

# 新規ビシクロ[4.1.0]ヘプタン-2、4-ジオン誘導体の合成とその除草活性

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## Synthesis of new bicyclo[4.1.0]heptane-2,4-dione derivatives and their herbicidal activity<sup>#</sup>

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Various triketone type 4-HPPD inhibitors were synthesized and their herbicidal activity and corn safety were evaluated. In the course of synthetic studies, we invented convenient methods to synthesize novel benzoyl-substituted bicyclo[4.1.0]heptanediones, and it was found that some showed excellent herbicidal activity against weeds in a corn field. Among these compounds, 3-(4-chloro-2-nitrobenzoyl)bicyclo[4.1.0]heptane-2,4-dione was found to be not only highly active against broadleaf weeds but also grass weeds, whereas it caused severe damage to corn. As a result of further efforts to modify benzoyl substituents, we found a compound, (1*R*\*,6*R*\*)-3-(2-chloro-4-methylsulfonylbenzoyl)bicyclo[4.1.0]heptane-2,4-dione, which provided a good combination of herbicidal activity and corn safety. © Pesticide Science Society of Japan

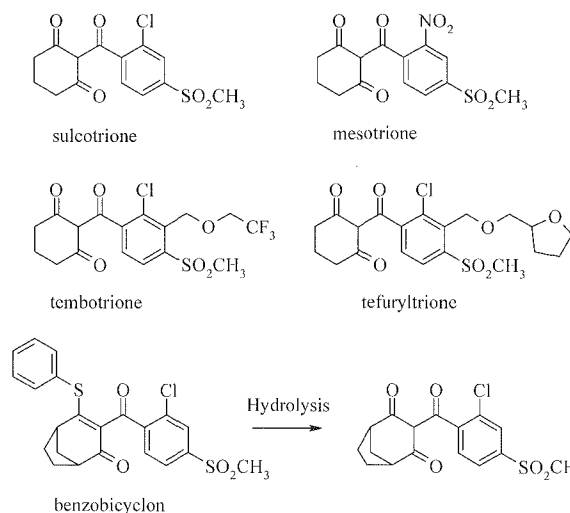
**Keywords:** herbicidal activity, cyclic 1,3-dione herbicide, HPPD, corn, bicyclo[4.1.0]heptane-2,4-dione.

### Introduction

Triketone-type herbicides interfering with HPPD (4-hydroxy-pyruvate dioxygenase<sup>1-3</sup>) have been actively studied since sulcotrione<sup>4</sup> was put on the market in 1992 by Zeneca. The subsequently useful corn herbicide mesotrione<sup>5</sup> (Syngenta, 2002) was commercialized, and recently it was said that other new herbicides such as tembotrione and tefuryltrione are under development. A novel triketone-type herbicide benzobicyclon<sup>6</sup> (SDS Biotech, 2001), enol thioether-type HPPD inhibitor, was put on the market for paddy fields. Benzobicyclon is a unique herbicide generating the actual herbicidal triketone structure by its hydrolysis in paddy water, soil, and plants<sup>6</sup> (Fig. 1).

We have been studying the relationships between cyclohexanedione ring substituents and their herbicidal activity in order to discover a higher performance HPPD inhibitor, since we are interested in the corn herbicidal characteristics of

HPPD inhibitor and the unique bicyclo-structure of benzobicyclon. In the course of synthetic studies of our triketones, we invented convenient methods to synthesize novel benzoyl-substituted bicyclo[4.1.0]heptanediones, and it was found that some bicyclo[4.1.0]heptanediones showed excellent herbicidal activity against weeds in a corn field.



**Fig. 1.** Structures of common triketone herbicides.

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<sup>#</sup> Synthesis and herbicidal activity of bicyclo[4.1.0]heptane-2,4-dione derivatives (Part 1)

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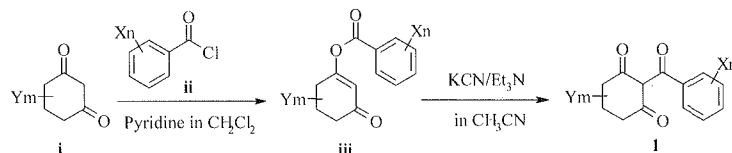


Fig. 2. Preparation of 2-benzoylcyclohexane-1,3-diones.

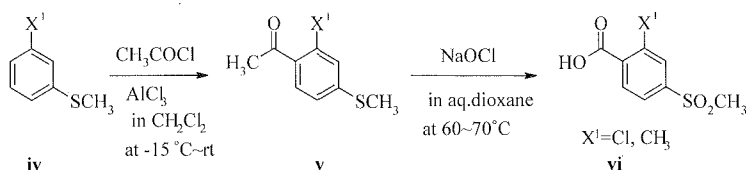


Fig. 3. Preparation of 2-substituted 4-methylsulfonylbenzoic acids.

In this paper, we describe the synthesis of various types of triketone compounds, the evaluation of their herbicidal activity and their SAR for herbicidal activity and safety for corn.

## Materials and Methods

### 1. Synthesis

#### 1.1. General procedure

General synthetic route for the synthesis of 2-benzoylcyclohexane-1,3-diones (**1a–i**) is outlined in Fig. 2.

The reaction of substituted benzoyl chlorides (**ii**) with substituted cyclohexane-1,3-diones (**i**) gave enol esters (**iii**), which were rearranged to the corresponding *C*-acyl isomers (**1**) in the presence of potassium cyanide and triethylamine. The phenyl ring with 4-methylsulfonyl group and chloro atom or nitro group at the 2-position were the structural feature of the HPPD inhibitor such as sulcotrione and mesotrione. Thus also prepared 2-substituted 4-methylsulfonylbenzoic acid according to the methods shown in Fig. 3. The Friedel–Crafts reaction of (3-substituted phenyl)methyl thioether (**iv**) with acetyl chloride gave acetophenones (**v**). The acetyl and methylthio groups were oxidized by sodium hypochlorite to provide the key intermediate **vi**. Cyclohexanediones as another starting material were prepared by a variety of methods reported in the literature.<sup>7,8)</sup>

The synthetic methods for bicyclo[4.4.0]decane-2,4-dione and bicyclo[4.3.0]nonane-2,4-dione are shown in Fig. 4. Bicyclo[4.3.0]nonane-2,4-dione (**ix**;  $p=2$ ) was prepared by the reaction of 1-cyclopentenyl methyl ketone (**vii**;  $p=2$ ) with diethyl malonate in the presence of sodium ethoxide followed by hydrolysis and subsequent decarboxylation. In the same way, bicyclo[4.4.0]decane-2,4-dione (**ix**;  $p=3$ ) was obtained.

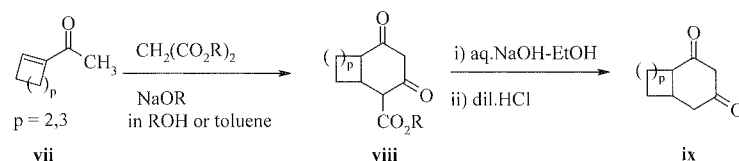


Fig. 4. Preparation of cycloalkane-fused cyclohexanediones.

As for bicyclo[4.1.0]heptane analogue (**ix**;  $p=0$ ), the final products, 3-benzoylbicyclo[4.1.0]heptane-2,4-diones (**10a–i**) were synthesized by the cyclopropanation of 2-benzoylcyclohexane-1,3-dione derivatives (**9**) as an intermediate, as summarized in Fig. 5.

5-*tert*-Butoxymethylcyclohexane-1,3-dione (**5**) was prepared by the reaction of ethyl 4-*tert*-butoxycrotonate with ethyl acetoacetate followed by hydrolysis and subsequent decarboxylation. The reaction of **5** with substituted benzoyl chlorides gave 2-benzoyl-5-(*tert*-butoxymethyl)cyclohexane-1,3-diones (**7**). The acid catalyzed cleavage of the *tert*-butyl group of compound **7** gave 5-hydroxymethyl intermediate **8**. The alcohol **8** was converted to mesylate **9** by the reaction with methanesulfonyl anhydride, and subsequent cyclization of intermediate **9** under basic condition yielded the final products, 3-benzoylbicyclo[4.1.0]heptane-2,4-diones (**10**).

#### 1.2. Typical procedure

<sup>1</sup>H NMR spectra were recorded on a JEOL AL 300 spectrometer at 300 MHz using CDCl<sub>3</sub> and D<sub>2</sub>O-NaOD as a solvent with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in ppm ( $\delta$  scale) downfield from TMS. Melting points were measured with a YANACO MP-3 micro melting point apparatus and are given uncorrected. Analytical TLC was performed on silica gel 60 F254 (Merck). Spots were detected under UV light. Column chromatography was performed using Wakogel C-200 (Wako).

##### 1.2.1. 4-Methylthio-2-nitrobenzoic acid

To a solution of methyl 2,4-dinitrobenzoate 10.4 g (46 mmol) and DMF (75 ml) was dropwise added aqueous 15% sodium methanethiolate 22.1 g (47 mmol) at 10–13°C in an ice-water bath, and the mixture was stirred at room temperature for a

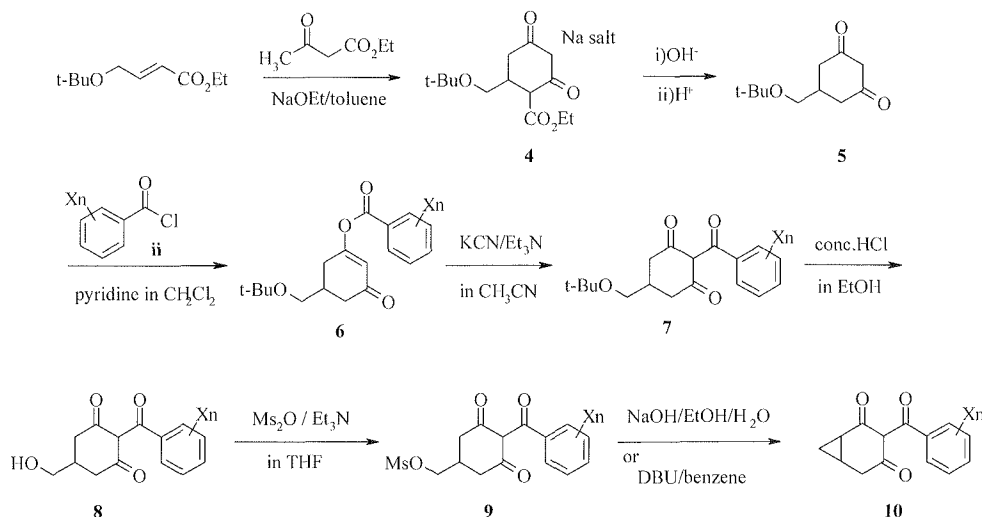


Fig. 5. Method for preparation of 3-benzoylbicyclo[4.1.0]heptane-2,4-diones.

further 20 hr. The reaction mixture was poured into ice-water, and then the precipitated solid was collected by filtration and washed with water to give a crude solid, which was dissolved in ethyl acetate. The ethyl acetate solution was washed with water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated to leave a solid. The resulting solid was triturated with *n*-hexane and dried to give methyl 4-methylthio-2-nitrobenzoate 8.2 g as a pale yellow solid.

To a solution of the obtained methyl 4-methylthio-2-nitrobenzoate 8.1 g (36 mmol) and methanol (80 ml) was added an aqueous solution of sodium hydroxide 4.28 g (107 mmol) and water (43 ml). The mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water and acidified with concentrated hydrochloric acid to precipitate the solid, which was collected by filtration. The solid was dissolved in ethyl acetate (1000 ml). The organic layer was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and evaporated to give 4-methylthio-2-nitrobenzoic acid 7.6 g as a white solid.

#### 1.2.2. 2-Chloro-4-methylthioacetophenone (v: $X^1=Cl$ )

To a methylene chloride (150 ml) solution of 3-methylthiochlorobenzene 10.5 g (66 mmol) and acetyl chloride 5.2 g (66 mmol) was added in portions 8.8 g (66 mmol) of anhydrous aluminum chloride over a 10-min period at  $-13^\circ\text{C}$  in a salt-ice bath. After the addition was complete, the cooling bath was removed and stirring was continued for 3.5 hr. The reaction mixture was poured into ice-cooled concentrated hydrochloric acid and the resulting mixture was stirred for 1 hr. Then the organic layer was separated, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by silica gel column chromatography with *n*-hexane/ethyl acetate (95 : 5 v/v) to give 2-chloro-4-methylthioacetophenone (v:  $X^1=Cl$ ) 8.5 g as a yellow solid.

#### 1.2.3. 2-Chloro-4-methylsulfonylbenzoic acid (vi: $X^1=Cl$ )

2-Chloro-4-methylthioacetophenone 7.7 g (42 mmol) was dissolved in dioxane (100 ml), and then 157.9 g (0.21 mol) of 10% aqueous sodium hypochlorite was added to the dioxane solution over 20 min at room temperature. The mixture was stirred at room temperature for a further 10 min and was heated under reflux for 6.5 hr. The reaction mixture was allowed to cool to room temperature, acidified with diluted hydrochloric acid and extracted with ethyl acetate. Then the organic layer was separated, washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give 2-chloro-4-methylsulfonylbenzoic acid 7.3 g as a white solid; mp  $193\text{--}196^\circ\text{C}$ .

#### 1.2.4. Bicyclo[4.3.0]nonane-2,4-dione (ix: $p=2$ )

Methyl malonate 3.61 g (27.3 mmol) was added to 5.28 g (27.4 mmol) of 28% sodium methoxide in methanol solution, and then cyclopentenyl methyl ketone 3.10 g (81% purity, 22.8 mmol) was added to the mixture over 2 hr at room temperature. After stirring overnight at room temperature, the reaction mixture poured into water, and the solution was washed with ether. The aqueous layer was acidified with diluted hydrochloric acid and extracted with ether. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and evaporated to give crude methyl 3,5-dioxo-2-bicyclo[4.3.0]nonanecarboxylate 4.23 g as an oil.

The water (50 ml) solution of the crude ester 4.23 g and sodium hydroxide 2.80 g (70 mmol) was refluxed for 2.5 hr. After the reaction was completed, the generated methanol was removed. The reaction mixture was acidified with 7.3 g of concentrated hydrochloric acid and heated at  $100^\circ\text{C}$  until completion of the evolution of carbon dioxide. The resulting mixture was allowed to cool to room temperature and extracted with ether. The ether solution was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated to give bicyclo[4.3.0]nonane-2,4-

dione 2.85 g as a brownish viscous oil.

1.2.5. *5-tert-Butoxymethylcyclohexane-1,3-dione (5)*

Ethyl 4-*tert*-butoxycrotonate<sup>9)</sup> 29.7 g (0.16 mmol) was added dropwise to a toluene (250 ml) solution of ethyl acetoacetate 41.5 g (0.32 mmol) and sodium ethoxide 17.0 g (0.24 mmol) at room temperature, and the mixture was stirred under reflux for 5 hr. After cooling to room temperature, the solid precipitated was collected by filtration to give ethyl 6-*tert*-butoxymethyl-2,4-dioxocyclohexanecarboxylate sodium salt (**4**) 33 g (71%) as a pale brown solid.

The water (100 ml) solution of **4** 9.0 g (31 mmol) and sodium hydroxide 3.7 g (93 mmol) was refluxed for 3 hr and acidified with concentrated hydrochloric acid, diluted with chloroform, and then stirred for 2 days at room temperature. The organic layer was then separated, washed with water and brine, dried over anhydrous magnesium sulfate, and then evaporated to give 5-*tert*-butoxymethylcyclohexane-1,3-dione **4.2** g (70%) as colorless crystals.

1.2.6. *2-(4-Chloro-2-nitrobenzoyl)-5-hydroxymethylcyclohexane-1,3-dione (8a)*

To a benzene (90 ml) solution of 4-chloro-2-nitrobenzoic acid 5.10 g (25 mmol) and thionyl chloride 3.91 g (33 mmol) was added a drop of pyridine, then the mixture was refluxed for 4 hr. The solvent was evaporated to give crude acid chloride. A methylene chloride (10 ml) solution of the resulting acid chloride was added dropwise to a methylene chloride (50 ml) solution of 5-*tert*-butoxymethylcyclohexane-1,3-dione (**5**) 5.00 g (25.3 mmol) and pyridine 2.20 g (27.8 mmol) at room temperature with stirring, then the mixture was stirred for 30 min. The reaction mixture was washed with diluted hydrochloric acid, water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated to dryness to give 5-*tert*-butoxymethyl-3-oxocyclohexenyl 4-chloro-2-nitrobenzoate (**6a**) as an oily product. The oil was dissolved in acetonitrile (80 ml), and then triethylamine 3.20 g (31.7 mmol) and KCN 0.60 g (9.2 mmol) were added to the solution. After stirring for 10 hr at room temperature, the reaction mixture was acidified with diluted hydrochloric acid and extracted with chloroform. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was dissolved in ethanol (60 ml), and concentrated hydrochloric acid (35 ml) was added to the ethanol solution, and then the mixture was stirred for 3 hr at 60–65°C. The reaction mixture was concentrated *in vacuo* and the resulting oil was dissolved in chloroform. The chloroform solution was washed with water and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated to leave a solid. The resulting solid was triturated with methanol and dried to give 2-(4-chloro-2-nitrobenzoyl)-5-hydroxymethylcyclohexane-1,3-dione (**8a**) 6.1 g as pale yellow crystals; mp 150–152°C; <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>): 2.23–2.45 (3H, m), 2.72–2.92 (2H, m), 3.59–3.70 (2H, m), 7.19 (1H, d,  $J=8.4$  Hz), 7.67 (1H, dd,  $J=8.4$  Hz and  $J=2.1$  Hz), 8.19 (1H, d,  $J=2.1$  Hz), 16.46 (1H, bs, OH).

1.2.7. *4-(4-Chloro-2-nitrobenzoyl)-3,5-dioxocyclohexylmethyl methanesulfonate (9a)*

Methanesulfonic anhydride 0.54 g (3.1 mmol) was added dropwise to a mixture of 2-(4-chloro-2-nitrobenzoyl)-5-hydroxymethylcyclohexane-1,3-dione (**8a**) 0.50 g (1.5 mmol), triethylamine 0.47 g (4.6 mmol) and tetrahydrofuran (15 ml) at room temperature with stirring. After stirring for 1 hr at room temperature, the reaction mixture was poured into ice water, acidified with diluted hydrochloric acid and extracted with chloroform. Then the organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated. The residue was purified by silica gel column chromatography with chloroform/acetone (19 : 1 v/v) to give 4-(4-chloro-2-nitrobenzoyl)-3,5-dioxocyclohexylmethyl methanesulfonate (**9a**) 0.50 g (1.4 mmol) as colorless crystals; mp 124–126°C; <sup>1</sup>H NMR  $\delta$  (CDCl<sub>3</sub>): 2.31 (1H, dd,  $J=16.8$  Hz and  $J=11.4$  Hz), 2.44 (1H, dd,  $J=16.8$  Hz and  $J=4.2$  Hz), 2.57–2.70 (1H, m), 2.78 (1H, dd,  $J=18.3$  Hz and  $J=10.1$  Hz), 2.97 (1H, dd,  $J=10.1$  Hz and  $J=5.1$  Hz), 3.05 (3H, s), 4.13–4.26 (2H, m), 7.20 (1H, d,  $J=8.4$  Hz), 7.68 (1H, dd,  $J=8.4$  Hz and  $J=1.8$  Hz), 8.20 (1H, d,  $J=1.8$  Hz), 16.47, (1H, bs, OH).

1.2.8. *(1R\*,6R\*)-3-(4-Chloro-2-nitrobenzoyl)bicyclo[4.1.0]heptane-2,4-dione (10a)*

A water (2 ml) solution of sodium hydroxide 0.17 g (4.3 mmol) was added to the mixture of 4-(4-chloro-2-nitrobenzoyl)-3,5-dioxocyclohexylmethyl methanesulfonate (**9a**) 0.50 g (1.4 mmol) and ethanol (15 ml) at room temperature with stirring, and the resulting mixture was stirred at room temperature for 2 hr. After the reaction was completed, the solvent was evaporated, and ethyl acetate (50 ml) and water (10 ml) were added to the obtained residue. The mixture was acidified with diluted hydrochloric acid. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by silica gel column chromatography with chloroform to give (1*R*\*,6*R*\*)-3-(4-chloro-2-nitrobenzoyl)-bicyclo[4.1.0]heptane-2,4-dione (**10a**) 0.38 g (86%) as pale yellow crystals; mp 132–134°C.

## 2. Biological tests

The herbicidal effects of the chemicals were evaluated by the following tests. Seeds of crabgrass, *Digitalia sanguinalis* (Ds), giant foxtail, *Setaria faberi* (Sf), vervetleaf, *Abutilon theoplasti* (At), redroot pigweed, *Amaranthus retroflexus* (Ar) and corn, *Zea mays* (corn) were planted in plastic pots (200 cm<sup>2</sup>) containing clay loam soil and were allowed to grow in a greenhouse. Each test compound (0.4 g) was dissolved in a mixture of xylene (1.1 g), dimethylformamide (0.3 g) and polyoxyethylene phenyl ether (0.2 g) to give an emulsifiable concentrate. When the plants were grown to a 5–10 cm height, aqueous suspensions, prepared by diluting an emulsifiable concentrate with water to a specified concentration, were sprayed onto the foliage of the plants at an application volume of 250 l/ha using a micro-sprayer.

**Table 1.**  $^1\text{H}$  NMR spectral data of (1*R*\*, 6*R*\*)-3-(4-chloro-2-nitrobenzoyl)bicyclo[4.1.0]heptane-2,4-dione (**10a**)

$\text{CDCl}_3$	$\text{D}_2\text{O-NaOD}$
0.77–0.82 (0.4H, m), 0.88–0.93 (0.6H, m)	0.59 (1H, ddd)
1.28–1.35 (1H, m)	1.17 (1H, m)
1.88–1.95 (0.4H, m), 1.60–1.70 (0.6H, m)	1.51–1.63 (2H, m)
2.07–2.13 (0.4H, m), 1.74–1.82 (0.6H, m)	
	2.43 (1H, d)
2.60–2.77 (0.8H, m), 2.98–3.22 (1.2H, m)	2.71 (1H, dd)
	7.07 (1H, d)
7.17–7.22 (1H, m)	
7.63–7.68 (1H, m)	7.57 (1H, dd)
8.16–8.17 (1H, m)	8.02 (1H, d)
16.86 (0.4H, bs), 16.19 (0.6H, bs)	

Three weeks after treatment, the degree of damage to each weed and crop safety were visually observed and evaluated on a scale of zero (no damage to weeds or crops) to 100 (complete killing of weeds or crops). Herbicidal data are reported as follows:  $\text{ED}_{80}$  shows the dosage causing visual damage of 80%, and  $\text{ED}_0$ , in the case of corn, the dosage which caused no damage.

## Results and Discussion

### 1. Synthesis

Various triketone-type HPPD inhibitors, including bicycle-type compounds such as benzobicyclon, have been synthesized and their herbicidal activity exhibited, but benzoyl-substituted bicyclo[4.1.0]heptanedione-type compounds have not yet been studied. The intermediate cyclic 1,3-dione compound, bicyclo[4.1.0]heptane-2,4-dione (**ix**:  $p=0$ ) has not been reported so far, although a number of synthetic studies of cyclohexane-1,3-dione derivatives have been reported.<sup>7,8,10,11</sup> Bicyclodione-type compounds such as bicyclo[4.3.0]nonane-2,4-dione (**ix**:  $p=2$ ) and bicyclo[4.4.0]decane-2,4-dione (**ix**:  $p=3$ ) were easily prepared by the reaction of malonic acid ester with the corresponding  $\alpha,\beta$ -unsaturated cycloalkenyl methyl ketones (**vii**:  $p=2,3$ ) (Fig. 4).

In the synthesis of the bicycloheptane analogue (**ix**:  $p=0$ ), cyclopropenyl methyl ketone was one of the possible starting materials, but there have been no reports because of its lack of stability. We planned different methods to prepare the desired bicycloheptane compounds, as summarized in Fig. 5. In this reaction, we did not use the 2-unsubstituted cyclohexanediones, but the 2-benzoyl analogue **9**, which had fewer reac-

tive points with electrophiles. Namely, 2-benzoyl-5-methylcyclohexane-1,3-diones **9** substituted by a leaving group such as the methoxy group at the carbon atom of the 5-methyl group underwent 1,3-elimination of  $\text{MsOH}$  in the presence of a base to give final cyclopropyl derivatives **10**.

Structural assignment of compound **10a** was supported by  $^1\text{H}$  NMR data. Spectral data are listed in Table 1. As for the structure of the benzene substituted triketones, it has been reported by Borisov *et al.*<sup>12</sup>) and Wu *et al.*<sup>13</sup>) that these compounds exist as a *cis*-enol tautomer with an intramolecular hydrogen bond. The triketone compounds such as **10a** mentioned in this article also suggested that there existed two enol-form isomers **10a-I** and **10a-II** (Fig. 6) as a mixture by the enolic hydrogens on the basis of  $^1\text{H}$  NMR spectra (Table 1).

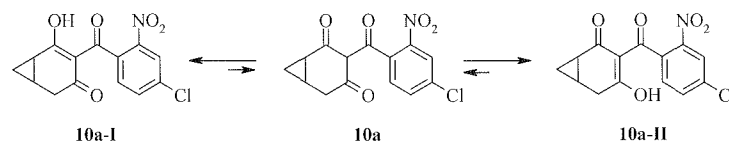
### 2. Herbicidal activity and crop safety

The initial investigation of the 2-benzoylcyclohexane-1,3-dione series focused on the effects of substituents at the cyclohexane ring against weeds (Ds, Sf, At and Ar) while fixing the 4-chloro-2-nitrobenzoyl group at the 2-position of the cyclohexane ring (Table 2).

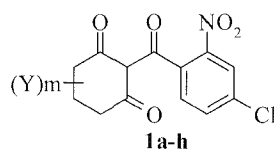
The basic compound **1a** showed higher activity against broadleaf weeds such as At and Ar than grass weeds such as Ds and Sf. 4-Methyl derivative **1b** increased the activity for the grass weed Ds, while the activity against broadleaf weeds such as At and Ar was reduced and safety for corn was decreased. Furthermore, the activity of 5-methyl derivative **1c** was significantly enhanced against grass species, in spite of reducing the activity against broadleaf weed At. Then, further optimization focused on the substituent on the cyclohexane ring at 5-position. Compounds **1d** and **1e** with bulky alkyl groups such as an isopropyl or an *n*-butyl group reduced the activity drastically. Compounds having a heteroatom-containing alkyl group, **1f** and **1g**, did not increase the activity. Also, disubstituted compound **1h** decreased the activity against broadleaf weeds such as At and Ar.

As a result, a methyl group, but not bulky substituents such as an isopropyl or a *n*-butyl group at the 4- or 5-position of cyclohexane ring of compound **1a** was preferable for herbicidal activity against grass weeds in spite of showing corn damage and reducing broadleaf weed activity. Since the introduction of a methyl group at the 4- or 5-position of cyclohexane ring enhanced herbicidal activity against grass species, we synthesized the 4,5-dimethyl compound and the compounds linked methylene chains at 4- and 5-position of the cyclohexane ring, and evaluated them.

Table 3 shows the herbicidal activity and corn safety of these compounds. The 4,5-dimethyl-substituted derivative **1i**



**Fig. 6.** Structures of **10a** in  $\text{CDCl}_3$  suggested by NMR spectrum.

**Table 2.** Herbicidal activity and crop safety of 2-(4-chloro-2-nitrobenzoyl)cyclohexane-1,3-dione derivatives.<sup>a)</sup>

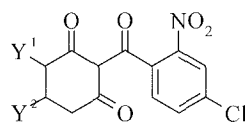
No.	(Y) <sub>m</sub>	mp (°C)	ED <sub>80</sub> (g a.i./ha)				ED <sub>0</sub> (g a.i./ha) corn <sup>f)</sup>
			Ds <sup>b)</sup>	Sf <sup>c)</sup>	At <sup>d)</sup>	Ar <sup>e)</sup>	
<b>1a</b> <sup>14)</sup>	—	175–177	250	500	31	125	500
<b>1b</b> <sup>14)</sup>	4-CH <sub>3</sub>	85–87	63	—	63	250	125
<b>1c</b> <sup>14)</sup>	5-CH <sub>3</sub>	121–122	31	16	125	125	63
<b>1d</b> <sup>14)</sup>	5-C <sub>3</sub> H <sub>7</sub> <sup>i)</sup>	108–109	500	—	>2000	2000	125
<b>1e</b> <sup>14)</sup>	5-C <sub>4</sub> H <sub>9</sub> <sup>g)</sup>	viscous oil	>2000	—	500	>2000	1000
<b>1f</b> <sup>15)</sup>	5-CH <sub>2</sub> SCH <sub>3</sub>	79–80	250	125	63	500	125
<b>1g</b> <sup>15)</sup>	5-CH <sub>2</sub> OCH <sub>3</sub>	95.5–97	500	—	125	125	125
<b>1h</b> <sup>14)</sup>	5,5-(CH <sub>3</sub> ) <sub>2</sub>	viscous oil	250	—	125	2000	500

<sup>a)</sup> Herbicidal activity and crop safety were evaluated visually three weeks after treatment and depicted by ED<sub>80</sub> (dosage causing damage of 80%) and Ed<sub>0</sub> (dosage causing no damage). <sup>b)</sup> Ds: *Digitalia sanguinalis*. <sup>c)</sup> Sf: *Setaria fberi*. <sup>d)</sup> Ar: *Abutilon theoplasti* <sup>e)</sup> Ar: *Amaranthus retroflexus*. <sup>f)</sup> corn: *Zea mays*.

showed the expected high level of activity against grass weeds such as Ds and Sf, but broadleaf weed Ar activity was extremely decreased, while compounds **2** and **3**, which had a six- or five-membered fused ring, drastically reduced the activity against all weeds. The new bicycloheptane derivative **10a** was the most active against all species among the fused ring compounds. In particular, compound **10a** significantly enhanced activity against broadleaf weeds such as At and Ar, whereas the expected activity against grass weeds was inferior to that of broadleaf weeds, and **10a** showed unacceptable damage to corn.

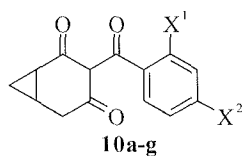
The next attempt focused on the effects of benzoyl substituents against weed activity and safety for corn while fixing

the bicycloheptanedione ring. Table 4 shows the herbicidal activity of various 3-(substituted benzoyl) derivatives of bicyclo[4.1.0]heptane-2,4-dione. Methoxy analogue **10b** remarkably reduced the activity against broadleaf weeds At and Ar, and the damage to corn remained severe. On the other hand, methylthio analogue **10c** improved the safety for corn while maintaining the broadleaf weed activity at a high level. The introduction of methylsulfonyl group **10d** offered safety for corn and showed good activity for broadleaf weeds such as At and Ar, although grass weed activity (Ds and Sf) was comparably poor. The point to notice was that compound **10d** showed corn safety even at the dosage controlling all the tested weed species. Compound **10e** substituted by an elec-

**Table 3.** Herbicidal activity and crop safety of 2-(4-chloro-2-nitrobenzoyl)cyclohexane-1,3-dione derivatives.<sup>a)</sup>

No.	Y <sup>1</sup>	Y <sup>2</sup>	mp (°C)	ED <sub>80</sub> (g a.i./ha)				ED <sub>0</sub> (g a.i./ha) corn
				Ds	Sf	At	Ar	
<b>1i</b> <sup>14)</sup>	CH <sub>3</sub>	CH <sub>3</sub>	viscous oil	31	31	125	500	125
<b>2</b> <sup>16)</sup>	(CH <sub>2</sub> ) <sub>4</sub>		109–112	500	2000	500	2000	500
<b>3</b> <sup>16)</sup>	(CH <sub>2</sub> ) <sub>3</sub>		viscous oil	250	500	500	500	63
<b>10a</b>	CH <sub>2</sub>		132–134	63	125	16	63	16

<sup>a)</sup> For abbreviations, see Table 2.

**Table 4.** Herbicidal activity and crop safety of 3-(substituted benzoyl)bicyclo[4.1.0]heptane-2,4-diones.<sup>a)</sup>

No.	X <sup>1</sup>	X <sup>2</sup>	mp (°C)	ED <sub>80</sub> (g a.i./ha)				ED <sub>0</sub> (g a.i./ha) corn
				Ds	Sf	At	Ar	
<b>10a</b>	NO <sub>2</sub>	Cl	132–134	63	125	16	63	16
<b>10b</b>	NO <sub>2</sub>	OCH <sub>3</sub>	76–81	125	125	125	500	31
<b>10c</b>	NO <sub>2</sub>	SCH <sub>3</sub>	98–100	63	250	16	31	125
<b>10d</b>	NO <sub>2</sub>	SO <sub>2</sub> CH <sub>3</sub>	161–162	125	250	16	63	250
<b>10e</b>	NO <sub>2</sub>	CF <sub>3</sub>	90–92	63	63	16	63	31
<b>10f</b>	Cl	SO <sub>2</sub> CH <sub>3</sub>	146–148	125	63	16	31	125
<b>10g</b>	CH <sub>3</sub>	SO <sub>2</sub> CH <sub>3</sub>	151–153	250	250	16	63	250
sulcotrione			139–141	125	250	16	250	250

<sup>a)</sup> For abbreviations, see Table 2.

tron-withdrawing CF<sub>3</sub> group, provided high level of activity against all weed species, especially grass weeds such as Ds and Sf; however, it caused severe damage to corn.

Then, further investigation of bicycloheptanedione derivatives focused on substituents at the 2-position at benzoyl moiety while retaining the methylsulfonyl group at the 4-position of the benzene ring. 2-Chloro compound **10f** showed a very high level of activity against broadleaf weeds, its activity against grass weed Sf was enhanced in comparison with **10d**, and it exhibited good corn safety. Moreover, as compared with sulcotrione, **10f** showed higher level of activity, especially against grass weed Sf and broadleaf weed Ar. Compound **10g** decreased activity against grass weeds such as Ds and Sf, but corn safety remained.

The results clearly showed that the methylsulfonyl group at 4-position combined with a proper substituent of 2-position of the phenyl ring was suitable for the bicycloheptane system for corn selectivity.

### Conclusions

In synthetic studies on triketone-type herbicides interfering with HPPD, we prepared compounds with introduced substituents at the cyclohexane ring and found the synthetic route of a new bicycloheptanedione skeleton. On herbicidal evaluation of the synthetic compounds, it was found that the introduction of less bulky substituents at the 4- or/and 5-position of the cyclohexane ring increased herbicidal activity, especially against grass weeds such as Ds and Sf. Consequently, it was suggested that the bicycloheptane skeleton was the preferable structure to promote activity. As a result of subsequent SAR studies focused on the benzoyl part fixing the bi-

cycloheptane ring, compound **10f** showed higher herbicidal activity than sulcotrione. Moreover, the damage to corn was within the tolerable range, even at 125 g a.i./ha. We found a new bicycloheptanedione skeleton as part of the triketone-type herbicides, which had potential as a total weed control herbicide in corn fields. Further investigations of synthesis and evaluation in order to increase grass weed activity and improve corn safety are now in progress.

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