath 180 °C/0.4 Torr) to give 12.25 g of oil. GLPC analysis showed that methoxy esters **5**, **6**, and **7** were obtained in 88% yield (**5**+**6**, 71%; **7**, 17%). Each ester was isolated by silica gel chromatography (benzene/hexane, 1/5—1/1). **5**: IR (neat) 1705, 1613 cm^{-1}; NMR ($CDCl_3$) δ 0.9—1.8 (s, 22H), 2.0—2.7 (m, 4H), 3.58 (s, 3H), 3.63 (s, 3H), *m/e* 296 (M^+). Found; C, 72.89; H, 10.63%. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%. **6**: bp 142—143 °C/0.5 Torr; $n_D^{20}=1.4880$; IR (neat) 1737, 1655 cm^{-1}; NMR ($CDCl_3$) δ 1.1—2.3 (m, 24H with a s at 1.30), 3.38—3.60 (m, 1H), 3.46 (s, 3H), 3.64 (s, 3H), 4.48 (t, J=7 Hz, 1H); *m/e* 296 (M^+). Found: C, 72.94; H, 10.95%. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88%. **7**: IR (neat) 1739 cm^{-1}; NMR (CCl_4) δ 1.0—2.0 (m, 26H with a s at 1.38), 2.73 (dd, J=3 and 11 Hz, 1H), 3.12 (s, 3H), 3.19 (s, 3H), 3.62 (s, 3H); *m/e* 328 (M^+). Found: C, 69.69; H, 10.89%. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.04%.

*Cyclopentadecanone (**1**).* A solution of sodium hydroxide (10.0 g, 250 mmol) in aqueous methanol (H_2O/MeOH, 1/3, 75 ml) was added to the ester mixture (14.8 g, **5**+**6** 90.9%, 45.4 mmol; **7** 6.7%, 3.0 mmol) and refluxed for 7 h. The reaction mixture was cooled and made acid to Bromophenol Blue by the addition of concentrated hydrochloric acid. After hydrochloric acid (35%, 30 ml) had been added, the reaction mixture was refluxed for 1 h, cooled, and extracted with benzene. The benzene extracts were washed with water and dried over anhydrous sodium sulfate. After the solvent had been removed the residue was distilled (oil bath 180 °C/0.4 Torr) to give 10.79 g of crude cyclopentadecanone. GLPC analysis showed one major peak due to cyclopentadecanone **1** (80% yield). Pure cyclopentadecanone was obtained by fractional distillation. The IR, NMR, and mass spectral data were identical with those of an authentic sample.

References

1) P. G. Stevens and J. L. E. Erickson, *J. Am. Chem. Soc.*, **64**, 144 (1942).
2) For recent syntheses see J. R. Sanderson, K. Paul, R. J. Winterdink, and J. Alford, *J. Org. Chem.*, **41**, 3767 (1976); M. Karpf and A. S. Dreiding, *Helv. Chim. Acta*, **58**, 2409 (1975); D, Felix, J. Schreiber, G. Ohloff, and A. A. Eschenmoser, *Helv. Chim. Acta*, **54**, 2896 (1971); B. D. Mookherjee, R. W. Trenkle, and R. P. Patel, *J. Org. Chem.*, **36**, 3266 (1971).
3) G. Hesse and F. Urbanek, *Chem. Ber.*, **91**, 2733 (1958).
4) M. Nishino, H. Kondo, and A. Miyake, *Chem. Lett.*, **1973**, 667.
5) H. B. Kagan, "Stereochemistry," Georg Thieme Publishers, Stuttgart (1977), Vol. 1, p. 50.
6) A. S. Kende, *Org. React.* **11**, 261 (1946).