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THE BAEYER-VILLIGER OXIDATION OF 7-ALKYLIDENEBICYCLO[2.2.1]HEPTENONE

Kunikazu SAKAI,* Mitsuo YAMASHITA, and Yoshiko SHIBATA
Sagami Chemical Research Center
Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229

The first example of the Baeyer-Villiger oxidation of 7-alkylidene-2-oxo-5-bicyclo[2.2.1]heptene is described to give 6-alkylidene-2-oxa-3-oxo-7-bicyclo[3.3.0]octene exclusively, which is the versatile precursor for the short-cut synthesis of Δ^{12}-prostaglandin A_2 analogs.

The Baeyer-Villiger oxidation is a well-known and a convenient reaction to provide an ester or a lactone from a ketone by oxygen insertion in a single reaction.[1] The reaction had played the important roles in the synthesis of the natural products, such as prostaglandins,[2] alkaloids,[3] β-lactams,[4] and others.[5] Although abundant examples of the Baeyer-Villiger oxidation of 2-oxo-5-bicyclo[2.2.1]heptene (**1**) revealed the production of 2-oxa-3-oxo-6-bicyclo[3.2.1]octene (**2**), followed by a rearrangement to 2-oxa-3-oxo-7-bicyclo[3.3.0]-octene (**3**),[1c] the Baeyer-Villiger oxidation of the 7-alkylidene derivative of bicyclo[2.2.1]heptenone was unknown to our knowledge. Thus, we have performed the Baeyer-Villiger reaction of 7-alkylidene-2-oxo-5-bicyclo[2.2.1]heptene (**4**).

Here, we will report the interesting results to obtain 6-alkylidene-2-oxa-3-oxo-7-bicyclo[3.3.0]octene (**5**) directly from **4** and an application to the short-cut synthesis of Δ^{12}-prostaglandin A_2 analogs from **5**, which have been expected to have an antitumor activity.[6]

The substrate for the Baeyer-Villiger oxidation, 7-alkylidenebicyclo[2.2.1]-heptenone (**4**), was prepared by the Diels-Alder reaction of the fulvene **6** with a ketene equivalent according to the method developed in our laboratory.[2d] The compound **4** was a mixture of geometrical isomers at C-7, and since they could not

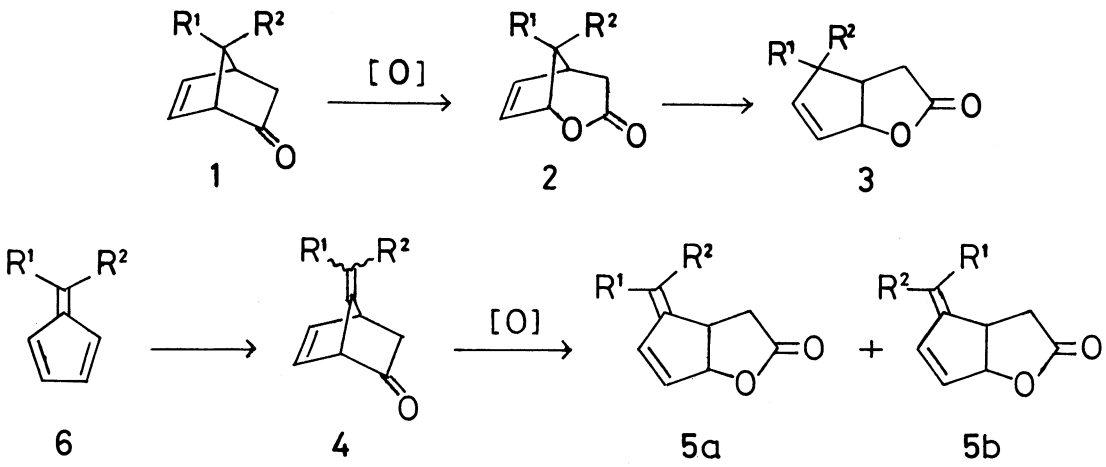
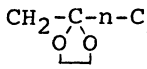
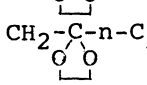
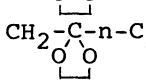
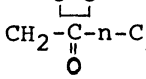


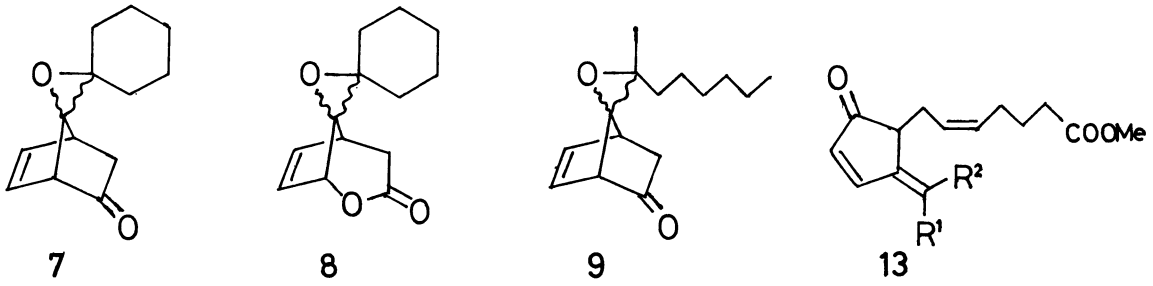
Table 1. The Baeyer-Villiger oxidation of 4

Entry	Substrate 4		Reaction conditions[a]	Products 5a and 5b	
	R^1	R^2		Yield/%	Ratio 5a/5b
1	H	n-C_7H_{15}	A	63	67/33
2	H	CH_2CH_2Ph	A	76	66/34
3	H	C_6H_4-p-C_3H_7	A	72	76/24
4	H	CH=CH-n-C_5H11	A	51	69/31
5	H	CH=CH-Ph	A	29	79/21
6	H		A	53	71/29
7	H		B	80	67/33
8	H		C	54	63/37
9	H		C	66	67/33
10	H		C	30	68/32
11	H		C	59	70/30
12			A	73	——
13	CH_3	n-C_6H_{13}	A	69	50/50

a) A, 3-5 equiv. 30% H_2O_2 + 3-5 equiv. 2 M NaOH in MeOH-H_2O, 0 °C-20 °C;
B, 3 equiv. 30% H_2O_2 + 3 equiv. 2 M NaOH in H_2O-ether, bilayer, 0 °C-20 °C;
C, 1.1-1.5 equiv. 40% CH_3COOOH in CH_3COOH + 3-5 equiv. $NaOCOCH_3$ in CH_2Cl_2, 0 °C-20 °C.

be separable at this stage, the reaction was carried out using a mixture of **4**. The reaction was examined applying 30% hydrogen peroxide, 40% peracetic acid, and m-chloroperbenzoic acid as the oxidizing agents under appropriate conditions for each (see footnotes in the Table 1). The results of the oxidation were summarized in Table 1 to give 6-alkylidenebicyclo[3.3.0]lactones (**5a** and **5b**) as a mixture of the isomers.

In the case of the reaction using hydrogen peroxide as an oxidizing agent a mixture of the isomers **5a** and **5b** was produced for all substituents of R^1 and R^2, and they were separable by column chromatography. The stereochemistry of the substituents R^1 and R^2 in **5a** and **5b** was assigned by a comparison of the chemical shifts of the olefinic protons in **5a** with that in **5b**.[7] The ratio **5a/5b** reflected the product ratio of the isomers in **4** at the Diels-Alder reaction of the fulvene **6**. When peracetic acid was used the oxidation sometimes occured as competitive reactions between epoxidation and lactonization to provide epoxides **7** and **8**, or **9**, in which both of R^1 and R^2 were substituted with alkyl groups. By the reaction with m-chloroperbenzoic acid (1.1-1.5 equiv. MCPBA + 3-5 equiv. $NaHCO_3$ in CH_2Cl_2, 0 °C-20 °C) the epoxidation always preferentially occured to the lactonization.

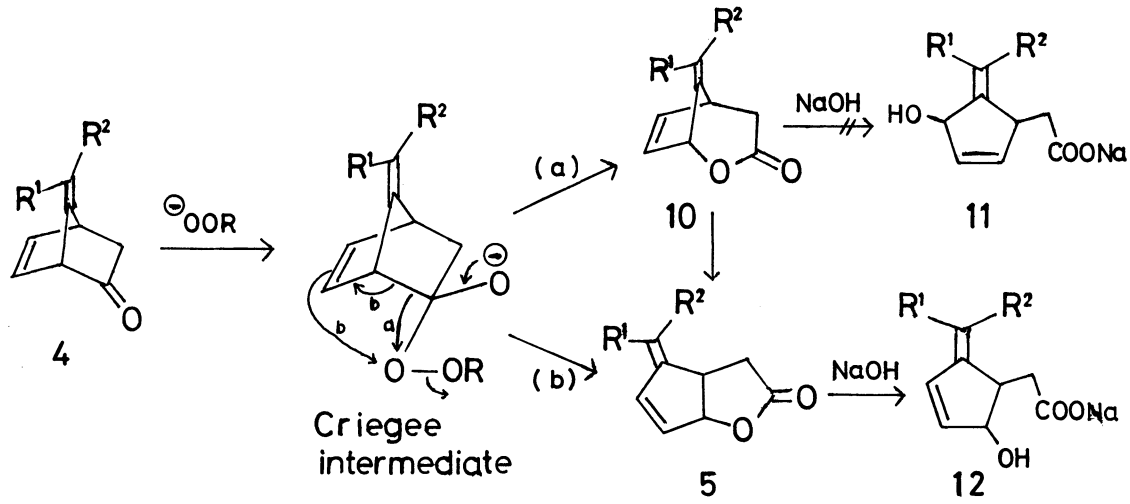


7 8 9 13

The reaction route to give **5** was considered to initiate in the formation of the Criegee intermediate[1b] by the stereospecific addition of hydroperoxide ion to **4**. Then, the oxygen insertion by path (a) gave 8-alkylidenebicyclo[3.2.1]lactone (**10**), followed by a fast rearrangement to **5** with a stable conjugate diene structure. However, the all efforts to obtain the evidence for the production of **10** during the course of the Baeyer-Villiger reaction[8] resulted in failures. An attempt to isolate the sodium salt **11** which would be formed from **10** in an alkaline solution by an ion exchange resin treatment[9] also resulted in the isolation of the already rearranged salt **12**. Since only negative evidences for the contribution of the structure **10** as an intermediate had been obtained, we also presumed that the direct production of **5** from **4** would take place without an intermediacy of **10** from the Criegee intermediate directly through the path (b).

The product **5** had been a versatile synthetic intermediate for a short-cut synthesis of Δ^{12}-prostaglandin A_2 analogs. The intermediate **5** already holds an ω-chain analog, and the elongation of α-chain was carried out according to the known established procedure.[2] The reduction of **5** with diisobutylaluminum hydride, followed by reaction with the Wittig reagent and oxidation afforded Δ^{12}-prostaglandin A_2 analog **13**. The synthesized prostaglandin A_2 analogs revealed the antitumor activity against P-388 and L-1210 leukemia cells *in vitro*.[10]

In conclusion, we clarified the direct formation of 6-alkylidene-2-oxa-3-oxo-7-bicyclo[3.3.0]octene (**5**) by the Baeyer-Villiger oxidation of 7-alkylidene-2-oxo-5-bicyclo[2.2.1]heptene (**4**) for the first time. And hydrogen peroxide and



4 10 11 5 12

peracetic acid were found out as the suitable reagants for the lactonization. The bicyclo[3.3.0]lactone **2** is an useful synthetic intermediate for the short-cut synthesis of antitumor-active Δ^{12}-prostaglandin A_2 analog **13**.

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7) The chemical shift of the exomethylene proton in **5a** (R^1= H) showed always lower value than that in **5b** (R^1= H). The relationship completely coinsided with that obtained by the calculation: E. Pretsch, J. Seibl, W. Simon, and T. Clerc, "Tabellen zur Strukturaufklarung organischer Verbindungen, zweite Auflage", Springer-Verlags, (1981), p.H215.
8) A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, and C. Gandolfi, J. Org. Chem., 45, 4776 (1980).
9) The reaction mixture was passed through a Dowex A-1 column and eluted with methanol.
10) The analog **13** (R^1=H, R^2= 2,2-ethylenedioxyheptyl) has IC_{50} values of 5.5 μg/ml against P-388 and 5.9 μg/ml against L-1210.

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