Original Article

Novel glycol benzyl ether herbicides: Herbicidal activity of 3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran derivatives

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The structure–activity relationship of novel glycol benzyl ether herbicides, 3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyrans (TFBs), was elucidated. Herbicidal activity against *Echinochloa crus-galli* and rice injury varied with substituents of the benzyloxy group at *C*-3. When substituents other than the benzyloxy group, such as the cyclohexylmethyloxy group or the benzoyloxy group, were introduced, the herbicidal activity of TFBs was reduced. Introduction of an (*S*)-methyl group at *C*-5 increased herbicidal activity but aggravated rice injury. When comparing the herbicidal activity of two stereoisomers, the 5-(*S*)-isomer showed stronger herbicidal activity than the 5-(*R*)-isomer. Even when the benzene ring of the fused ring system of TFB was replaced by thiophene or furan, high herbicidal activity was manifested. In particular, TFB partly replaced by thiophene showed the highest herbicidal activity among all compounds examined in this study, with slight injury to rice plants. The 2,6-dioxabicyclo[3,3,0]octane derivative, produced as a by-product, also showed high herbicidal activity. © Pesticide Science Society of Japan

Keywords: glycol benzyl ether herbicides, 3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyrans, *Echinochloa crus-galli*, structure–activity relationship.

Introduction

Many glycol benzyl ether herbicides, including cinmethylin (Fig. 1, compound **1**)^{1,2)} have been reported. The structural features of these compounds were an oxygen-containing heterocyclic ring with a substituted benzyloxy group. We hypothesized that if the orientation of the oxygen atom in the heterocyclic systems and that of benzyl ether were fixed in a favorable direction for interaction with the binding site by a rigid cyclic system, herbicidal activity could be increased. Chiral cyclic benzyl ethers, which have a rigid cyclic system, were synthesized and their herbicidal activities were examined. As a result, we found that chiral 3,3a,5,9b-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyrans (TFBs, compound **2**, Fig. 1)³⁾ were herbicidally active against annual paddy weeds. Our TFBs are

highly novel compounds synthesized from D-glucose. Of natural TFBs, only monocerin (compound **3**, Fig. 1), an antifungal compound produced by *Helminthosporium monoceras*, has been reported,⁴⁾ and there is no report that TFBs other than TFB **2** show any herbicidal activity.

We reported previously that TFBs with an ethyl group at the *C*-2 position (TFBs **2**, R¹=CH₂CH₃) had high herbicidal activity, while those with a methyl group at the *C*-5 position (TFBs **2**, R²=CH₃), a methyl group at the *C*-6 position or a methoxy group at the *C*-7 position (TFB **2**, Y_n=6-CH₃; TFB **2**, Y_n=7-OCH₃) showed improved herbicidal activity.⁵⁾ This paper reports the structure–activity relationship of TFBs showing the effect of the benzyloxy group at the *C*-3 position, substituents at the *C*-5 position and an aromatic ring on the TFB ring system.

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Fig. 1. Chemical structures of cinmethylin, TFBs and monocerin.

Material and Methods

1. Synthesis of TFBs

1.1. Synthesis of (2*R*,3*S*,3*aS*,9*bR*)-3-(*tert*-butyldimethylsilyloxy)-2-ethyl-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran-5-one (**12**)

To a solution of compound **11**⁶⁾ (6.63 g) in carbon tetrachloride (30 ml), ruthenium oxide (0.79 g), sodium metaperiodate (16.96 g), and water (50 ml) were added. The reaction mixture was stirred for 5 hr at room temperature. After filtration of the reaction mixture through celite, 2-propanol (50 ml) was added to the filtrate, and extracted with dichloromethane. The organic solution was washed with a saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The resulting organic solution was evaporated to dryness and the residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate=5:1) to give compound **12** (6.29 g, 91%) as a yellow syrup. ¹H-NMR δ_H (CDCl₃): 0.16 (6H, s), 0.94 (12H, s), 1.58–1.78 (2H, m), 4.15–4.22 (1H, m), 4.47–4.49 (1H, m), 4.82 (1H, br), 5.06 (1H, d, *J*=3.0 Hz), 7.53–7.66 (3H, m), 8.15–8.18 (1H, m). IR ν_{max} (film) cm⁻¹: 2956, 2883, 2858, 1736, 1608, 1463, 1363, 1264, 1215. Elemental analysis: Found: C, 65.50; H, 8.15%. Calcd. for C₁₉H₂₈O₄Si: C, 65.48; H, 8.10%.

1.2. Synthesis of (2*R*,3*S*,3*aS*,9*bR*)-2-ethyl-3-hydroxy-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran-5-one (**13**)

To a solution of compound **12** (4.58 g) in tetrahydrofuran (50 ml), a solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1 M, 15.8 ml) was added, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was evaporated to dryness under reduced pressure, and the resulting residue was dissolved in ethyl acetate. The organic solution was washed with saturated sodium chloride solution, and dried over anhydrous sodium sulfate. The resulting organic solution was evaporated to dryness and the residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate=2:1) to give compound **13** (2.90 g, 94%) as a white crystal. Mp: 114.8–115.8°C. ¹H-NMR δ_H (CDCl₃): 1.00 (3H, t, *J*=7.3 Hz), 1.65–1.84 (2H, m), 2.23 (1H, d, *J*=4.4 Hz), 4.20–4.26 (1H, m), 4.57–4.60 (1H, m), 4.98–5.00 (1H, m), 5.14 (1H, d, *J*=2.9 Hz), 7.52–7.71 (3H, m), 8.16–8.19 (1H, m). Elemental analysis: Found: C, 66.81; H, 6.11%. Calcd. for C₁₃H₁₄O₄: C, 66.66; H, 6.02%.

1.3. Synthesis of (2*R*,3*S*,3*aS*,9*bR*)-2-ethyl-3-(2-methylbenzyloxy)-3,3*a*,5,9*b*-tetrahydro-2*H*-furo[3,2-*c*][2]benzopyran-5-one (**14**)

To a suspension of sodium hydride (60% oil suspension, 0.49 g) in tetrahydrofuran (10 ml), a solution of compound **13** in tetrahydrofuran (20 ml) was added dropwise under ice cooling. The reaction mixture was stirred at room temperature for 1 hr, tetra-*n*-butylammonium iodide (0.10 g) and 2-methylbenzyl bromide (1.80 g) were added, and the resulting mixture was stirred at room temperature for 3 hr. To the reaction mixture, a diluted hydrogen chloride solution was added under ice cooling, and extracted with ethyl acetate. The organic solution was washed with water and saturated sodium hydrogen carbonate, and dried over anhydrous sodium sulfate. The resulting organic solution was evaporated to dryness and the residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate=5:1) to give compound **14** (2.41 g, 88%) as a pale yellow solid. ¹H-NMR δ_H (CDCl₃): 0.89 (3H, t, *J*=7.3 Hz), 1.75 (2H, dq, *J*=7.3, 7.3 Hz), 2.37 (3H, s), 4.20–4.29 (2H, m), 4.62 (1H, d, *J*=11.7 Hz), 4.73 (1H, d, *J*=11.7 Hz), 5.03–5.09 (2H, m), 7.16–7.54 (7H, m), 8.15 (1H, m). Elemental analysis: Found: C, 74.35; H, 6.64%. Calcd. for C₂₁H₂₂O₄: C, 74.54; H, 6.55%.

1.4. Synthesis of (1*R*,3*R*,4*S*,5*S*,7*R*)-3-ethyl-4-(2-fluorobenzyloxy)-7-methyl-7-phenyl-2,6-dioxabicyclo[3,3,0]octane (**20**)

To a solution of compound **15**⁵⁾ (2.00 g) and α-methylstyrene (1.50 g) in tetrahydrofuran (30 ml), 70% HClO₄ aq. (catalytic amount) was added under ice cooling, and stirred at room temperature for 24 hr. The reaction mixture was neutralized with saturated sodium hydrogen carbonate, and concentrated under reduced pressure. Water was added to the residue, and extracted with ethyl acetate. The extract was washed with water and dried over anhydrous sodium sulfate. The organic solution was washed with water, and saturated sodium hydrogen carbonate, and then dried over anhydrous sodium sulfate. The resulting organic solution was evaporated to dryness and the residue was purified by silica gel column chromatography (*n*-hexane:ethyl acetate=9:1) to give compound **20** (0.19 g, 6%) as a pale yellow syrup. ¹H-NMR δ_H (CDCl₃): 0.84 (3H, t, *J*=7.3 Hz), 1.46 (3H, s), 1.66 (2H, dq, *J*=7.3, 7.3 Hz), 2.15 (1H, dd, *J*=4.4, 13.2 Hz), 2.52 (1H, dd, *J*=7.3, 13.2 Hz), 3.73 (1H, dt, *J*=3.7, 7.3 Hz), 3.93 (1H, d, *J*=3.7 Hz), 4.60 (1H, d, *J*=12.7 Hz), 4.73 (1H, d, *J*=5.1 Hz), 4.83 (1H, d, *J*=12.7 Hz),

Table 1. Physical data of synthesized TFBs

No.	Property	¹ H-NMR δ (CDCl ₃ , 400 MHz)
10	mp 137.0–139.4	0.99 (3H, t, $J=7.3$ Hz), 1.65–1.80 (3H, m), 4.07–4.09 (1H, m), 4.24 (1H, d, $J=3.7$ Hz), 4.28 (1H, br: 1H, d, $J=2.2$ Hz by D ₂ O exchange), 4.61 (1H, d, $J=14.7$ Hz), 4.92 (1H, d, $J=3.7$ Hz), 7.05–7.54 (4H, m).
11	oil	0.14 (3H, s), 0.15 (3H, s), 0.93 (12H, s), 1.62–1.76 (2H, m), 4.00–4.11 (2H, m), 4.21–4.24 (1H, m), 4.63 (1H, d, $J=14.7$ Hz), 4.75 (1H, d, $J=14.7$ Hz), 4.88 (1H, d, $J=2.9$ Hz), 7.03–7.55 (4H, m).
17	oil	0.89 (3H, t, $J=7.3$ Hz), 1.58–1.67 (3H, m), 1.75 (2H, dq, $J=7.3, 7.3$ Hz), 3.45 (1H, d, $J=12.5$ Hz), 3.69 (1H, d, $J=12.5$ Hz), 4.12–4.18 (2H, m), 4.51 (1H, d, $J=2.9$ Hz), 4.67 (1H, d, $J=12.5$ Hz), 4.83 (1H, d, $J=12.5$ Hz), 4.86 (1H, d, $J=2.9$ Hz), 7.02–7.53 (8H, m).
24	oil	0.90 (3H, t, $J=7.3$ Hz), 1.74–1.82 (2H, m), 4.00 (1H, d, $J=3.7$ Hz), 4.10–4.11 (1H, m), 4.31 (1H, d, $J=3.7$ Hz), 4.60 (1H, d, $J=11.7$ Hz), 4.62 (1H, d, $J=14.7$ Hz), 4.74 (1H, d, $J=14.7$ Hz), 4.76 (1H, d, $J=11.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 7.04–7.52 (9H, m).
25	oil	0.90 (3H, t, $J=7.3$ Hz), 1.72–1.80 (2H, m), 4.04 (1H, d, $J=2.9$ Hz), 4.10–4.15 (1H, m), 4.35 (1H, d, $J=3.7$ Hz), 4.64 (1H, d, $J=14.7$ Hz), 4.65 (1H, d, $J=12.5$ Hz), 4.76 (1H, d, $J=12.5$ Hz), 4.83 (1H, d, $J=14.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 7.03–7.52 (8H, m).
26	oil	0.92 (3H, t, $J=7.3$ Hz), 1.77–1.80 (2H, m), 4.01 (1H, d, $J=3.7$ Hz), 4.11–4.16 (1H, m), 4.32 (1H, d, $J=3.7$ Hz), 4.59 (1H, d, $J=11.7$ Hz), 4.62 (1H, d, $J=14.7$ Hz), 4.75 (1H, d, $J=14.7$ Hz), 4.76 (1H, d, $J=11.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 6.95–7.30 (7H, m), 7.52 (1H, d, $J=7.3$ Hz).
27	oil	0.89 (3H, t, $J=7.3$ Hz), 1.72–1.79 (2H, m), 4.00 (1H, d, $J=3.7$ Hz), 4.08–4.12 (1H, m), 4.30 (1H, d, $J=3.7$ Hz), 4.55 (1H, d, $J=11.7$ Hz), 4.62 (1H, d, $J=14.7$ Hz), 4.72 (1H, d, $J=11.7$ Hz), 4.75 (1H, d, $J=14.7$ Hz), 4.88 (1H, d, $J=3.7$ Hz), 7.02–7.36 (7H, m), 7.51 (1H, d, $J=7.3$ Hz).
28	oil	0.93 (3H, t, $J=7.3$ Hz), 1.77–1.85 (2H, m), 4.08 (1H, d, $J=3.0$ Hz), 4.13–4.18 (1H, m), 4.39 (1H, d, $J=2.9$ Hz), 4.65 (1H, d, $J=14.7$ Hz), 4.67 (1H, d, $J=12.5$ Hz), 4.74 (1H, d, $J=14.7$ Hz), 4.86 (1H, d, $J=12.5$ Hz), 4.92 (1H, d, $J=2.9$ Hz), 7.05–7.55 (8H, m).
29	oil	0.87 (3H, t, $J=7.3$ Hz), 1.72–1.80 (2H, m), 2.37 (3H, s), 4.02 (1H, d, $J=3.7$ Hz), 4.08–4.11 (1H, m), 4.33 (1H, d, $J=2.9$ Hz), 4.57 (1H, d, $J=12.5$ Hz), 4.64 (1H, d, $J=13.9$ Hz), 4.75 (1H, dd, $J=12.5, 13.9$ Hz), 4.89 (1H, d, $J=2.9$ Hz), 7.04–7.52 (8H, m).
30	oil	0.88 (3H, t, $J=7.3$ Hz), 1.25 (3H, t, $J=7.3$ Hz), 1.76 (2H, dq, $J=7.3, 7.3$ Hz), 2.71 (2H, dq, $J=7.3, 7.3$ Hz), 4.03 (1H, d, $J=3.7$ Hz), 4.12 (1H, dt, $J=3.7, 7.3$ Hz), 4.34 (1H, d, $J=3.7$ Hz), 4.60 (1H, d, $J=11.7$ Hz), 4.64 (1H, d, $J=13.2$ Hz), 4.76 (1H, d, $J=13.2$ Hz), 4.78 (1H, d, $J=11.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 7.04–7.53 (8H, m).
31	oil	0.95 (3H, t, $J=7.3$ Hz), 1.77–1.83 (2H, m), 4.08 (1H, d, $J=3.7$ Hz), 4.13–4.18 (1H, m), 4.44 (1H, d, $J=3.7$ Hz), 4.65 (1H, d, $J=14.7$ Hz), 4.75 (1H, d, $J=12.5$ Hz), 4.77 (1H, d, $J=14.7$ Hz), 4.91 (1H, d, $J=3.7$ Hz), 4.97 (1H, d, $J=12.5$ Hz), 7.05 (1H, d, $J=7.3$ Hz), 7.24–7.68 (7H, m).
32	oil	0.95 (3H, t, $J=7.3$ Hz), 1.77–1.83 (2H, m), 4.07 (1H, d, $J=3.7$ Hz), 4.16–4.18 (1H, m), 4.36 (1H, d, $J=3.7$ Hz), 4.65 (1H, d, $J=14.7$ Hz), 4.76 (1H, d, $J=11.0$ Hz), 4.77 (1H, d, $J=14.7$ Hz), 4.90 (1H, d, $J=3.7$ Hz), 4.95 (1H, d, $J=11.0$ Hz), 7.06 (1H, d, $J=6.6$ Hz), 7.25–7.59 (5H, m), 7.65 (1H, d, $J=8.1$ Hz), 7.75 (1H, d, $J=8.1$ Hz).
33	oil	0.72–1.03 (3H, m), 1.48–1.51 (3H, m), 1.62–1.88 (2H, m), 3.78–4.16 (3H, m), 4.33–4.94 (4H, m), 6.07–7.56 (9H, m).
34	oil	0.96 (3H, t, $J=7.3$ Hz), 1.67–1.75 (2H, m), 2.04–2.20 (1H, m), 2.38–2.51 (1H, m), 2.77–2.87 (1H, m), 3.03–3.16 (1H, m), 4.07–4.38 (3H, m), 4.59–4.82 (2H, m), 4.87–4.91 (1H, m), 5.05–5.14 (1H, m), 7.05–7.54 (8H, m).

Table 1. (Continued)

No.	Property	$^1\text{H-NMR } \delta$ (CDCl_3 , 400 MHz)
35	oil	0.88 (3H, t, $J=7.3$ Hz), 1.74 (2H, dq, $J=7.3$, 7.3 Hz), 4.02–4.06 (1H, m), 4.07–4.12 (1H, m), 4.26 (1H, d, $J=7.3$ Hz), 4.61 (1H, d, $J=14.7$ Hz), 4.73 (1H, d, $J=14.7$ Hz), 4.77 (1H, d, $J=12.5$ Hz), 4.88 (1H, d, $J=3.7$ Hz), 4.89 (1H, d, $J=12.5$ Hz), 6.97–7.06 (3H, m), 7.23–7.32 (3H, m), 7.49–7.53 (1H, m).
36	oil	0.89 (3H, t, $J=7.3$ Hz), 1.75 (2H, dq, $J=7.3$, 7.3 Hz), 4.00 (1H, d, $J=2.9$ Hz), 4.04–4.12 (1H, m), 4.27 (1H, d, $J=2.9$ Hz), 4.62 (1H, d, $J=14.7$ Hz), 4.63 (1H, d, $J=14.7$ Hz), 4.73 (1H, d, $J=14.7$ Hz), 4.76 (1H, d, $J=12.5$ Hz), 4.88 (1H, d, $J=3.7$ Hz), 7.03–7.09 (2H, m), 7.23–7.33 (4H, m), 7.50–7.53 (1H, m).
37	oil	0.93 (3H, t, $J=7.3$ Hz), 1.75 (2H, dq, $J=7.3$, 7.3 Hz), 4.01 (1H, d, $J=3.7$ Hz), 4.12 (1H, dq, $J=6.6$, 2.9 Hz), 4.34 (1H, d, $J=3.7$ Hz), 4.58 (1H, d, $J=12.5$ Hz), 4.63 (2H, d, $J=12.5$ Hz), 4.74 (1H, d, $J=12.5$ Hz), 4.76 (1H, d, $J=12.5$ Hz), 4.87 (1H, d, $J=2.9$ Hz), 7.00–7.70 (11H, m), 8.38 (1H, d, $J=1.5$ Hz).
38	oil	0.72 (3H, t, $J=7.3$ Hz), 1.71 (2H, dq, $J=7.3$, 7.3 Hz), 4.09 (1H, d, $J=3.7$ Hz), 4.10 (1H, dt, $J=3.7$, 7.3 Hz), 4.34 (1H, d, $J=3.7$ Hz), 4.61 (1H, d, $J=14.7$ Hz), 4.73 (2H, d, $J=14.7$ Hz), 4.90 (1H, d, $J=3.7$ Hz), 5.01 (1H, d, $J=12.5$ Hz), 5.23 (1H, d, $J=12.5$ Hz), 7.02–7.57 (8H, m), 7.81–7.88 (2H, m), 8.11–8.15 (1H, m).
39	oil	0.89–1.83 (16H, m), 3.29 (1H, dd, $J=6.6$, 8.8 Hz), 3.48 (1H, dd, $J=5.9$, 8.8 Hz), 3.83 (1H, d, $J=3.7$ Hz), 4.08–4.11 (1H, m), 4.24 (1H, d, $J=3.7$ Hz), 4.63 (1H, d, $J=14.7$ Hz), 4.74 (1H, d, $J=14.7$ Hz), 4.84 (1H, d, $J=2.9$ Hz), 7.04–7.52 (4H, m).
40	oil	0.96 (3H, t, $J=7.3$ Hz), 1.68–1.89 (2H, m), 4.30–4.33 (1H, m), 4.37 (1H, d, $J=3.7$ Hz), 4.64 (1H, d, $J=14.7$ Hz), 4.80 (1H, d, $J=14.7$ Hz), 4.98 (1H, d, $J=3.7$ Hz), 5.60 (1H, d, $J=2.9$ Hz), 7.07–7.62 (7H, m), 8.08–8.12 (2H, m).
41	oil	0.94 (3H, t, $J=7.3$ Hz), 1.57–1.73 (2H, m), 2.15 (3H, s), 4.17–4.22 (1H, m), 4.24 (1H, d, $J=3.7$ Hz), 4.60 (1H, d, $J=14.7$ Hz), 4.75 (1H, d, $J=14.7$ Hz), 4.87 (1H, d, $J=3.7$ Hz), 5.35 (1H, d, $J=2.9$ Hz), 7.05–7.53 (4H, m).
42	oil	0.90 (3H, t, $J=7.3$ Hz), 1.59 (3H, d, $J=6.6$ Hz), 1.77 (2H, dq, $J=7.3$, 7.3 Hz), 4.05 (1H, d, $J=3.7$ Hz), 4.15 (1H, dt, $J=3.7$, 7.3 Hz), 4.41 (1H, d, $J=2.9$ Hz), 4.64 (1H, q, $J=6.6$ Hz), 4.66 (1H, d, $J=12.7$ Hz), 4.83 (1H, d, $J=12.7$ Hz), 4.88 (1H, d, $J=2.9$ Hz), 7.02–7.52 (8H, m).
43	oil	0.90 (3H, t, $J=7.3$ Hz), 1.50 (3H, d, $J=6.6$ Hz), 1.76 (2H, dq, $J=7.3$, 7.3 Hz), 4.02 (1H, d, $J=3.7$ Hz), 4.11 (1H, dt, $J=3.7$, 7.3 Hz), 4.56 (1H, d, $J=3.7$ Hz), 4.67 (1H, d, $J=11.7$ Hz), 4.81 (1H, d, $J=11.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 4.89 (1H, d, $J=3.7$ Hz), 5.00 (1H, q, $J=6.6$ Hz), 7.03–7.49 (8H, m).
44	oil	0.91 (3H, t, $J=7.3$ Hz), 0.97 (3H, t, $J=7.3$ Hz), 1.72–1.92 (3H, m), 2.04–2.17 (1H, m), 4.05 (1H, d, $J=3.7$ Hz), 4.11–4.18 (1H, m), 4.36 (1H, d, $J=3.7$ Hz), 4.54 (1H, dd, $J=3.7$, 6.6 Hz), 4.66 (1H, d, $J=11.7$ Hz), 4.82 (1H, d, $J=11.7$ Hz), 4.86 (1H, d, $J=3.7$ Hz), 7.01–7.52 (8H, m).
45	oil	0.88 (3H, t, $J=7.3$ Hz), 1.11 (3H, t, $J=7.3$ Hz), 1.57–1.89 (4H, m), 4.00 (1H, d, $J=3.7$ Hz), 4.09 (1H, dt, $J=3.7$, 7.3 Hz), 4.48 (1H, d, $J=3.7$ Hz), 4.64 (1H, dd, $J=3.7$, 11.0 Hz), 4.68 (1H, d, $J=12.5$ Hz), 4.79 (1H, d, $J=12.5$ Hz), 4.87 (1H, d, $J=3.7$ Hz), 7.01–7.51 (8H, m).
46	oil	0.87 (3H, t, $J=7.3$ Hz), 1.59 (3H, d, $J=6.6$ Hz), 1.72–1.80 (2H, m), 2.36 (3H, s), 4.02 (1H, d, $J=3.6$ Hz), 4.09–4.15 (1H, m), 4.38 (1H, d, $J=3.6$ Hz), 4.56 (1H, d, $J=11.7$ Hz), 4.64 (1H, q, $J=6.6$ Hz), 4.76 (1H, d, $J=11.7$ Hz), 4.87 (1H, d, $J=3.6$ Hz), 7.13–7.52 (8H, m).
47	oil	0.90 (3H, t, $J=7.3$ Hz), 1.75 (2H, dq, $J=7.3$, 7.3 Hz), 4.04 (1H, d, $J=3.7$ Hz), 4.20 (1H, d, $J=3.7$, 7.3 Hz), 4.29 (1H, d, $J=3.7$ Hz), 4.60 (1H, d, $J=14.7$ Hz), 4.64 (1H, d, $J=12.5$ Hz), 4.81 (1H, d, $J=12.5$ Hz), 4.83 (1H, d, $J=14.7$ Hz), 5.00 (1H, d, $J=3.7$ Hz), 6.78 (1H, d, $J=5.1$ Hz), 7.02–7.09 (1H, m), 7.12–7.18 (1H, m), 7.26–7.34 (2H, m), 7.42–7.47 (1H, m).
48	oil	0.89 (3H, t, $J=7.3$ Hz), 1.75 (2H, dq, $J=7.3$, 7.3 Hz), 4.02 (1H, d, $J=3.7$ Hz), 4.12–4.18 (1H, m), 4.28 (1H, d, $J=2.9$ Hz), 4.65 (1H, d, $J=11.7$ Hz), 4.71 (1H, d, $J=14.7$ Hz), 4.81 (1H, d, $J=11.7$ Hz), 4.90 (1H, d, $J=2.9$ Hz), 4.91 (1H, d, $J=14.7$ Hz), 7.42–7.48 (1H, m), 7.02–7.31 (5H, m), 7.42–7.42 (1H, m).

No.	Property	$^1\text{H-NMR } \delta$ (CDCl_3 , 400 MHz)
50	oil	0.86 (3H, t, $J=7.3$ Hz), 1.73 (2H, dq, $J=7.3$, 7.3 Hz), 2.36 (3H, s), 4.01 (1H, d, $J=3.7$ Hz), 4.11–4.16 (1H, m), 4.26 (1H, d, $J=2.9$ Hz), 4.56 (1H, d, $J=11.7$ Hz), 4.70 (1H, d, $J=14.7$ Hz), 4.75 (1H, d, $J=11.7$ Hz), 4.91 (1H, d, $J=14.7$ Hz), 4.89 (1H, d, $J=2.9$ Hz), 7.13–7.24 (5H, m), 7.35–7.38 (1H, m).
51	oil	0.87 (3H, t, $J=7.3$ Hz), 1.74 (2H, dq, $J=7.3$, 7.3 Hz), 2.35 (3H, s), 3.97 (1H, d, $J=2.9$ Hz), 4.16–4.23 (1H, m), 4.27 (1H, d, $J=2.9$ Hz), 4.54 (1H, d, $J=11.7$ Hz), 4.56 (1H, d, $J=13.9$ Hz), 4.70 (1H, d, $J=13.9$ Hz), 4.73 (1H, d, $J=11.7$ Hz), 4.89 (1H, d, $J=2.9$ Hz), 6.23 (1H, d, $J=2.2$ Hz), 7.15–7.26 (3H, m), 7.33–7.39 (2H, m).

5.05–5.09 (1H, m), 7.03–7.46 (9H, m). Elemental analysis: Found: C, 74.25; H, 6.98%. Calcd. for $\text{C}_{22}\text{H}_{25}\text{FO}_3$: C, 74.13; H, 7.07%.

1.5. Synthesis of (2*R*,3*S*,3*aS*,8*bS*)-2-ethyl-3-(2-methylbenzyloxy)-3,3*a*,5,8*b*-tetrahydro-2*H*-thieno[2,3-*d*]furo[3,2-*b*]pyran (49)

To a solution of ethyl 5-deoxy-5-*C*-methyl-3-*O*-(2-methylbenzyl)-2-*O*-[(3-thienyl)methyl]- D -xylofranoside (1.00 g) in dichloromethane (10 ml), trifluoroacetic acid (1.0 g) was slowly added dropwise at 0°C . The mixture was stirred for 3 hr at room temperature. The reaction mixture was poured into a cold saturated sodium hydrogen carbonate solution, extracted with dichloromethane and dried over anhydrous magnesium sulfate. The resulting organic solution was evaporated to dryness and the residue was purified by silica gel column chromatography (*n*-hexane: ethyl acetate=10:1) to give TFB 49 (0.76 g, 83%) as a pale yellow syrup. $^1\text{H-NMR } \delta_{\text{H}}$ (CDCl_3): 0.87 (3H, t, $J=7.3$ Hz), 1.75 (2H, dq, $J=7.3$, 7.3 Hz), 2.36 (3H, s), 4.02 (1H, d, $J=2.9$ Hz), 4.16–4.23 (1H, m), 4.27 (1H, d, $J=2.9$ Hz), 4.55 (1H, d, $J=11.7$ Hz), 4.59 (1H, d, $J=13.9$ Hz), 4.75 (1H, d, $J=11.7$ Hz), 4.83 (1H, d, $J=13.9$ Hz), 5.00 (1H, d, $J=2.9$ Hz), 6.78 (1H, d, $J=5.1$ Hz), 7.15–7.30 (4H, m), 7.34–7.37 (1H, m). Elemental analysis: Found: C, 69.23; H, 6.68%. Calcd. for $\text{C}_{19}\text{H}_{22}\text{O}_3\text{S}$: C, 69.06; H, 6.71%.

1.6. Other TFBs

The other TFBs were prepared according to the reported procedure.^{3,5–7} $^1\text{H-NMR}$ spectra of synthesized compounds are listed in Table 1.

2. Analytical method

All melting points were uncorrected. $^1\text{H-NMR}$ spectra were measured with a JEOL JNM-A400 FT-NMR system at 400 MHz, using tetramethylsilane as an internal standard.

3. Basic herbicidal activities of TFBs

Basic herbicidal activities of TFBs against *Echinochloa crus-galli* were evaluated by the procedure reported previously.⁵⁾

4. Post-emergence herbicidal activities of TFBs

Post-emergence herbicidal activities of TFBs against *E. crus-galli* and rice injuries were examined according to the reported procedure.⁵⁾

Results and Discussion

1. Synthesis of TFBs

In order to examine the effect of substituents (R) at the *C*-3 position on herbicidal activity, TFBs were synthesized with a different substituent (R). The hydroxyl group of diacetone- D -glucose 4 was modified with various alkylating and acylating agents to give ether 5. Ether 5 was converted to diether 7 by five processes. The intramolecular cyclization⁸⁾ of diether 7 by Lewis acid gave TFB 8 (Fig. 2).

To elucidate the effect of substituents (R^2) at the *C*-5 position on herbicidal activity, TFBs were synthesized with a different substituent (R^2). TFBs with a single substituent (R^2) at the *C*-5 position were synthesized using the method shown in Fig. 2. 5-Keto-TFB 14 was synthesized by the method shown in Fig. 3. TFB 9, produced by the method shown in Fig. 2, un-

Fig. 2. General synthetic route of TFBs 8.

Fig. 3. Synthesis of TFB 14.

derwent deprotection of a benzoyl group to give alcohol **10**, followed by protection with a *tert*-butyldimethylsilyl (TBDMS) group to give silyl ether **11**. Silyl ether **11** was oxidized in the presence of RuO_2 and NaIO_4 to give lactone **12**. After deprotection of the TBDMS group with TBAF,⁹⁾ lactone **13** thus prepared was alkylated to give TFB **14**.

In order to synthesize TFB with a *gem*-dimethyl group at the *C*-5 position, alcohol **15** and α -methylstyrene were reacted in the presence of NBS and HClO_4 ,¹⁰⁾ to prepare benzyl ether **16**, which was then cyclized by Lewis acid to prepare TFB **17**. Although TFB **17** was subjected to the reductive dehalogenation of a bromomethyl group using tri-*n*-butyltin hydride¹¹⁾ and lithium aluminium hydride, the target TFB **19** was not obtained. Condensation of alcohol **15** and α -methylstyrene in the presence of HClO_4 ¹²⁾ did not give the target compound **18**. Instead, 2,6-dioxabicyclo[3,3,0]octane **20** with (*R*)-configuration at the *C*-7 position was obtained¹³⁾ (Fig. 4).

It is considered that this intramolecular cyclization progresses *via* an intermediate, a formed oxonium cation **21** to which α -methylstyrene is added. There are two possible intermediates, **22** and **23**. In intermediate **22**, the protons at the *C*-1 position of the sugar moiety and at the benzene ring cause steric hindrance. It was estimated, therefore, that the intramolecular cyclization progresses *via* intermediate **23** due to the absence of such steric hindrance, and only 2,6-dioxabicyclo[3,3,0]octane **20** having the (*R*)-configuration was obtained (Fig. 5).

TFB with a heterocycle instead of benzene in the TFB ring

system was synthesized, as with the compound with the benzene ring, by intramolecular cyclization using an acidic catalyst.¹³⁾

2. Herbicidal activity against *E. crus-galli* and rice injury of synthesized TFBs

The effect of the substituents (*R*) of the benzyl group at the *C*-3 position on herbicidal activity was examined (Table 2). TFB **10** (*R*=H) did not show herbicidal activity even at the highest rate. Focusing on the effects of substituents on the benzene ring of the benzyl group, compounds with a substituted benzyl group showed high activity, with an MIC lower than 1 ppm, in the basic herbicidal activity test, except TFB **31** (*R*=2-cyanobenzyl). The post-emergence herbicidal activities of TFB **25** (*R*=2-fluorobenzyl), **26** (*R*=3-fluorobenzyl), **27** (*R*=4-fluorobenzyl), **28** (*R*=2-chlorobenzyl) and **29** (*R*=2-methylbenzyl) were comparable to or higher than that of TFB **24** (*R*=benzyl). Furthermore, rice injury caused by TFBs **25**, **26**, **27** and **28** was reduced as compared with non-substituted **24**. It seemed that the introduction of a halogen atom on the benzene ring of the benzyloxy group was effective for reducing rice injury. The position-specific effect of the ring substituents was examined. In the case of fluorine derivatives, post-emergence activity of 2-F analog **25** was lower than that of 3-F analog **26** and 4-F analog **27**, but rice injury of **25** was more severe. Meanwhile, the α -substituted TFBs **33** and **34** did not enhance post-emergence herbicidal activity.

When a substituent (*R*) other than the benzyl group was in-

Fig. 4. Reaction of alcohol **15** with α -methylstyrene.

Fig. 5. Proposed mechanism of reaction of **15** and α -methylstyrene.

roduced at the *C*-3 position, the post-emergence herbicidal activity of all compounds listed in Table 3 was obviously inferior to that of TFB **24**, although TFBs **35** [R=(2-thienyl)-methyl] and **36** [R=(3-thienyl)methyl] retained high basic herbicidal activity with an MIC lower than 1 ppm.

The effect of substituent (R^2) at the *C*-5 position and its stereochemistry on herbicidal activity was examined (Table 4). Fixing substituent (X_n) as 2-F, the sequence of post-emergence activity of substituent (R^2) was (*S*)-Me>H (non-substituted)=(*R*)-Me>(*S*)-Et>(*R*)-Et. (*S*)-Isomers are likely to be

Table 2. Effects of substituent R on herbicidal activity and rice injury

No.	Substituent R	MIC (ppm)	Herbicidal activity ^{a)}			Rice injury ^{a)}	
			30 g a ⁻¹	3 g a ⁻¹	1 g a ⁻¹	30 g a ⁻¹	10 g a ⁻¹
10	H	NT ^{b)}	0	0	0	0	0
24	benzyl	0.4	5	4	3	5	3
25	2-fluorobenzyl	0.2	5	4	3	3	1
26	3-fluorobenzyl	0.3	5	5	3	0	0
27	4-fluorobenzyl	1.0	5	5	3	1	0
28	2-chlorobenzyl	0.2	5	4	NT	0	0
29	2-methylbenzyl	0.4	5	5	3	5	3
30	2-ethylbenzyl	0.6	5	3	NT	0	0
31	2-cyanobenzyl	3.2	5	0	0	0	0
32	2-CF ₃ -benzyl	0.4	5	1	0	0	0
33	α -methylbenzyl	3.0	5	2	NT	0	0
34	1-indanyl	0.3	5	2	NT	0	0

^{a)} Index: 5; growth rate 0–5% (dead), 4; growth rate 6–10% (severe), 3; growth rate 11–40% (medium), 2; growth rate 41–70% (small), 1; growth rate 71–90% (slight), 0; growth rate 91–100% (no damage). ^{b)} Not tested.

Table 3. Effects of substituent R (except substituted benzyl group) on herbicidal activity and rice injury

No.	Substituent R	MIC (ppm)	Herbicidal activity ^{a)}			Rice injury ^{a)}	
			30 g a ⁻¹	3 g a ⁻¹	1 g a ⁻¹	30 g a ⁻¹	10 g a ⁻¹
24	benzyl	0.4	5	4	3	5	3
35	(2-thienyl)methyl	0.8	5	3	0	0	0
36	(3-thienyl)methyl	0.3	5	1	NT ^{b)}	0	0
37	(2-naphthyl)methyl	>10.0	0	0	0	0	0
38	(1-naphthyl)methyl	10.0	0	0	0	0	0
39	cyclohexylmethyl	10.0	3	0	NT	0	0
40	benzoyl	3.3	4	0	NT	0	0
41	acetyl	80	0	0	0	0	0
11	TBDMS	>100	0	0	0	0	0

^{a)} See Table 2. ^{b)} Not tested.

more favorable for potentiating activity than (*R*)-isomers. The basic herbicidal activity of the 5-(*S*)-methyl isomer **42** was comparable to that of TFB **25** ($R^2=H$), but post-emergence herbicidal activity was dramatically improved. Although 5-(*R*)-methyl isomer **43** had the same post-emergence herbicidal

activity as that of TFB **25**, it caused severe injury to rice plants. The herbicidal activity of 5-disubstituted analog **17** was decreased in both tests. In comparison with TFB **29**, 5-(*RS*)-methyl analog **46** showed higher post-emergence herbicidal activity with an MIC value of 0.2 ppm. It was suggested

Table 4. Effects of substituent R^2 on herbicidal activity and rice injury

No.	X_n	R^2	MIC (ppm)	Herbicidal activity ^{a)}			Rice injury ^{a)}	
				30 g a ⁻¹	3 g a ⁻¹	1 g a ⁻¹	30 g a ⁻¹	10 g a ⁻¹
24	H	H	0.4	5	4	3	5	3
25	2-F	H	0.2	5	4	3	3	1
29	2-Me	H	0.4	5	5	3	5	3
42	2-F	(<i>S</i>)-Me	0.2	5	5	5	5	3
43	2-F	(<i>R</i>)-Me	0.7	5	4	3	5	0
44	2-F	(<i>S</i>)-Et	0.4	5	3	0	5	NT
45	2-F	(<i>R</i>)-Et	0.8	5	0	0	1	NT
17	2-F	Me, CH ₂ Br	>3.0	5	1	NT	0	0
46	2-Me	(<i>RS</i>)-Me	0.2	5	5	4	3	3
14	2-Me	=O	3.0	3	NT ^{b)}	NT	0	0
20	Bicyclo[3,3,0]octane		0.1	5	4	NT	4	0

^{a)} See Table 2. ^{b)} Not tested.

Table 5. Effects of aromatic ring of TFB ring on herbicidal activity and rice injury

No.	Structure	MIC (ppm)	Herbicidal activity ^{a)}			Rice injury ^{a)}	
			30 g a ⁻¹	3 g a ⁻¹	1 g a ⁻¹	30 g a ⁻¹	10 g a ⁻¹
25		0.2	5	4	3	3	1
29		0.4	5	5	3	5	3
47		0.1	5	5	4	5	4
48		0.3	5	5	4	0	0
49		0.1	5	5	4	0	0
50		0.7	5	3	NT ^{b)}	0	0
51		0.2	4	2	0	1	0
1	Cinmethylin	0.1	5	5	5	3	2

^{a)} See Table 2. ^{b)} Not tested.

that introduction of an (*S*)-methyl group at C-5 was most favorable for post-emergence herbicidal activity. Carbonyl analog **14** showed a marked reduction in both activities as compared with TFB **29**. 2,6-Dioxabicyclo[3,3,0]octane **20**, pro-

duced as a by-product, showed high post-emergence herbicidal activity, but it caused significant injury to rice plants.

In order to examine the effect of the benzene ring part of the TFB ring system on herbicidal activity, the benzene ring

was replaced by the heterocyclic ring, which is likely to be biologically isosteric to the benzene ring (Table 5). Thiophene analog **47–50** and furan analog **51** showed high basic herbicidal activity with an MIC lower than 1 ppm. Thiophene analog **47–49** also showed high post-emergence herbicidal activity. Considering basic herbicidal activity, **47** and **49**, whose sulfur atoms of the thiophene ring were located on the same side of the oxygen atoms of furan ring, showed more potent herbicidal activity than **48** and **50**, whose sulfur atoms were located on the opposite side of oxygen atoms. The post-emergence herbicidal activity of furan isomer **51** was lower than those of the corresponding benzene-ring analog **29** and thiophene analogs **47–49**. Of all compounds examined in this study, thiophene analog **49**, in particular, exhibited the most suitable property as a rice herbicide, with high herbicidal activity and rice plant safety. The basic activity of thiophene analog **49** was identical to that of cinmethylin **1**, but the post-emergence herbicidal activity of **49** was still inferior to that of cinmethylin. In contrast, no rice injury was caused by **49** even at the highest rate, while cinmethylin showed severe rice injury.

Conclusion

It was revealed that while substituents on the benzene ring of the benzyloxy group at the C-3 position did not contribute to a significant improvement of herbicidal activity, halogen substituents contributed to reducing rice injury. It is known that the (*S*)-methyl group at the C-5 position contributed to a remarkable improvement of herbicidal activity, with an unfavorable tendency to aggravate rice injury. When the benzene ring of the TFB ring system was replaced with the thiophene ring, the biological properties of TFBs **48** and **49** for a rice herbicide were superior to their benzene analogs **25** and **29**, respectively.

The concept in designing TFBs was to generate herbicidal activity by fixing the distance between the oxygen atom of benzyl ether and that of the heterocyclic ring by means of a chiral and rigidly condensed ring. It is interesting that 2,6-dioxabicyclo[3,3,0]octane **20** and thieno[2,3-*d*]furo[3,2-*b*]pyran **49** show herbicidal activity because our concept in designing TFB is applicable to these compounds. As well as TFBs, **20** and **49** are novel compounds, different from hitherto

reported glycol benzyl ether herbicides,^{14–16} and we intend to establish their structure–activity relationships using related compounds for synthesis.

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