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Regular Article

Synthesis and herbicidal activity of optically active cinmethylin, its enantiomer, and C3-substituted cinmethylin analogs

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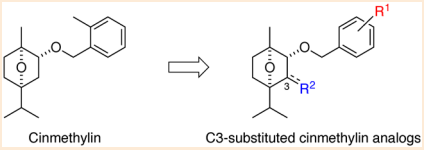
Supplementary material

We investigated the synthesis and herbicidal activity of optically active cinmethylin, its enantiomer, and C3-substituted cinmethylin analogs. Optically active cinmethylin could be obtained in seven steps with the Sharpless asymmetric dihydroxylation of *α*-terpinene. The synthesized cinmethylin and its enantiomer showed similar herbicidal activity, which was independent of the stereochemistry. Next, we synthesized cinmethylin analogs with various substituents at the C3 position. We found that analogs with methylene, oxime, ketone, or methyl groups at the C3 position show excellent herbicidal activity.



Keywords: cinmethylin, herbicidal activity, 1,4-cineole, fatty acid thioesterases.

Introduction

Cinmethylin (**1**), which is derived by adding a benzyl ether moiety to the C2 position of 1,4-cineole (**2**), was developed by Shell plc in the early 1980s as an herbicide for grass weeds, and has been on the market for about 40 years (Fig. 1).[1,2] The environment around herbicides in agricultural producing countries has changed over the past 40 years, and in recent years the emergence of weeds that have acquired resistance to herbicides through repeated use of the same chemical class of herbicides has become a serious problem. Cinmethylin is an herbicide that has sparked intense interest because no other herbicide of the same chemical class has yet been developed. In 2018, Campe *et al.* attributed the herbicidal activity of cinmethylin to fatty acid thioesterases, the mechanism of which differs from that of other lipid synthesis inhibitors.[3] Then, cinmethylin has been redeveloped by BASF.[4] The herbicide has been introduced to cereal crops in Australia, where it shows good efficacy against *Lolium rigidum* and other species that have developed resistance to other herbicides.[5] At present, the global application of cinmethylin, especially in Europe, is under consideration owing to its potential benefits in resistance management.

Payne *et al.*[1,2] and Allan *et al.*[6] reported the synthesis of racemic cinmethylin, and Ditrich *et al.*[4] reported the synthesis of optically active cinmethylin. However, the available herbicidal activity studies only consider racemic form, and no report on optically active form has yet been published. Therefore, the biological activity of enantiomeric form deserves further investigation. In this study, we synthesized the optically active cinmethylin by novel synthetic method and tested its herbicidal activity. We also studied the synthesis and herbicidal activity of novel cinmethylin analogs with a substituent introduced at the C3 position using a synthetic intermediate.

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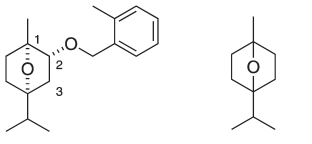


Fig. 1. Structures of cinmethylin (**1**) and 1,4-cineole (**2**)

Materials and methods

*1. Synthesis of optically active (−)-cinmethylin [(−)-**1**]*

*1.1. (1S,2R)-4-Isopropyl-1-methylcyclohex-3-ene-1,2-diol (**4**)*

To a solution of AD-mix-β (40.0 g) in *t*-BuOH (100 mL) and H_2O (100 mL) was added methanesulfonamide (2.69 g, 28.3 mmol). After being stirred at 0°C for 10 min, α-terpinene (**3**) (5.10 mL, 28.3 mmol) added. The mixture was stirred at 0°C for 17 hr and was added Na_2SO_3 (15.0 g). The resulting mixture was extracted with EtOAc three times, and the combined extracts were dried over $MgSO_4$. After removal of solvent, the residue was purified by chromatography on silica gel (hexane/EtOAc) to give diol **4** (3.24 g, 67%): 73% ee determined by HPLC analysis of mono-MTPA ester [Chiralcel OD-H, 0.5% *i*-PrOH/hexane, 1.0 mL/min, t_R/min=8.4 [(−)-isomer, major], 12.3 [(+)-isomer, minor]]; R_f=0.22 (hexane/EtOAc=3:1); $[\alpha]_D^{22}$ −43.5 (*c* 1.01, $CHCl_3$); IR (KBr) 3366, 2960, 1418, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J*=6.8 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.21 (s, 3H), 1.56–1.64 (m, 1H), 1.80 (ddd, *J*=13.2, 7.5, 5.9, 1H), 1.95–2.04 (m, 2H), 2.12–2.27 (m, 2H), 2.29 (s, 1H), 3.80 (d, *J*=5.2 Hz, 1H), 5.43–5.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.35, 21.42, 24.4, 24.5, 32.4, 34.5, 70.1, 71.8, 119.6, 147.8; HRMS (FD) calcd for $C_{10}H_{18}O_2$ $[M]^+$ 170.13068, found 170.13031.

*1.2. (1R,2R,3S,6R)-2-[(tert-Butyldimethylsilyl)oxy]-6-isopropyl-3-methyl-7-oxabicyclo[4.1.0]heptan-3-ol (**5**)*

To a solution of diol **4** (1.37 g, 8.02 mmol) in DMF (80 mL) were added imidazole (1.37 g, 20.1 mmol) and TBSCl (2.42 g, 16.0 mmol). After being stirred at room temperature for 10 hr, the mixture was diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give the crude silyl ether, which was used for the next reaction without further purification.

To a solution of the above silyl ether in CH_2Cl_2 (80 mL) was added *m*-CPBA (70% in H_2O, 2.37 g, 9.62 mmol). The mixture was stirred at room temperature for 5 hr and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give epoxide **5** (1.24 g, 51%): R_f=0.45 (hexane/EtOAc=15:1); $[\alpha]_D^{19}$ −16.6 (*c* 0.994, $CHCl_3$); IR (neat) 3565, 2961, 1259, 1094, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.18 (s, 3H), 0.955 (s, 9H), 0.957 (d, *J*=6.8 H, 3H), 0.98 (d, *J*=6.8 H, 3H), 1.09 (s, 3H), 1.22–1.34 (m, 1H), 1.47–1.56 (m, 2H), 1.64–1.72 (m, 1H), 2.04 (ddd, *J*=14.6, 12.4, 5.4 Hz, 1H), 2.57 (d, *J*=2.4 Hz, 1H), 2.63 (s, 1H), 3.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.3, 17.6, 18.1, 18.4, 18.7, 25.9 (3C), 27.9, 28.2, 34.4, 61.3, 65.3, 68.0, 73.1; HRMS (FI) calcd for $C_{16}H_{33}O_3Si_1$ $[M+H]^+$ 301.21990, found 301.221933.

*1.3. (1S,2R,3R,4S)-3-[(tert-Butyldimethylsilyl)oxy]-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptan-2-ol (**6**)*

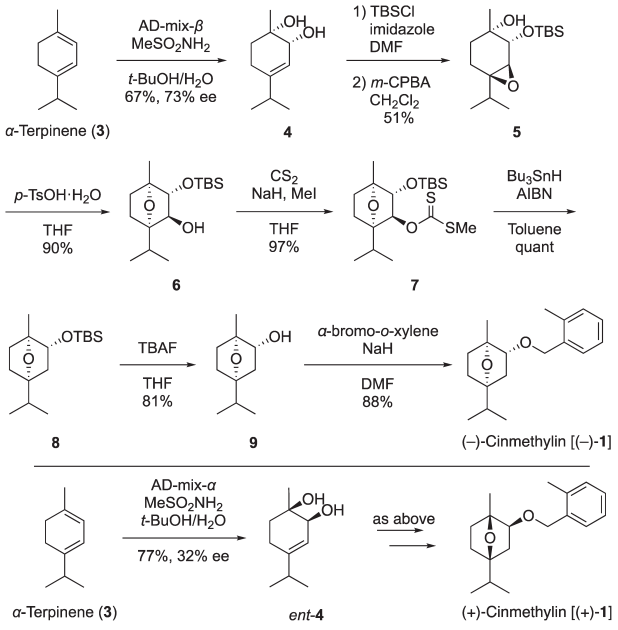
To a solution of epoxide **5** (880 mg, 2.93 mmol) in THF (30 mL) was added *p*-TsOH·H_2O (557 mg, 2.93 mmol). The resulting mixture was stirred at room temperature for 2.5 hr and diluted with saturated $NaHCO_3$. The mixture was extracted with EtOAc three times, and the combined extracts were dried over $MgSO_4$. After removal of solvent, the residue was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **6** (793 mg, 90%): R_f=0.43 (hexane/EtOAc=10:1); $[\alpha]_D^{23}$ −9.41 (*c* 1.02, $CHCl_3$): IR (neat) 3465, 1463, 1258 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.92 (s, 9H), 0.97 (d, *J*=6.8 Hz, 3H), 0.99 (d, *J*=6.8 Hz, 3H), 1.29 (s, 3H), 1.40–1.51 (m, 1H), 1.52–1.62 (m, 3H), 2.02–2.10 (m, 2H), 3.50 (s, 1H), 3.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.4, 16.9, 18.1, 18.3, 24.4, 25.9 (3C), 32.0 (2C), 34.3, 85.6, 85.7, 86.0, 89.0; HRMS (FI) calcd for $C_{16}H_{32}O_3Si_1$ $[M]^+$ 300.21207 found 300.21241.

*1.4. O-[(1S,3R,4S)-3-[(tert-Butyldimethylsilyl)oxy]-1-isopropyl-4-methyl-7-oxabicyclo[2.2.1]heptan-2-yl]S-methyl carbonodithioate (**7**)*

To an ice-cold solution of alcohol **6** (1.00 g, 3.33 mmol) in THF (33 mL) was added NaH (55% dispersion in mineral oil, 290 mg, 6.65 mmol). After being stirred at room temperature for 1 hr, CS_2 (0.40 mL, 6.65 mmol) was added. After being stirred at room temperature for 1.5 hr, MeI (0.42 mL, 6.65 mmol) was added. The mixture was stirred at room temperature for 12 hr and concentrated. The residue was added water and then extracted with EtOAc twice. The combined extracts were concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give dithioester **6** (1.26 g, 97%): R_f=0.70 (hexane/EtOAc=10:1); $[\alpha]_D^{28}$ −4.60 (*c* 1.04, $CHCl_3$); IR (neat) 2959, 1471, 1217, 1079 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.89 (s, 9H), 0.92 (d, *J*=6.8 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H), 1.34 (s, 3H), 1.54–1.75 (m, 3H), 2.00–2.13 (m, 2H), 2.59 (s, 3H), 3.72 (d, *J*=2.0 Hz, 1H), 6.00 (t, *J*=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.75, −4.71, 17.1, 17.66, 17.70, 18.2, 19.4, 25.8 (3C), 27.3, 31.5, 34.1, 83.0, 86.4, 89.0, 91.9, 215.0; HRMS (FI) calcd for $C_{18}H_{34}O_3S_2Si_1$ $[M]^+$ 390.17186, found 390.1722.

*1.5. tert-Butyl[[(1S,2R,4R)-4-isopropyl-1-methyl-7-oxabicyclo[2.2.1]heptan-2-yl]oxy]dimethylsilane (**8**)*

A solution of dithioester **7** (1.24 g, 3.17 mmol), Bu_3SnH (1.70 mL, 6.34 mmol), and AIBN (323 mg, 1.97 mmol) in toluene (32 mL) was refluxed for 2 hr. The resulting mixture was concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to silyl ether **8** (904 mg, quant): R_f=0.36 (hexane/EtOAc=25:1); $[\alpha]_D^{24}$ −19.3 (*c* 1.01, $CHCl_3$); IR (neat) 2959, 1471, 1256, 10796, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.89 (s, 9H), 0.95 (d, *J*=6.8 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 1.36 (s, 3H), 1.38–1.44 (m, 3H), 1.50–1.60 (m, 2H), 1.97–2.13 (m, 2H), 3.79 (dd, *J*=6.8, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.7, −4.5, 16.7, 18.1, 18.4, 26.0 (4C), 31.4, 32.6, 33.4, 46.5, 85.8, 88.4 (2C); HRMS (FD) calcd for $C_{16}H_{32}O_2Si_1$ $[M]^+$ 283.20933, found 283.21037.



Scheme 1. Synthesis of optically active (−)-cinmethylin [(−)-**1**] and its enantiomer (+)-**1**

1.6. (*1*S,*2*R,*4*R)-*4-Isopropyl-1-methyl-7-oxabicyclo[2.2.1]heptan-2-ol* (***9***)

To a solution of silyl ether **8** (870 mg, 3.06 mmol) in THF (30 mL) was added TBAF (1.0 M in THF, 3.67 mL, 3.67 mmol). The solution was stirred at room temperature for 21 hr and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give alcohol **8** (420 mg, 81%): R_f=0.25 (hexane/EtOAc=2:1); $[\alpha]_D^{25}$ −0.875 (*c* 1.02, $CHCl_3$); IR (neat) 3254, 2964, 1117, 1053 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 3H), 0.97 (s, 3H), 1.34–1.41 (m, 1H), 1.43 (s, 3H), 1.45–1.51 (m, 2H), 1.51–1.65 (m, 3H), 2.01–2.14 (m, 2H), 3.69–3.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 18.1, 18.2, 32.58, 32.61, 32.9, 45.1, 76.9, 85.6, 88.7; HRMS (FI) calcd for $C_{10}H_{18}O_2$ $[M]^+$ 170.13068, found 170.13095.

1.7. (−)-*Cinmethylin* [(−)-***1***]

To a solution of alcohol **8** (120 mg, 0.71 mmol) in THF (33 mL) was added NaH (55% dispersion in mineral oil, 76.8 mg, 1.76 mmol). After being stirred at room temperature for 1 hr, *α*-bromo-*o*-xylene (0.19 mL, 1.4 mmol) was added. The mixture was stirred at room temperature for 19 hr and diluted with saturated NH_4Cl. The resulting mixture was extracted with (hexane/EtOAc=4:1) three times. The combined extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give (−)-cinmethylin [(−)-**1**] (248 mg, 88%) as a colorless oil: R_f=0.76 (hexane/EtOAc=2:1); $[\alpha]_D^{21}$ −48.8 (*c* 0.855, $CHCl_3$); IR (neat) 2962, 1465, 1212, 1068, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J*=6.8 Hz, 6H), 1.40–1.47 (m, 2H), 1.48 (s, 3H), 1.50–1.68 (m, 3H), 1.95 (dd, *J*=6.8 Hz, 1H), 2.12 (quint, *J*=6.8 Hz, 1H), 2.32 (s, 3H), 3.54 (t, *J*=6.8 Hz, 1H), 4.36 (d, *J*=12.4 Hz, 1H), 4.55 (d, *J*=12.4 Hz, 1H), 7.12–7.22 (m, 3H), 7.30–7.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.7, 18.2, 18.3, 18.9, 32.0, 32.8, 34.0, 42.0, 68.4, 82.7, 85.5, 88.7, 125.7, 127.6, 128.5, 130.1, 136.5, 136.7; HRMS (FD) calcd for $C_{18}H_{26}O_2$ $[M]^+$ 274.19328, found 274.19393.

2. Evaluation of herbicidal activity on weeds of rice paddy field

Plastic pots (100 cm^2) were filled with paddy soil (clay loam). Water, fertilizer and soil puddling were added successively. Seeds of *Echinochloa crus-galli* (L.) var. *formosensis* (ECHCS), and *Scirpus juncoides* var. *ohwianus* (SCPJU) were sown on the soil surface. The pots were filled with water 3 cm from the rim. Each test compound was dissolved in a mixture acetone, polyoxyethylene styryl phenyl ether, and calcium dodecylbenzene sulfonate to give an emulsifiable concentrate. An amount of the water-diluted agent solutions was dropped on the water surface at 7 days after sowing for application. The dosage of the compounds was 1200 g a.i./hectare. The herbicidal effect was determined by visual observation of the treated plants in comparison with the untreated controls. The herbicidal rating score ranged from 0 (same growth as untreated) to 100 (complete kill).

Results and discussion

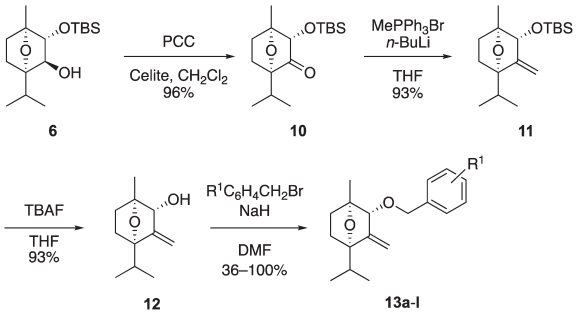
1. Synthesis of optically active (−)-*cinmethylin* [(−)-***1***] *and its enantiomer* (+)-***1***

The synthesis of (−)-cinmethylin [(−)-**1**] and its enantiomer (+)-**1** is shown in Scheme 1. Dihydroxylation of *α*-terpinene

Table 1. Herbicidal activity of (−)-**1** and (+)-**1**

		Paddy/water surface application[a),b)]			
		Pre-emergence		Early-post emergence	
Sample	Dose of sample (g a.i./hectare)	ECHCS	SCPJU	ECHCS	SCPJU
cinmethylin	300	100	100	100	100
	75	100	100	100	100
	19	100	90	100	70
	4.8	100	80	85	40
	2.4	100	40	40	0
(−)-**1**	300	100	100	100	100
	75	100	100	100	100
	19	100	90	100	70
	4.8	100	80	90	40
	2.4	100	0	70	0
(+)-**1**	300	100	100	100	100
	75	100	90	100	90
	19	100	80	100	60
	4.8	100	70	70	40
	2.4	100	0	50	0

[a)] Rating scale: 0 (no effect)–100 (completely effective). [b)] ECHCS: *Echinochloa crus-galli* (L.) var. *formosensis*; SCPJU: *Scirpus juncoides* var. *ohwianus*



Scheme 2. Synthesis of methylene analogs **13a–l**

(**3**) with AD-mix-β afforded diol **4**[7] in 67% yield with 73% ee, as determined by chiral HPLC analysis. Sharpless *et al.* reported that the desired diol was obtained at 86% ee, and our results under similar conditions showed a decrease in stereoselectivity. We tried to increase the equivalence of the ligand and to lower the reaction temperature, but the stereoselectivity did not improve. The secondary hydroxy group in **4** was then protected with TBSCl, and olefin part was subjected to epoxidation with *m*-CPBA to afford **5** in 51% yield. The epoxide ring opening of **5** with *p*-TsOH·H_2O gave alcohol **6** in 90% yield. Alcohol **6** was converted to silyl ether **8** by Barton–McCombie deoxygenation.[8] Deprotection of **8** with TBAF gave alcohol **9** in 81% yield. Finally, alkylation of **9** with α-bromo-*o*-xylene afforded (−)-cinmethylin [(−)-**1**] in 88% yield. Dihydroxylation of α-terpinene gave *ent*-**4** with AD-mix-α in 77% yield and 32% ee, as determined by chiral HPLC analysis. The product *ent*-**4** was then converted to (+)-**1** using the same synthetic method described above.

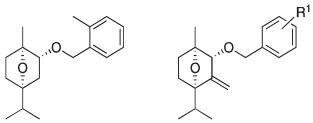
2. *Herbicidal activity of* (−)-*cinmethylin* [(−)-***1***] *and its enantiomer* (+)-***1***

We examined the herbicidal activity of the synthesized materials against two typical weeds found in paddy rice crops, namely, *Echinochloa crus-galli* (L.) var. *formosensis* (ECHCS) and *Scirpus juncoides* var. *ohwianus* (SCPJU), in a pot trial (Table 1). Both enantiomers of cinmethylin showed strong herbicidal activity against these weed species even at low doses. In addition, the (−)-**1** showed higher herbicidal activity than the (+)-**1**. Cinmethylin is mainly absorbed by the roots and partly by the stems and leaves, and kills weeds by inhibiting cell division at the root growth points.[9] We expect that pre-emergence (chemical treatment on seeds) will be more active than early-emergence (chemical treatment after germination), because cinmethylin is more readily absorbed by the root meristem. Next, we synthesized various cinmethylin analogs with a substituent at the C3 position using alcohol **6** as a key intermediate. The analogs were designed based on the above result that the (−)-form showed slightly higher herbicidal activity and the (−)-form showed higher enantiomeric excess. Then, Campe *et al.* reported the crystal structure of cinmethylin bound to FAT, and there is a space between the C3 position of cinmethylin with FAT.[3] We focused on this space and devised a cinmethylin analogs with a substituent at the C3 position. Therefore, we considered that a analogs with a substituent at the C3-position could be a novel herbicide.

3. *Synthesis of methylene analogs* ***13a–l***

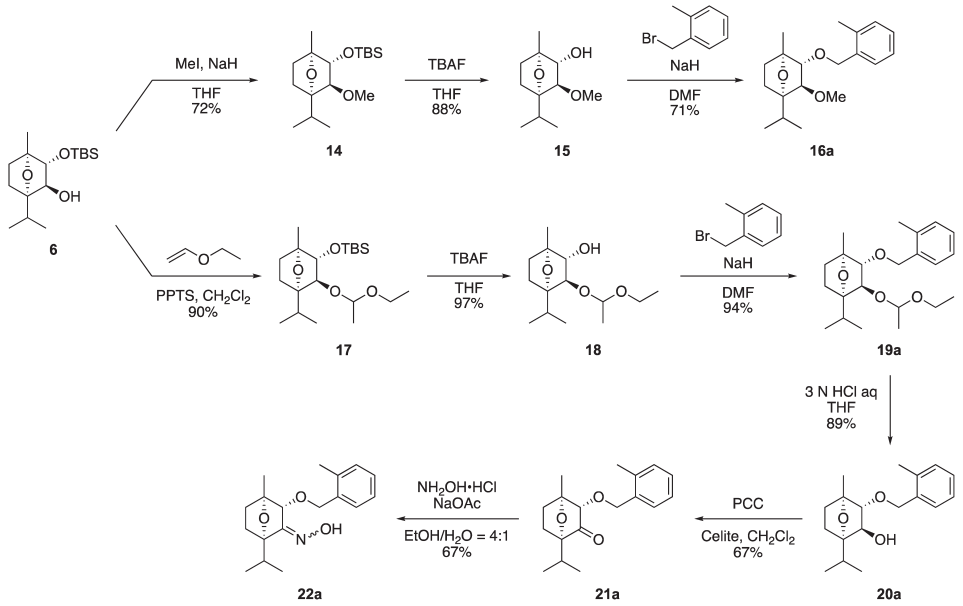
The synthesis of **13** is shown in Scheme 2. Oxidation of **6** gave ketone **10** in 96% yield. The generation of the ylide from CH_3PPh_3Br and *n*-BuLi in THF, followed by the addition of ketone **10**, resulted in olefin **11** (93%). Deprotection of **11** with TBAF afforded alcohol **12** in 93% yield. The analogs **13a–l** were synthesized *via* the alkylation of **12** with corresponding benzyl bromides.

Table 2. Herbicidal activity of methylene analogs **13a–l**



			Paddy/water surface application[a),b)]			
			Pre-emergence		Early-post emergence	
Sample	R^1	Dose of sample (g a.i./hectare)	ECHCS	SCPJU	ECHCS	SCPJU
(−)-**1**	2-Me	300	100	100	100	100
		75	100	100	100	100
13a	2-Me	300	100	100	100	0
		75	100	100	100	0
13b	3-Me	300	90	0	90	0
		75	0	0	0	0
13c	4-Me	300	100	90	100	0
		75	0	0	0	0
13d	2-OMe	300	100	100	100	100
		75	100	100	70	100
13e	3-OMe	300	0	0	0	0
		75	0	0	0	0
13f	4-OMe	300	0	0	0	0
		75	0	0	0	0
13g	2-F	300	100	90	100	80
		75	100	90	100	70
13h	3-F	300	100	100	100	100
		75	0	0	0	0
13i	4-F	300	100	0	100	0
		75	100	0	0	0
13j	2-Cl	300	100	100	100	70
		75	100	90	100	70
13k	2-CF_3	300	0	0	0	0
		75	0	0	0	0
13l	2-OCF_3	300	0	0	0	0
		75	0	0	0	0

[a)] Rating scale: 0 (no effect)–100 (completely effective). [b)] ECHCS: *Echinochloa crus-galli* (L.) var. *formosensis*; SCPJU: *Scirpus juncoides* var. *ohwianus*



Scheme 3. Synthesis of analogs **16a**, **20a**–**22a**

*4. Herbicidal activity of methylene analogs **13a**–**l***

First, we investigated the herbicidal activity of C3 methylene analogs **13a**–**l** (Table 2), against ECHCS and SCPJU. Analogs **13a**–**c** exhibited herbicidal activity against ECHCS when applied at a dose of 300 g a.i./hectare, but only **13a** showed high herbicidal activity at a low concentration of 75 g a.i./hectare. Analogs **13a**–**c** did not show herbicidal activity against SCPJU in the early post-emergence stage. This decreases in activity with substitution position was similar to that observed when substituents other than the methyl group (**13d**–**i**) were applied. As cinmethylin (**1**) also has a methyl group at the C2 position on its benzene ring, the position of the substituent on the benzene ring has a significant effect on the herbicidal activity of the product. Next, we examined the effect of the type of substituent on the herbicidal activity of analogs **13d**–**l**. Analogs with methyl and methoxy groups, which are electron-donating groups, as well as halogens, which are electron-withdrawing groups, showed excellent herbicidal activity even at low concentrations (**13a**, **13d**, **13g**, and **13j**). By contrast, analogs with slightly bulky substituents, such as trifluoromethyl (**13k**) and trifluoromethoxy (**13l**) groups, did not show herbicidal activity. Analogs **13a**, **13d**, **13g**, and **13j** and cinmethylin showed similarly high herbicidal activity against ECHCS.

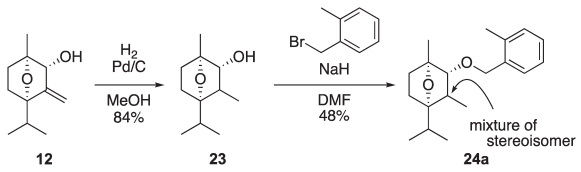
*5. Synthesis of analogs **16a**–**24a***

Next, we synthesized a novel cinmethylin analogs with a substituent at the C3 position (Scheme 3). Alkylation of alcohol **6**, followed by deprotection with TBAF, afforded alcohol **15**. Alkylation of **15** with *α*-bromo-*o*-xylene resulted in the synthesis of **16a** in 71% yield. Then, protection of alcohol **6** with ethyl vinyl ether/PPTS, followed by deprotection with TBAF, afforded alcohol **18** in good yield. Alkylation of alcohol **18** with *α*-bromo-*o*-xylene afforded ether **19a** in 94% yield. Ether **19a** was converted to alcohol **20a** under acidic conditions in 89% yield. Alcohol **20a** was oxidized with PCC to give **21a** in 67% yield. Finally, ketone **21a** was converted to oxime **22a** using $NH_2OH \cdot HCl/NaOAc$ in 67% yield.

The synthesis of methyl analog **24a** with a methyl group at the C3 position is shown in Scheme 4. Reduction of olefin **12** and subsequent alkylation of the alcohol gave **24a**. ^1H NMR analysis indicated that the stereoisomeric ratio of **24a** at the C3 position was 44 : 56. Thus, analog **24a** was as such subjected to the herbicidal activity test.

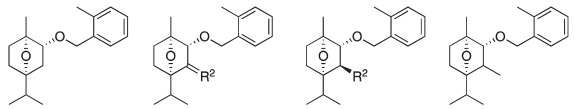
*6. Herbicidal activity of analogs **13a**–**24a***

The herbicidal activity of the cinmethylin analogs with various substituents at the C3 position are shown in Table 3. The carbonyl analog **21a** and oxime analog **22a** showed excellent activity against ECHCS, even at low concentrations, similar to (−)-**1** and the methylene analog **13a**. The herbicidal activity of methoxy analog **16a** and hydroxy analog **20a** was evident at 300 g a.i./hectare but decreased or disappeared at 75 g a.i./hectare. The methyl analog **24a** showed high activity even at low concentrations. These results suggest that the substituent at the C3 position affects the herbicidal activity of the resultant compound. Studies on the relationship between the type of substituent at the C3 position and herbicidal activity of the cinmethylin analog are ongoing in our laboratory.



Scheme 4. Synthesis of methyl analog **24a**

Table 3. Herbicidal activity of analogs **13a**–**24a**



		Paddy/water surface application[a),b)]			
		Pre-emergence		Early-post emergence	
Sample	Dose of sample (g a.i./hectare)	ECHCS	SCPJU	ECHCS	SCPJU
(−)-**1**	300	100	100	100	100
	75	100	100	100	100
13a	300	100	100	100	0
	75	100	100	100	0
21a	300	100	100	100	0
	75	100	80	100	0
22a	300	100	100	100	100
	75	100	100	100	70
16a	300	90	90	90	40
	75	0	0	0	0
20a	300	90	100	100	80
	75	40	40	0	0
24a	300	90	90	90	90
	75	90	90	90	50

[a)] Rating scale: 0 (no effect)–100 (completely effective). [b)] ECHCS: *Echinochloa crus-galli* (L.) var. *formosensis*; SCPJU: *Scirpus juncoides* var. *ohwianus*

Conclusion

We successfully synthesized optically active (−)-cinmethylin [(−)-**1**] and its enantiomer (+)-**1**. Both enantiomers showed similar herbicidal activity against two weed species. We found that the stereochemistry of **1** did not affect its herbicidal activity or spectrum. We then synthesized C3-substituted cinmethylin analogs and assessed their herbicidal activity tests as well. Substitution at the C2 position on the benzene ring of the cinmethylin analogs led to excellent activity. High herbicidal activity was observed when the substituents on the benzene ring were composed of electron-donating methyl and methoxy groups or electron-withdrawing halogen groups. Substitution with methyl and methylene groups at the C3 position of cinmethylin also led to high herbicidal activity and a wide herbicidal spectrum. The results provide a preliminary reference for further research on the biological activity of cinmethylin-based compounds. Given these encouraging results, we will continue to study new herbicides based on cinmethylin in future work.

Electronic supplementary materials

The online version of this article contains supplementary materials which is available at https://www.jstage.jst.go.jp/browse/jpestics/.

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