



Photochemical reduction of flavone with NaBH₄ in batch and micro-channel reactors using excimer lasers

Akihiko Ouchi*, Hitoshi Sakai, Takeshi Oishi, Masayuki Kaneda, Toshiaki Suzuki, Atsushi Saruwatari, Toru Obata

National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8565, Japan

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ABSTRACT

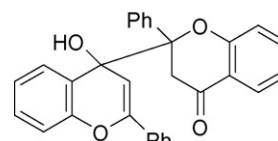
Photochemical reduction of a stable enone, flavone (**1**), was accomplished by excimer laser photolysis using NaBH₄ in ethanol, which formed flavanone (**2**) as a primary product in contrast to the formation of dimers that predominate in conventional photolysis. Flavanone (**2**) underwent successive thermal reduction with NaBH₄ leading to flavanol (**3**) and photolysis to ethyl salicylate (**4**), in which the formation of **4** was completely suppressed when a single laser shot was used for the photolysis. The photolysis was conducted using quartz batch reactors having different optical paths and a quartz micro-channel reactor, in combination with KrF and XeCl excimer laser irradiation. This showed a considerable acceleration of the reaction with the micro-channel reactor, and the selectivity of the photoproducts **2**, **3**, and **4** depended on the optical path of the reactors, the laser wavelengths, the concentration of NaBH₄, and the laser repetition rate. An optimal irradiation condition - application of sufficient time interval between the XeCl laser pulses, a low concentration of **1**, and high concentration of NaBH₄ - showed a considerable increase in the selectivity of **3** by eliminating the formation of **2** and **4**.

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1. Introduction

Flavone (**1**) is a basic unit of a large class of compounds known as flavonoids that exist widely in plants. It is one of the stable enones which is not susceptible to reduction by NaBH₄ under normal reaction conditions. The photolysis of **1** has been extensively studied [1–5], particularly in the presence of H-donors, in order to clarify the photophysical and photochemical properties of many flavonoids that have significant biological activities in the natural environment. These studies revealed that ketyl radicals are formed via a T₁ state and that the radicals undergo disproportionation and coupling to give three products, flavanone (**2**), a *meso*-dimer, and a *dl*-dimer in the ratio of 1:2.2:2 (Scheme 1) [1,2].

The same three photoproducts are also formed in different ratios by the photolysis of **1** in the presence of H-donors, alcohols [3] and amines in aprotic solvents [4]. In the latter case, the formation of a different dimer **A** is also reported [5].



dimer **A**

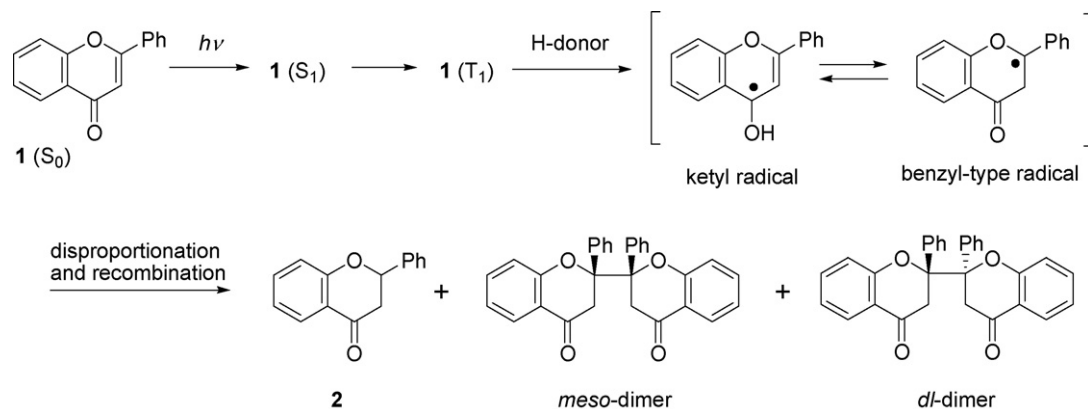
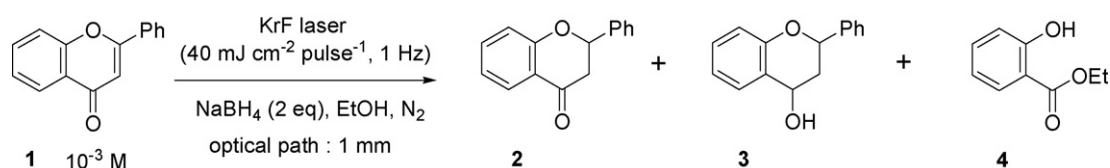
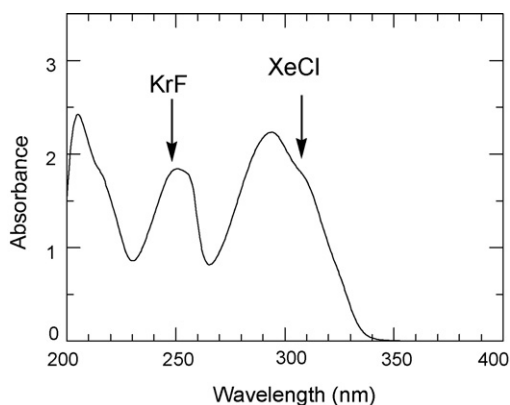
When hydride-type H-donors, NaBH₄ and tin hydrides, are used, benzyl-type radicals are detected by a CIDEP study but the efficiency of the radical formation and the yields of final products have not been reported [5]. Although photochemical reductions of aromatic rings [6,7] and thymidine [8] using NaBH₄, and of aromatic compounds using NaBH₄ in combination with dicyanobenzene [9] or aromatic amines [10] have been reported, to the best of our knowledge, quantitative studies on the photochemical reduction of stable enones using NaBH₄ have not yet been reported. Therefore, we have conducted a systematic study on the photochemical reduction of a stable enone **1**, the basic skeleton of flavonoids, using NaBH₄ in batch and micro-channel [11] reactors.

2. Results and discussions

2.1. Photolysis of flavone (**1**) and NaBH₄ in a batch reactor

Flavone (**1**) is stable in ethanol solution in the presence of NaBH₄ without irradiation of light. However, KrF (248 nm) and

* Corresponding author. Tel.: +81 29 861 4550.
E-mail address: ouchi.akihiho@aist.go.jp (A. Ouchi).

Scheme 1. Photochemical reaction of **1**.Scheme 2. Photochemical reduction of **1** by NaBH_4 .Fig. 1. Absorption spectrum of flavone (**1**). Concentration: 0.1 mM in EtOH, optical path: 10 mm. The wavelengths of KrF and XeCl excimer laser emissions are marked in the figure.

XeCl (308 nm) excimer laser photolysis of **1** in an ethanol solution of NaBH_4 gave a reduction product flavanone (**2**) together with a considerable amount of flavanol (**3**) and a small amount of ethyl salicylate (**4**) as monomeric products (Scheme 2). Excimer lasers were used to accelerate the photolysis and to eliminate the effect of secondary photolysis, particularly at the first laser shot. An experiment on the laser intensity effect showed that the consumption of **1** and the formation of **2** and **3** proceeded by one-photon processes [12], which eliminates the possibility of multi-photon processes that are often involved in laser photolyses.

As seen in Fig. 1, the wavelength of the KrF laser corresponds to the second absorption band of **1** and that of a XeCl laser the first absorption band. In contrast, absorption by NaBH_4 is negligible at both excimer laser wavelengths [12].

The consumption of **1** and the selectivities [13] of **2**, **3**, and **4** in the course of the KrF and XeCl excimer laser photolyses are shown in Fig. 2; **2** and **3** were major products and **4** was a minor product. The analyses of the products were conducted just after the laser irradiation because a considerable decrease in the selectivity of **2** and an increase in that of **3** were observed with increasing time between the end of the laser irradiation and the analysis of the products;

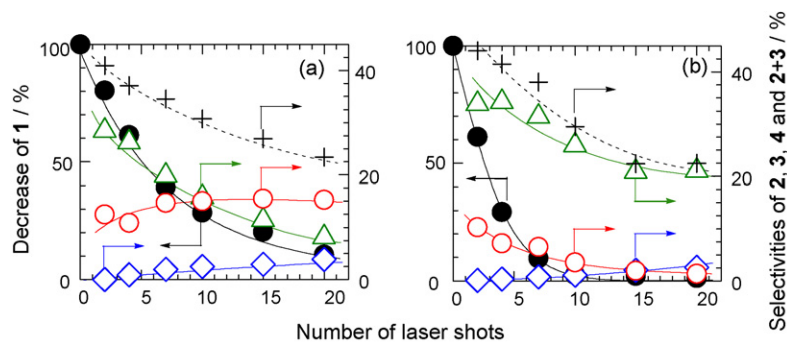


Fig. 2. KrF (a) and XeCl (b) excimer laser photolyses of **1** with NaBH_4 using a quartz cell [20b]. Decrease of **1** (●) and selectivities [13] of flavanone (**2**, ○), flavanol (**3**, △), ethyl salicylate (**4**, ◇), and **2+3** (+) as a function of the number of laser shots. Concentration: 1 mM of **1** and 2 mM of NaBH_4 in EtOH, optical path: 1 mm, laser fluence: 40 (KrF) and 32 (XeCl) $\text{mJ cm}^{-2} \text{ pulse}^{-1}$ ($5.0 \times 10^{16} \text{ photons cm}^{-2} \text{ pulse}^{-2}$), 1 Hz, N_2 atmosphere, room temperature.

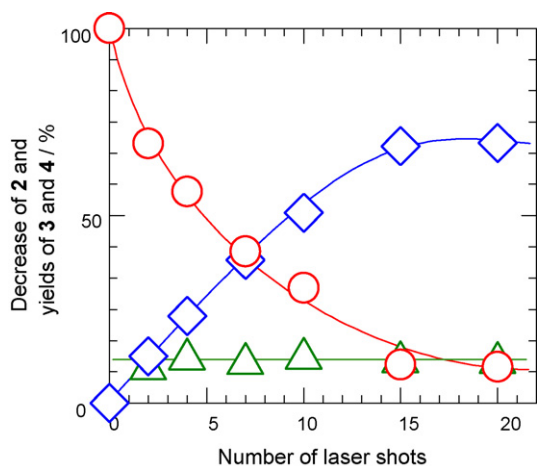


Fig. 3. KrF excimer laser photolysis of **2** with NaBH_4 using a quartz cell [20a]. Decrease of **2** (○) and yields [21] of flavanol (**3**, △) and ethyl salicylate (**4**, ◇) as a function of the number of laser shots. The ethanol solutions of **2** and NaBH_4 were mixed just before the photolysis to minimize thermal reduction of **2** into **3**. Concentration: 1 mM of **2** and 2 mM of NaBH_4 in EtOH, optical path: 1 mm, laser fluence: $40 \text{ mJ cm}^{-2} \text{ pulse}^{-1}$, 1 Hz, N_2 atmosphere, room temperature.

[12] this is the result of normal thermal reduction of **2** into **3** by NaBH_4 . The thermal reduction was confirmed by an independent experiment using **2** and NaBH_4 . Therefore, the sum of the selectivities of **2** + **3**, should be used for the discussions on the selectivity of primary photochemical reduction of **1** rather than an independent consideration of **2** and **3**.

As seen in Fig. 2, the photolysis proceeded faster with the XeCl laser and, at the same time, the selectivity of **2** + **3** was slightly higher for photolysis with the XeCl laser compared with KrF laser, both showing their maximum after a single laser shot. The figure also shows the decrease in the selectivity of **2** + **3** and a slight increase of the selectivity of **4** with the progress of the photolysis, mostly due to the decrease in the selectivity of **3**. These results can be explained by secondary photolysis of **2** by the excimer lasers. Indeed, KrF laser photolysis of **2** under the same conditions as that of **1** gave **4** as the major photoproduct (Fig. 3). In contrast, KrF laser photolysis of **3** [12] was very slow under the same photolysis conditions compared with those of **1** and **2**, which can be explained by

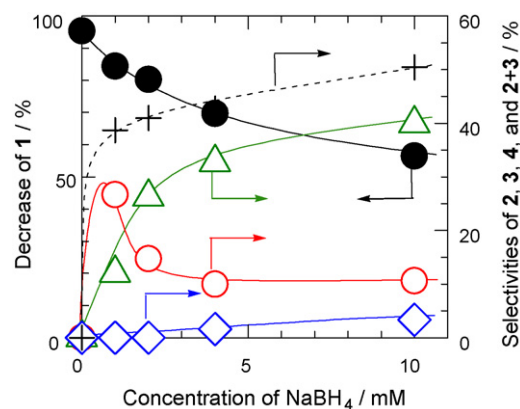


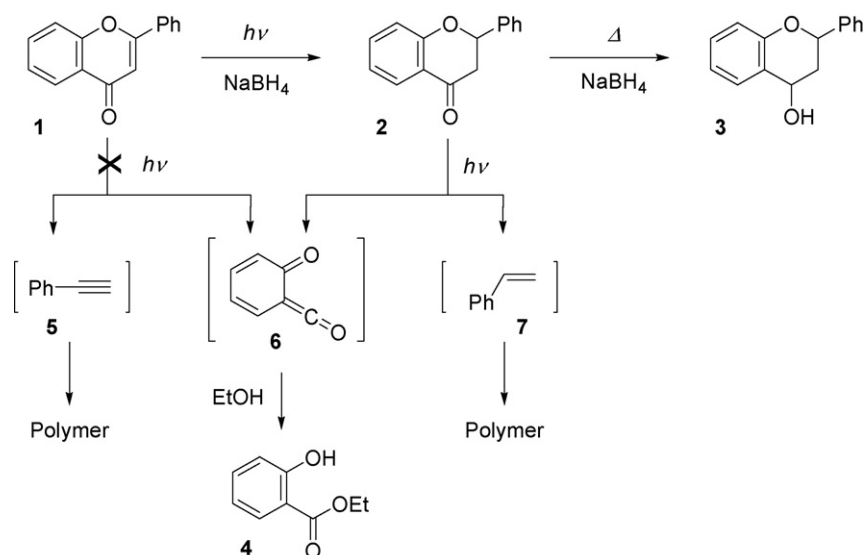
Fig. 4. NaBH_4 concentration dependence of the photochemical reduction of **1** using a quartz cell [20b]. Decrease of **1** (●) and selectivities [13] of flavanone (**2**, ○), flavanol (**3**, △), ethyl salicylate (**4**, ◇), and **2** + **3** (+) as a function of the NaBH_4 concentration. Concentration: 1 mM of **1** in EtOH, optical path: 1 mm, laser fluence: $40 \text{ mJ cm}^{-2} \text{ pulse}^{-1}$, 1 Hz, number of laser shots: 2 shots, N_2 atmosphere, room temperature.

the low absorption of **3** [12] at 248 nm compared to those of **1** (cf. Fig. 1) and **2** [12].

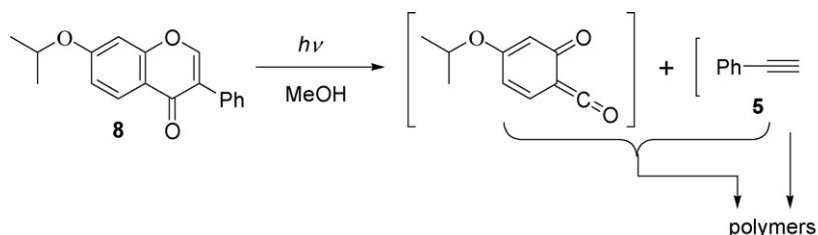
The effect of oxygen in the photolysis of **1** was investigated by photolysis in air [12]. Although a slight retardation of the reaction was observed, the selectivity of the products was not much affected by the presence of oxygen.

2.2. Effect of NaBH_4 concentration in the photolysis of flavone (**1**) in a batch reactor

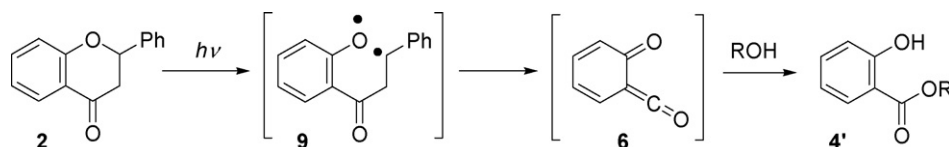
As shown in Fig. 4, the consumption of **1** increased with an increase of NaBH_4 concentration. Although it is reported that the photolysis of **1** in the presence of H-donors forms **2** [3,14] this was not detected in the absence of NaBH_4 (shown as a concentration of 0% in Fig. 4). In contrast, significant acceleration of the reaction and an increase in the selectivity of **2** + **3** was observed with an increase of the concentration of NaBH_4 . When one equivalent of NaBH_4 to **1** was used, the selectivity of **2** predominated over that of **3** but a rapid increase in the selectivity of **3** and a decrease in the selectivity of **2** was observed with increasing NaBH_4 concentration. This



Scheme 3. Plausible reaction path for the photochemical reduction of **1** by NaBH_4 .



Scheme 4. Proposed photochemical reaction path of 7-isopropoxyisoflavone (**8**) [15].



Scheme 5. Photochemical reaction path of flavanone (**2**) [16].

change in the selectivities can be rationalized by an over-reduction of **2** by excess NaBH_4 via a thermal reaction.

2.3. Reaction path of photochemical reduction of flavone (**1**) by NaBH_4

Scheme 3 shows a plausible reaction path for the photolysis of **1** in the presence of NaBH_4 . Both NaBH_4 and irradiation of light is indispensable for the reaction **1** \rightarrow **2** to proceed effectively. Flavone (**1**) does not react with NaBH_4 in the absence of light and the consumption of **1** was very slow in the absence of NaBH_4 (cf. Fig. 4, concentration of NaBH_4 at 0%). The reaction **1** \rightarrow **2** is expected to proceed via a triplet state as shown in Scheme 1. However, Scheme 1 also shows the formation of a considerable quantity of dimers of **1** by the photolysis of **1** in the presence of H-donors. Indeed, the KrF laser photolysis of **1** under the same photolysis conditions as the experiments in Fig. 2 but without NaBH_4 showed the presence of dimers by LCMS analyses. The analysis of the reaction mixture after 50 shots of the KrF laser on to **1** (consumption of **1**: 78%) showed a peak that corresponds to **1** at m/e 223 ($M+1$) together with that of the dimers of **1** at m/e 447 ($M+1$), in which the ratio of the relative intensities of the signals (dimers: m/e 447)/(1: m/e 223) was 0.340. In contrast, LCMS analysis of the products in Fig. 2 showed only a small quantity of the dimers after 10 laser shots. The ratio of the relative intensities of the signals (dimers: m/e 447 + 449 + 451)/(1: m/e 223) was 0.166; m/e 449 and 451 correspond to dimers in which one and two ketones of the original dimers are reduced to alcohol(s) by NaBH_4 . This result indicates that NaBH_4 has a different H-donor property from those of amines and alcohols.

A facile thermal reaction **2** \rightarrow **3** was confirmed by our reference experiment, which indicates that complete suppression of the secondary reaction **2** \rightarrow **3** is very difficult once **2** is formed by the photolysis.

The presence of a photochemical reaction path **1** \rightarrow **5** + **6** is expected from the analogy with the proposed reaction mechanism for the photolysis of 7-isopropoxyisoflavone (**8**) (Scheme 4) [15]. However, **4** was not detected by the photolysis of **1** in the absence of NaBH_4 (cf. Fig. 4), which excludes the photochemical reaction path **1** \rightarrow **5** + **6** from major reaction pathways.

The presence of a photochemical reaction path **2** \rightarrow **6** is also reported (Scheme 5) [16]. As shown in Scheme 5, **2** is reported to form the ketene **6** via a diradical **9** that is generated by photochemical ring opening of the dihydropyrone ring. When the KrF laser photolysis was conducted in *n*-propanol in place of ethanol, propyl

salicylate was formed instead of **4**. This result supports the presence of a ketene intermediate **6**, as shown in Scheme 3.

2.4. Photochemical reduction of flavone (**1**) by NaBH_4 in a micro-channel reactor

To conduct continuous photolysis of **1** and to increase the efficiency of the photolysis, the reaction was also carried out using a quartz micro-channel reactor having a channel width of 100 μm and depth of 40 μm . The number of laser shots to a unit volume of the solution was controlled by varying the laser repetition frequency. Fig. 5 shows the results of the photochemical reduction of **1** by NaBH_4 using this micro-channel reactor. As can be seen in the figure, a considerable acceleration of the photolysis took place in the micro-channel reactor compared with the batch reactor (cf. Fig. 2a). Although the trend of the photolysis was similar to that in the batch reactor, the photoproducts **2**–**4** were formed with different selectivity [13] and a slight decrease in the selectivity of **2** + **3** in the micro-channel reactor was observed compared to that in the batch reactor.

The effect of oxygen was similar to that in the batch reactor; [12] the conversion of **1** was slightly slower and the selectivities

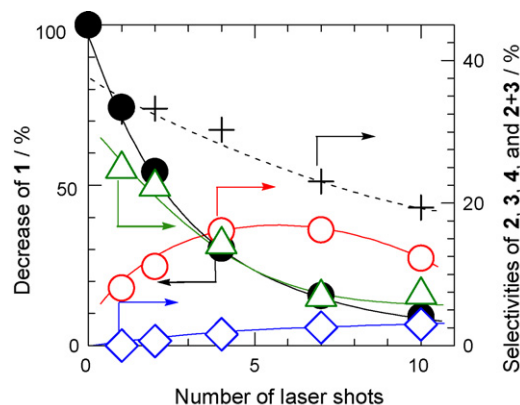


Fig. 5. KrF excimer laser photolysis of **1** with NaBH_4 using a quartz micro-channel reactor [20b]. Decrease of **1** (●) and selectivities [13] of flavanone (**2**, ○), flavanol (**3**, △), ethyl salicylate (**4**, ◇), and **2** + **3** (+) as a function of the number of the laser shots. Concentration: 1 mM of **1** and 2 mM of NaBH_4 in EtOH, optical path: 40 μm , channel width: 100 μm , laser fluence: 40 mJ cm^{-2} pulse $^{-1}$, irradiation length: 16.5 mm, flow rate: 0.4 mL h^{-1} , laser frequency was varied from 2 to 40 Hz, N_2 atmosphere, room temperature.

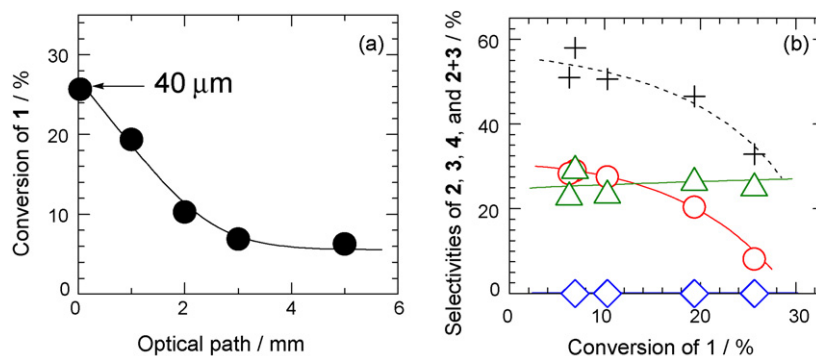


Fig. 6. Effect of the length of the optical path on the KrF excimer laser photolysis of **1** with NaBH₄ [20b]. (a) Conversion of **1** (●) as a function of the optical path and (b) selectivities [13] of **2** (○), **3** (△), **4** (◇), and **2+3** (+) as a function of the conversion of **1** shown in (a). Concentration: 1 mM of **1** and 2 mM of NaBH₄ in EtOH, number of laser shots: 1 shot, laser fluence: 40 mJ cm⁻² pulse⁻¹, N₂ atmosphere, room temperature.

of products **2–4** were slightly lower than those under a nitrogen atmosphere.

2.5. Effect of optical path in the photochemical reduction of flavone (**1**) by NaBH₄

To understand the difference in the reaction between the batch and micro-channel reactor, photolyses using different optical paths were conducted. These used a single laser shot to avoid the effect of secondary photolysis. Fig. 6a shows the conversion of **1** by one laser shot as a function of the optical path of the reactors. As seen in Fig. 6a, the conversion of **1** decreased with an increase in the optical path and leveled off for an optical path greater than 3 mm. Such dependence on the optical path has been reported in other laser photolysis experiments [17]. This is due to the fact that the average photon density in the irradiated solution is higher when the optical path is small because the intensity of the light at the exit decreases by increasing the optical path.

Fig. 6b shows the selectivity of **2**, **3**, **4**, and **2+3** as a function of the conversion of **1**. The figure shows that the selectivity of **2** decreased with the increase of the conversion of **1** whereas that of **3** slightly increased. This can be explained by the formation of higher concentrations of ketyl and benzyl-type radicals at higher conversion of **1** that most probably lead to the formation of dimers within a laser pulse because dimers were detected by LCMS analyses in the photolysis using a micro-channel reactor but not in a cell with a 1-mm optical path. This result indicates that contribution of dimer formation is not important in the reactions conducted with batch reactors. It is interesting to note that product **4** was not detected in the experiments with a single laser shot, which clearly shows that **4** is a secondary photolysis product as shown in Scheme 3. This suppression of the secondary photolysis is a significant advantage of using pulsed lasers for the photolysis.

2.6. Optimization of the photolysis condition by suppression of the secondary photochemical path

In contrast to the predominant formation of dimers of **1** in conventional photolyses without NaBH₄, the monomeric products **2**, **3**, and **4** were obtained in our experiments with NaBH₄. It was confirmed that **3** and **4** were formed by secondary reactions of **2**, the primary photochemical product; **3** was formed by a thermal reduction of **2** by NaBH₄ and **4** by a secondary photolysis of **2**.

Although selective formation of **2** is difficult due to the presence of the thermal reduction **2** → **3**, selective formation of **3** together with its increasing yield can be accomplished by suppression of the secondary photochemical path **2** → **4**. Our experiments showed

that the photolysis **2** → **4** can be completely suppressed by using a single laser shot (cf. Fig. 6) and photochemical decomposition of **3** is very small even with a KrF laser [12]. Therefore, the use of a slow repetition rate for the excimer laser, which enables **2** to have sufficient time for the thermal reduction **2** → **3**, should not only increase the selectivity but also the yield of **3** by multi-pulse irradiation. Our experiments also indicate that the use of a high concentration of NaBH₄ and a low concentration of **1** are other factors for the optimization of the reaction. Indeed, the photolysis of 0.5 mM **1** and 10 mM NaBH₄ in EtOH by three shots of a XeCl laser (48 mJ cm⁻² pulse⁻¹) using a batch cell having a 1-mm optical path with laser pulse interval of 10 min gave 93% consumption of **1** with 57% selectivity for **3**, and 0% for both **2** and **4**; the selectivity of **3** was much higher than that of **2+3** in Fig. 2b for a similar consumption of **1**.

3. Experimental

3.1. General aspects

Solvent for the photolysis and the following samples were purchased and used as bought or after purification: ethanol (spectral grade), sodium borohydride, flavone (recrystallized from *n*-hexane), flavanone, and ethyl salicylate. Flavanol was synthesized from flavanone according to the reported procedure [18]. The lasers used for photolyses were KrF [pulsewidth (fwhm): 23 ns] and XeCl [pulsewidth (fwhm): 20 ns (typical)] excimer lasers whose intensities were controlled by using quartz convex lenses. The consumption of **1** and the product yields were analyzed on a capillary glc (Neutrabond-1, 60 m, 0.25 mmID, GL Sciences Inc.) and a HPLC pump (Supersphere 100, RP-8e, 250 mm, 4 mmID, Merck) fitted with a UV detector (detected at 254 nm), by comparison with authentic samples.

3.2. Photolysis in batch reactors

Photolyses were conducted on 50 μL ethanol solutions under a nitrogen atmosphere at room temperature using a synthetic quartz cell of 10-mm width and 1-mm optical path. The solutions for the photolysis of **1** and NaBH₄, and those of **3** and NaBH₄ were prepared as mixtures and degassed with four freeze-pump-thaw cycles before photolysis. For the photolysis of **2** and NaBH₄, the solutions of **2** and NaBH₄ were prepared separately, degassed with four freeze-pump-thaw cycles, and the solutions mixed under nitrogen just before photolysis. The photolysis in air was conducted similarly using air saturated ethanol solutions of **1** and NaBH₄. Experiments on the flow dependence were conducted similarly by a single laser shot in the same experimental set-up.

3.3. Photolysis in a micro-channel reactor [19]

A quartz micro-channel reactor with the channel of 100- μm width and 40- μm depth was used for the photolyses at room temperature. An ethanol solution of 1 mM **1** and 2 mM NaBH_4 was used for the photolyses. The solution was degassed with four freeze-pump-thaw cycles and transferred to a 1-mL syringe under a nitrogen atmosphere. The syringe was connected to the inlet of a micro-channel by a Teflon tube and the exit of the micro-channel was connected to a glass test tube by another Teflon tube. The syringe was fixed on a micro-feeder apparatus that was set up under a nitrogen atmosphere and the solution was pumped at a rate of 0.4 mL h^{-1} . The laser was used to irradiate 16.5 mm length of the micro-channel using a mask 16.5 mm long and 10 mm wide. The number of laser shots per unit volume of the solution was controlled by varying the repetition rate of the KrF excimer laser from 2 to 40 Hz. The photolyses in air was conducted similarly using air saturated ethanol solutions of **1** and NaBH_4 .

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jphotochem.2008.05.024.

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- [13] Selectivities of the products are based on the consumption of **1**.
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- [19] Experimental set-up is shown in the Supplementary data.
- [20] The results are the average of (a) two or (b) at least two independent runs.
- [21] Yields of products are based on the initial amount of **1**.