# Replacement of a Carbonyl Group of Camphor by an Oxygen Atom. Synthesis of 1,7,7-Trimethyl-2-oxabicyclo[2.2.1]heptane[1)]

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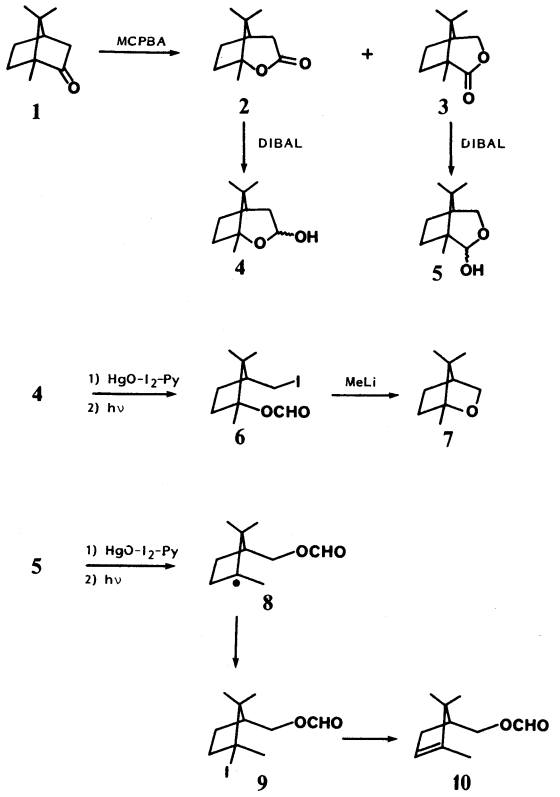
**Synopsis.** A four-step transformation of (+)-camphor into a hitherto undescribed 1,7,7-trimethyl-2-oxabicyclo[2.2.1]-heptane is described.

Only a limited number of the general methods for the synthesis of cyclic ethers have been available. We have recently reported a new and versatile method involving β-scission of alkoxyl radicals for transforming cyclic ketones into cyclic ethers with the original ring size and the transformation of number of steroidal ketones[2,3)] and adamantanone[3)] into the corresponding cyclic ethers has been achieved by this method.

In this paper we report the transformation of camphor, a representative bridged bicyclic ketone, into a hitherto undescribed 1,7,7-trimethyl-2-oxabicyclo-[2.2.1]heptane by this method[3)]. The results may demonstrate that the method can be applied to the preparation of bridged oxabicyclics and oxaterpenoids in general by the substitution of the carbonyl group of a variety of bridged bicyclic ketones, mono- and sesquiterpenoids. These bridged oxabicyclic compounds and oxaterpenoids may be of potential utility as the molecules having interesting biological as well as physical properties.

The Baeyer-Villiger oxidation of camphor has been well investigated.[4)] We have found that the oxidation of (+)-camphor (**1**) with *m*-chloroperbenzoic acid in dichloromethane gives 1,8,8-trimethyl-2-oxabicyclo-[3.2.1]-octan-3-one (**2**) as the major product together with 1,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-3-one (**3**). The isolated yields of these isomeric lactones were 48 and 26% respectively. Reduction of **2** with diisobutylaluminium hydride (DIBAL) gave a 5.5:1 ratio of *endo* to *exo* lactols **4**. A similar reduction of **3** afforded a 5:1 ratio of *endo* and *exo* lactol **5** as judged by the $^1$H NMR spectra. A mixture of lactols **4** in benzene was transformed into the corresponding hypoiodite with mercury(II) oxide and iodine in the presence of pyridine and then irradiated in an atmosphere of a nitrogen with a Pyrex-filtered light to give an oily iodo formate **6** in a 60% yield with an accompanying formation of lactone **2** (26%). The treatment of iodo formate **6** with methyllithium gave 1,7,7-trimethyl-2-oxabicyclo[2.2.1]heptane (**7**) in a 79% yield. On the other hand, a similar photolysis of the hypoiodite derived from a mixture of lactol **5** as above afforded an oily product **10** in a 60% yield together with lactone **3** (21%). High-resolution mass spectrometry indicated that it had the molecular formula $C_{10}H_{16}O_2$ and the IR, $^1$H NMR and mass spectra indicated that it was (*R*)-4-formyloxymethyl-2,3,3-trimethylcyclopentene (**10**). It is apparently formed *via* the elimination of HI from the intermediate **9** generated from a carbon-centered radical **8** as outlined in the Scheme. The major parts of parent lactones **2** and **3** in these photolysis are formed by disproportionation of the alkoxyl radicals.




Scheme

## Experimental

Mp's were determined with a Yanagimoto micro mp apparatus. IR spectra were determined for Nujol mulls, unless stated otherwise, with a Hitachi Model 285 infrared spectrophotometer. $^1$H NMR spectra were determined with a JEOL PS200 high-resolution FT-NMR spectrometer (200 MHz) (solvent, $CDCl_3$, $SiMe_4$ as an internal reference). TLC was carried out on Merck Kiesel gel 60, PF254. The high- and low-resolution mass spectra were recorded with a JEOL JMS-D-300 spectrometer (70 eV) (Faculty of Agriculture of this university).

*Baeyer-Villiger Oxidation of (+)-Camphor (1).* To a solution of (+)-camphor (1 g) (Wako Pure Chemical Ind. Ltd.) in dichloromethane (20 ml) was added *m*-chloroperbenzoic acid (2.5 g) and *p*-toluenesulfonic acid (0.5 g). The solution was set aside for a week at room temperature while stirring. The solution was worked up in the usual way to give a mixture of two lactones. The product was subjected to column chromatography (Merck Kiesel gel 60, 70—230 mesh, 50 g). Elution with a 10:1 benzene–diethyl ether afforded first the starting camphor (**1**) (90 mg) and then lactone **3** (312 mg) and finally lactone **2** (542 mg).

*Reduction of 1,8,8-Trimethyl-2-oxabicyclo[3.2.1]octan-3-one (2) with DIBAL.* To a solution of the lactone **2** (359 mg) in dry toluene (50 ml) cooled at −78 °C, was added dropwise DIBAL in hexane (3 ml). The solution was stirred for 1.5 h at −78 °C and poured into iced water. After the solution was filtered, the filtrate was worked up by the usual method. A crude product (365 mg) was subjected to column chromatography (Merck Kiesel gel 60, 70—230 mesh). Elution with a 5:1 benzene–diethyl ether gave an amorphous solid (309 mg) which was a 1:5.5 mixture of *endo* and *exo* lactols **4**. (Found: $M^+$, 170. 1316. Calcd for $C_{10}H_{18}O_2$: 170. 1306); IR; 3370 (OH), 1120, 1061, 1012, 927, and 855 $cm^{-1}$; $^1H$ NMR $\delta$=0.86 (3H, s, Me), 1.09 (3H, s, Me), 1.11 (3H, s, Me), 3.41 (1H, d, $J$=6.35 Hz, OH), 5.14 (0.86 H, m, CHOH of the *endo* isomer), and 5.28; (0.14 H, m, CHOH of the *exo* isomer); MS. *m/z* (rel. intensity), 170 ($M^+$, 0.6%), 152 ($M^+ - H_2O$, 0.7), 124 (3.5), 109 (100), 67 (23.9), 55 (21.1) and 41 (38.8).

*Reduction of 1,8,8-Trimethyl-3-oxabicyclo[3.2.1]octan-2-one (3) with DIBAL.* To a solution of the lactone **3** (300 mg) in dry toluene (50 ml) cooled at −78 °C, was added dropwise DIBAL in hexane (2.5 ml). The solution was stirred for 3 h at −78 °C and poured into iced water. After the solution had been filtered, the filtrate was worked up by the usual method. A crude product (298 mg) was subjected to preparative TLC with a 5:1 benzene–diethyl ether to give a lactol **5** (250 mg). (Found: $M^+$ 170. 1334. Calcd for $C_{10}H_{18}O_2$: 170, 1307); IR 3380 (OH), 1086, and 1009 $cm^{-1}$; $^1H$ NMR $\delta$=0.86, 0.90, and 1.07 (each 3H, each s, 1,8,8-Me of *endo* isomer), 0.87, 0.92, and 1.00 (each 3H, each s, 1,8,8-Me of *exo* isomer), 3.50 (lH, dd, $J$=11.23 and 2.46, 4-H of *endo* isomer), 4.07 (1H, d, $J$=11.23, 4-H of *endo* isomer), 4.89 (1H, d, $J$=6.33, 3H of *endo* isomer), 3.39 (1H, dd, $J$=10.74 and 2.93, 4-H of *exo* isomer), 4.23 (1H, d, $J$=10.74, 4-H of *exo* isomer), and 4.70 (1H, d, $J$= 2.93, 3H of *exo* isomer); MS *m/z* (rel. intensity), 170 ($M^+$, 0.6), 152 ($M^+ - H_2O$, 0.7), 124 (3.5), 109 (100%).

*Irradiation of the Hypoiodite of the Lactol 4 in the Presence of Mercury(II) Oxide and Iodine.* To the lactol **4** (200 mg) in dry benzene (59 ml) containing pyridine (0.5 ml) was added mercury(II) oxide (598 mg) and iodine (598 mg). The solution in a Pyrex vessel was flushed with nitrogen and irradiated with a 100-W high pressure Hg arc for 1.5 h. The solution was filtered and the filtrate was worked up in the usual manner to give a crude oily product (285 mg). This product was subjected to preparative TLC to give a TLC more mobile fraction A (208 mg) and a TLC less mobile fraction B (52 mg). The oily fraction A was an iodo formate **6**. (Found: $M^+$, 296. 0311), Calcd for $C_{10}H_{17}IO_2$: 296. 0274; IR (neat) 1724 (CHO), and 1180 $cm^{-1}$ (OCHO); $^1H$ NMR, $\delta$=0.87 (3H, s, Me), 0.99 (3H, s, Me), 1.43 (3H, s, Me), 2.03—2.22 (4H, s, $-CH_2CH_2-$), 3.00 (1H, dd, $J$=10.74 and 9.28 Hz, one of $CH_2I$), 3.34 (1H, dd, $J$=9.28 and 3.24 Hz, one of $CH_2I$) and 8.02 (1H, s, OCHO); MS *m/z* (rel. intensity) 296 ($M^+$, 0.2%), 250 ($M^+ - OCH_2O$, 1.5), 123 ($M^+ - I - OCH_2O$, 100), 81 (14.3), 71 (12.7), 55 (18.7), and 43 (28.5). The fraction B was lactone **2**.

*Irradiation of the Hypoiodite of the Lactol 5 in the Presence of Mercury(II) Oxide and Iodine.* To the lactol **5** (188 mg) in dry benzene (55 ml) containing pyridine (0.5 ml) was added mercury(II) oxide (477 mg) and iodine (564 mg). The solution in a Pyrex vessel was irradiated for 70 min as in the case of the lactol **4**. The solution was worked up as usual. The crude product was subjected to preparative TLC to give a TLC more mobile fraction A (111 mg) and a TLC less mobile fraction B (39 mg). The fraction A was an oily formate **10**. (Found: $M^+$ 168. 1121. Calcd for $C_{10}H_{18}O_2$: IR (neat) 1726 (CHO), and 1169 $cm^{-1}$ (OCHO); $^1H$ NMR, $\delta$=0.87 (3H, s, Me), 1.08 (3H, s, Me), 1.60 (3H, br, s, C=C-Me), 1.91—2.41 (3H, m, $\rangle CH-CH_2-CH=C\langle$ 5.22 (1H, br, s, CH=C) and 8.08 (1H, s, OCHO), MS *m/z* 168 ($M^+$, 0.4%), 122 ($M^+ - OCH_2O$, 10.9), 107 (100) and 91 (15.0). The fraction B was lactone **3**.

*1,7,7-Trimethyl-2-oxabicyclo[2.1.1]heptane (7).* A solution of the formate (65 mg) in THF (25 ml) was cooled at −78 °C by Dry Ice–methanol. To this solution was added dropwise methyllithium in diethyl ether [1 M (1 M=1 mol $dm^{-3}$) solution] (0.6 ml). After the solution had been stirred for 1 h at −78 °C, the temperature of the solution rose to room temperature. The solvent was removed by a rotary evaporator as much as possible and the concentrate was diluted with diethyl ether. The solution was washed with water and dried over anhydrous $Na_2SO_4$. After the removal of $Na_2SO_4$, the residual solution was concentrated. The yield of 2-oxabicyclo[2.1.1]heptane (**7**) determined by GLC was 79%. The pure 2-oxabicyclo[2.1.1]heptane (**7**), mp 34—37 °C, was isolated by preparative gas chromatography. (Found: $M^+$, 140. 1192. Calcd for $C_9H_{16}O$: 140. 1199); IR (neat) 1089, 1022, 975, and 930 $cm^{-1}$; $^1H$ NMR, $\delta$=0.95, 0.99 and 1.11 (each 3H, each s, 1,7,7-Me), 3.45 (1H, d, $J$=7.33, *endo* 3-H), 3.87 (1H, m, *exo* 3-H).

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