

水稻の幼苗根の成育およびトウモロコシの草丈に対するククルビン酸類縁体の構造活性相関

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Original Article

Structure-Activity Relationships of (\pm)-Cucurbic Acid Analogs on the Root Growth of Rice Seedlings and Height of Young Corn Plants

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All the stereoisomers of cucurbic acid and its various analogs were stereoselectively synthesized in a racemic form, and their inhibitory activities on the root growth of rice seedlings and plant height of young corn plants were assessed in order to study the structure-activity relationships and to explore practical compounds for agricultural use as plant growth regulators. Essential structural factors to enhance the activity on the root growth of rice seedlings were 1) *cis*-configuration of C-1 and C-2 substituents, 2) free hydroxyl group at the C-3 position, 3) alkenyl or alkyl group represented by (*Z*)-2'-pentenyl or butyl group at the C-2 position, and 4) methyl acetate substituent at the C-1 position. Although none of cucurbic acid analogs tested so far surpassed the corresponding 3-oxo derivatives such as methyl jasmonate and methyl epijasmonate in the inhibitory activities on rice seedlings, some compounds showed somewhat higher activities on the plant height of young corn plants by foliar application, where the hydroxyl group at the C-3 position and the alkyl substituent at the C-2 position seemed to be more suitable than the corresponding keto function and alkenyl substituent, respectively.

INTRODUCTION

Jasmonic acid, 2-(*cis*-pent-2'-enyl)-3-oxocyclopentylacetic acid (JA: **1a**), and its methyl ester (MJA: **1b**) are important subjects in plant physiology, because they are known to occur widely in plants and possess growth-regulating properties like abscisic acid (ABA); *e.g.* inhibition of length and root growth and of seed and pollen germination, and promotion of leaf senescence and stomata closure.¹⁾

Recent studies on naturally occurring JA-related compounds, however, have suggested that C-2 epimers of JA and MJA, *i.e.*, epijasmonic acid (epi-JA; **2a**) and methyl epijasmonate (epi-MJA; **2b**), are more important in plant physiology. In 1984, Vick & Zim-

merman assigned (–)-**2a** as a real metabolite of biosynthesis of natural jasmonoids starting from linoleic acid,²⁾ and several intriguing findings reported so far support the stereospecific aspects of epijasmonoid structures, *i.e.*, the *cis*-configuration between C-1 and C-2 substituents, on the bioactivities. Recently, Nishida *et al.* have identified (+)-**2b** as a synergistic component of male sex pheromone of the oriental fruit moth, *Grapholitha molesta* BUSK,^{3,4)} and testified that it is an essential component of jasmin flavor.^{5,6)} More recently, Yoshihara *et al.* identified glucosyl tuberronic acid, a glycoside of ω -hydroxyl epijasmonic acid, as a tuber-inducing stimulus from potato leaves.⁷⁾ In all these cases, none of their C-2 epimers showed the activities. Recent studies by Miersch *et al.* have also showed that epijasmonoid **2a** or **2b** was more active than jasmonoid **1a** or **1b** in some bioassays using plants, respectively.⁸⁾

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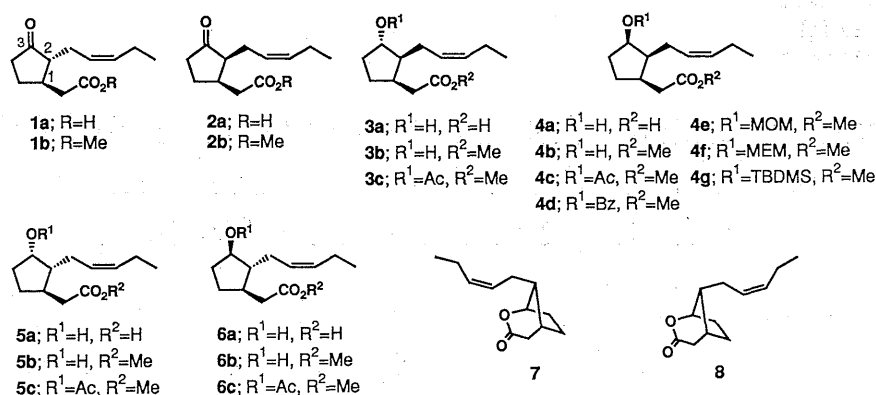


Fig. 1 Structures of JA, epi-JA and their methyl esters, and CA analogs.

However, studies on structure-activity relationships have been centered only on easily available jasmonoid analogs^{9,10} and, up to date, little has been studied on epijasmonoids, especially in conjunction with their exact stereochemistry. Recently, we have developed an efficient method for stereo-controlled synthesis of racemic epijasmonoids.¹¹ It now has enabled us to prepare extensively modified cucurbitic acid, 2-(*cis*-pent-2'-enyl)-3-hydroxycyclopentylacetic acid (CA; **3a**), a member of epijasmonoids isolated from *Cucurbita pepo* L. as a plant growth inhibitor,^{12,13} for biological studies. With a view to exploring practical compounds to be used as plant growth regulators in agriculture, we report here the synthesis of a variety of CA analogs and their inhibitory activity on plant growth, and discuss structure-activity relationships of these compounds, in which CA analogs are considered to have an intrinsic effect due to the stereochemistry of C-1 and C-2 substituents because configuration is fixed at the C-2 position, in contrary to the corresponding 3-oxo derivatives such as JA and epi-JA analogs, whose interconversion through epimerization by keto function in the bioassay systems should be always suspected.

The chemical structures of JA, MJA, epi-JA, epi-MJA and CA are illustrated in Fig. 1.

MATERIALS AND METHODS

1. Syntheses of Compounds

A series of epijasmonoids (**2b**, **3a**, **3b**, **4a**, **4b**) were prepared as previously reported.¹¹ MJA

(**1b**) was a gift from Shiono Koryo Co., Ltd., and 3-hydroxyl derivatives, **5b** and **6b**, were prepared by reduction of **1b** with NaBH₄ in MeOH at 0°C in 35% and 62% yields, respectively, after separation of the obtained diastereomeric mixture by column chromatography. Then, both the esters (**5b**, **6b**) were respectively converted to carboxylic acids (**5a**, **6a**) by saponification with aq. KOH in MeOH. ¹H NMR chemical shifts of these hydroxyl esters (**3b–6b**) are listed in Table 1 along with their acetates (**3c–6c**) which were prepared by acetylation with Ac₂O and Et₃N in the presence of a catalytic amount of 4-dimethylamino-pyridine (4-DMAP) in CH₂Cl₂ at 0°C.

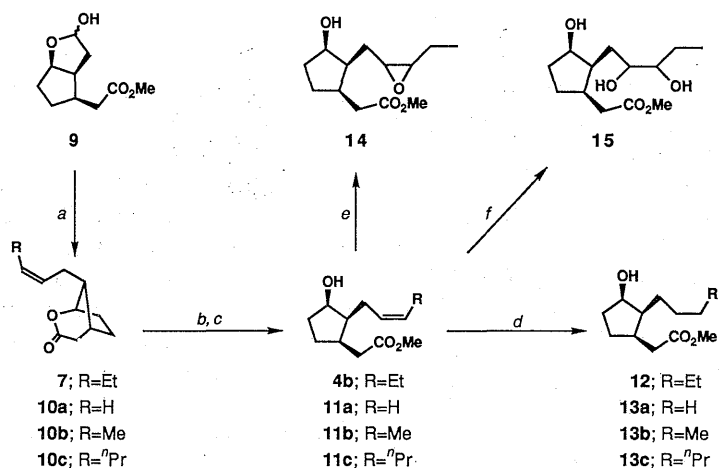
A bridged lactone (**7**) [¹H NMR (400 MHz, CDCl₃) δ ppm: 0.97 (3H, t, *J*=7.6 Hz), 1.68–1.84 (2H), 1.89–2.43 (9H), 2.75 (1H, ddd, *J*=18.8, 5.1, 2.2 Hz), 4.60 (1H, m), 5.44 (1H, dtt, *J*=10.8, 7.3, 1.5 Hz), 5.37 (1H, dtt, *J*=10.8, 7.3, 1.5 Hz)] was obtained in the course of preparing compound **4b** as illustrated in Fig. 2, and another epimeric lactone (**8**) [¹H NMR (90 MHz, CDCl₃) δ ppm: 0.97 (3H, t, *J*=7.4 Hz), 1.49–2.94 (12H), 4.56 (1H, m), 5.12–5.69 (2H)] was prepared by lactonization of the hydroxy acid (**6a**) with AcONa and Ac₂O in benzene under reflux in 90% yield.

Benzoyl (Bz) ester (**4d**) [BzCl, Py, r.t.], methoxymethyl (MOM) ether (**4e**) [MOMCl, *i*-Pr₂EtN, Et₃N, cat. 4-DMAP, CH₂Cl₂, r.t.], methoxyethoxymethyl (MEM) ether (**4f**) [MEMCl, *i*-Pr₂EtN, Et₃N, cat. 4-DMAP, CH₂Cl₂, r.t.] and *t*-butyldimethylsilyl (TBDMS)

Table 1 ^1H NMR data^{a)} of MCAs and their acetates.

Compound	3-H	Olefinic protons	$\omega\text{-CH}_3$	CO_2CH_3	OCOCH_3
3b	4.00 (m)	5.17–5.64	0.97 (t, $J=7.5$)	3.67 (s)	
3c	4.91 (m)	5.13–5.63	0.96 (t, $J=7.4$)	3.67 (s)	2.01 (s)
4b	4.20 (m)	5.18–5.64	0.97 (t, $J=7.5$)	3.66 (s)	
4c	5.18 (m)	5.10–5.57	0.95 (t, $J=7.5$)	3.68 (s)	2.07 (s)
5b	4.22 (m)	5.21–5.63	0.97 (t, $J=7.5$)	3.67 (s)	
5c	5.16 (m)	5.10–5.57	0.95 (t, $J=7.5$)	3.68 (s)	2.02 (s)
6b	3.89 (m)	5.21–5.65	0.97 (t, $J=7.5$)	3.66 (s)	
6c	4.84 (m)	5.13–5.64	0.95 (t, $J=7.5$)	3.67 (s)	2.01 (s)

^{a)} In CDCl_3 with Me_4Si as the internal standard at 90 MHz.



a; $\text{Ph}_3\text{P}=\text{CHR}$, THF, -78°C – r.t.; b; aq. KOH, MeOH, r.t.; c; CH_2N_2 , Et_2O ; d; H_2 , 10% Pd-C, AcOEt; e; m-CPBA, CH_2Cl_2 , 0°C ; f; OsO_4 , N-methylmorpholine-N-oxide, H_2O , acetone, r.t.

Fig. 2

ether (**4g**) [TBDMSCl, imidazole, DMF, r.t.] were prepared respectively from the alcohol (**4b**) according to the usual methods given in the reference.¹⁴⁾

Compounds **11a–c** with an *n*-alk-2-enyl substituent at the C-2 position were synthesized from a lactol (**9**) by employing the same reaction sequence as for preparation of compound **4b**¹¹⁾ in 85–90% overall yields, respectively (Fig. 2), *i.e.*, Wittig reaction with a salt-free triphenylalkylidene phosphorane in THF at reaction temperatures of -78°C to r.t., and alkaline hydrolysis with aq. KOH in MeOH at r.t., then esterification with diazomethane in Et_2O [^1H NMR (90 MHz, CDCl_3) δ ppm: **11a**; 3.66 (3H, s), 4.20 (1H, m), 4.88–5.22 (2H),

5.89 (1H, ddt, $J=16.5, 9.9, 6.6$ Hz). **11b**; 1.63 (3H, br d, $J=5.1$ Hz), 3.66 (3H, s), 4.21 (1H, m), 5.20–5.70 (2H). **11c**; 0.91 (3H, t, $J=7.7$ Hz), 3.66 (3H, s), 4.22 (1H, m), 5.20–5.60 (2H)].

Then, dihydro compounds **12** and **13a–c** were respectively synthesized from the corresponding alkenes (**4b**, **11a–c**) by catalytic hydrogenation in the presence of a catalytic amount of 10% palladium-charcoal in AcOEt at r.t. in quantitative yields [^1H NMR (90 MHz, CDCl_3) δ ppm: **13a**; 0.94 (3H, m), 3.66 (3H, s), 4.20 (1H, m). **13b**; 0.91 (3H, m), 3.66 (3H, s), 4.20 (1H, m). **12**; 0.89 (3H, m), 3.66 (3H, s), 4.20 (1H, m). **13c**; 0.89 (3H, m), 3.66 (3H, s), 4.20 (1H, m)].

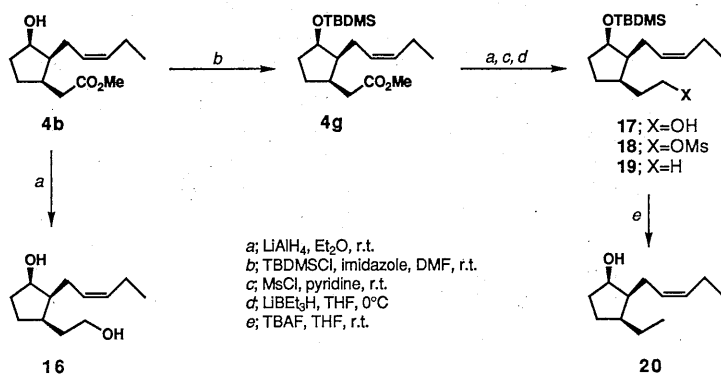


Fig. 3

Oxirane (**14**) [^1H NMR (90 MHz, CDCl_3) δ ppm: 0.99 (3H, br t, $J=6.9$ Hz), 2.60–3.04 (1H, m), 3.10–3.60 (1H, m), 3.68 (3H, s), 4.58 (1H, m)] was prepared by epoxidation of the alkene (**4b**) with *m*-CPBA in CH_2Cl_2 at 0°C in 57% yield. Triol (**15**) [^1H NMR (90 MHz, CDCl_3) δ ppm: 0.99 (3H, br t, $J=7.2$ Hz), 3.30–4.05 (2H), 3.66 (3H, s), 4.32 (1H, m)] was obtained by oxidation of **4b** with *N*-methylmorpholine-*N*-oxide in the presence of a catalytic amount of OsO_4 in wet acetone at r.t. in 42% yield.

Diol (**16**) [^1H NMR (90 MHz, CDCl_3) δ ppm: 0.98 (3H, t, $J=7.5$ Hz), 3.20–3.82 (2H), 4.20 (1H, m), 5.16–5.68 (2H)] was prepared by reduction of the hydroxyl ester (**4b**) with LiAlH_4 in Et_2O at r.t. in 98% yield, and monool (**20**) [^1H NMR (90 MHz, CDCl_3) δ ppm: 0.85 (3H, t, $J=7.3$ Hz), 0.97 (3H, t, $J=7.3$ Hz), 4.20 (1H, m), 5.27–5.76 (2H)] was synthesized from **4b** in 76% overall yield by following the reaction sequence shown in Fig. 3: After protection of the hydroxyl group in **4b** as *t*-butyldimethylsilyl ether by reaction with TBDMSCl and imidazole in DMF at r.t., the obtained ester (**4g**) was reduced with LiAlH_4 in Et_2O at r.t., giving alcohol (**17**), which was treated with methanesulfonyl chloride (MsCl) in pyridine at r.t. to be converted to mesylate (**18**). Then, **18** was reduced with LiBEt_3H in THF at r.t. to give compound **19**, which was subjected to deprotection of the silyl group by treatment with tetrabutylammonium fluoride hydrate (TBAF) in THF at r.t., giving alcohol (**20**).

2. Test Method for Plant Growth Regulating Activities

2.1 Rice seedlings

A definite amount of test sample in acetone was poured on a sheet of filter paper in a petri dish (7 cm diameter, 3 cm deep). After evaporation of the solvent, 5 ml of distilled H_2O was added. Eight germinated seeds of rice (*Oryza sativa* L. vc Nihonbare) were sowed in each dish and grown at 25°C under constant illumination of incandescent light (5000 lux) for 7 days. The length of the seminal roots was measured. The average length and the growth rate (%) against the control were calculated.

2.2 Young corn plants

Seeds were sown singly in plastic pots (5 cm diameter, 10 cm deep) containing soil and grown in a greenhouse at temperatures of 18 to 30°C . The third-true-leaf-old plants were treated with an emulsifiable aq. solution (500 ppm) of test sample by the spray method (20 ml/4 plants/each application). The height of the fifth-true-leaf-old plants was measured. The average plant height and the growth rate (%) against the control were calculated.

RESULTS AND DISCUSSION

Table 2 indicates the biological activity of MJA (**1b**), epi-MJA (**2b**) and CA analogs depicted in Fig. 1. These compounds were applied on rice seedlings by dipping and on intact young corn plants by foliar spraying. In all cases of CAs (**3a–6a**), MCAs (**3b–6b**) and acetates (**3c–6c**), *cis*-configuration between C-1 and C-2 substituents was obviously more con-

Table 2 Effects of MJA, epi-MJA and CA analogs listed in Fig. 1 on the root growth of rice seedlings and the plant height of young corn plants.

Compound	Root growth rate (%)			Plant height rate (%)
	100	20	4 ppm	500 ppm
1b	0	0	52	69
2b	0	0	45	79
3a	0	54	90	74
3b	0	15	30	64
3c	0	51	106	74
4a	12	52	70	69
4b	0	13	42	65
4c	0	46	104	74
5a	18	54	88	74
5b	11	45	71	64
5c	36	107	110	65
6a	73	88	108	60
6b	62	78	104	64
6c	63	99	119	66
7	66	92	110	88
8	48	104	108	91
Cont. (0 ppm)	100.0% (5.6 cm) ^{a)}			100.0% (66.8 cm) ^{b)}

^{a)} The length of seminal root.

^{b)} The plant height at fifth-true-leaf-old.

tributive to the inhibitory activity on the root growth of rice seedlings than *trans*-configuration, although no significant differences were observed between MJA (**1b**) and epi-MJA (**2b**). All CA analogs were less active than the corresponding 3-oxo derivatives (**1b**, **2b**) on rice seedlings, but on the plant height of intact young corn plants, MCAs (**3b–6b**) was comparably active to **1b** and **2b**, where their stereochemistry was not influential to the activity.

Conversion of CAs (**3a–6a**) to methyl esters (**3b–6b**) enhanced their activity in both bioassays. This is consistent with the results reported by Koshimizu *et al.*, in which natural carboxylic acids, (+)-CA and its glycoside, were less inhibitory than the corresponding methyl esters on the second leaf growth of rice seedlings.¹²⁾ The same propensity has been observed with JA (**1a**)^{9,10)} and ABA¹⁵⁻¹⁷⁾ in both inhibitory activity on the second leaf growth of rice seedlings and promoting activity on oat leaf senescence. On the similar argument applied to ABA and JA, it could be assumed that this general tendency might be due to

easier penetration of methyl esters into plant tissues than free acids.

Acetylation of MCAs (**3b–6b**) resulting in acetates (**3c–6c**) reduced the activity, but **3c** and **4c** were still active enough to be comparable to their parent acids, **3a** and **4a**, on rice seedlings. The bridged lactones (**7**, **8**) were nearly inactive in both assays.

Then, we further modified a stereoisomer of MCAs, **4b**, which would serve our purpose of seeking a compound for practical use in agriculture, because **4b** can be more easily provided and modified in a stereo-controlled manner by our synthetic method¹¹⁾ than other candidates such as **3b**, **5b**, **6b**, all of which were also considerably active on intact plant growth.

Table 3 shows the biological activity of a variety of modified substances of compound **4b**. As shown in the results of compounds **4b–g**, the protection of the C-3 hydroxyl group reduced the activity in both assays, the strength of which was in the following order; H (**4b**) > Ac (**4c**) > MOM (**4e**) > TBDMS (**4g**), Bz (**4d**), MEM (**4f**) = inactive. It seems that

Table 3 Effects of further modified compounds related to **4b** on the root growth of rice seedlings and the plant height of young corn plants.

Compound	Root growth rate (%)			Plant height rate (%)
	100	20	4 ppm	500 ppm
4b	0	13	42	65
4c	0	46	104	74
4d	89	99	110	89
4e	28	71	112	82
4f	99	116	131	93
4g	80	106	107	90
11a	79	107	109	84
11b	0	25	56	79
11c	0	26	63	72
13a	21	87	96	56
13b	0	12	49	52
12	0	33	79	61
13c	77	102	115	60
14	100	111	99	90
15	117	98	98	94
16	15	38	80	88
20	70	94	97	80
Cont. (0 ppm)	100.0% (5.6 cm) ^{a)}			100.0% (66.8 cm) ^{b)}

^{a)} The length of seminal root.

^{b)} The plant height at fifth-true-leaf-old.

increasing the bulkiness of the protecting group of hydroxyl function decreased the activity.

The results with compounds **11a-c**, **12**, **13a-c**, **14** and **15** show the influence of variation of C-2 substituent in compound **4b** on the activity. On rice seedlings, the activity order for *n*-alk-2-enyl substituents was pentenyl (**4b**)>butenyl (**11b**)>hexenyl (**11c**)>propenyl (**11a**), while that for *n*-alkyl substituents was butyl (**13b**)>pentyl (**12**)>propyl (**13a**)>hexyl (**13c**), where **11b**, **11c**, **13b** and **12** were active as comparably as the parent compound **4b**. These orders appear to suggest that deviation of the linear length of C-2 aliphatic chain from the optimal one, namely pentenyl for alkenyl and butyl for alkyl, causes a decrease in the activity. The linear lengths of pentenyl and butyl chains are considered to be close to each other on the basis of the values: 3.1 Å for C-C=C-C and 2.6 Å for C-C-C estimated by the Dreiding Model. On the other hand, by the foliar application on intact young corn plants, compounds **13a** and **13b** slightly improved the activity compared with the parent

compound **4b**.

In further modifications of C-2 substituent on the compound **4b**, both oxirane (**14**) and diol (**15**) were inactive even at 100 ppm, indicating that disruption of lipophilicity of C-2 substituent completely eliminates the activity. It is presumed that the aliphatic chain with a certain range of linear length at C-2 position is indispensable to inhibitory activity.

The results with compounds **16** and **20** show the influence of variation of C-1 substituent in compound **4b** on the activity. Hydroxyethyl and ethyl analogs, **16** and **20**, were much less active than the corresponding free acid (**4a**). These results suggest that moderate hydrophilicity at the 2'-position of C-1 ethyl substituent may produce the greatest inhibitory activity; methyl acetate is best hitherto.

On the basis of the present results, we concluded that the partial structures of CA analogs required for higher inhibitory activity on the root growth of rice seedlings are 1) *cis*-relationship between the C-1 and C-2 substituents, 2) hydroxyl group at the C-3 posi-

tion, 3) alkenyl or alkyl substituents represented by (*Z*)-2'-pentenyl or butyl at the C-2 position, which are defined by a certain range of linear length, and 4) methyl acetate substituent at the C-1 position satisfying moderate hydrophilicity.

From a viewpoint of agricultural use, it should be pointed out that even though the activity of all CA analogs tested could not surpass 3-oxo compounds, MJA (**1b**) and epi-MJA (**2b**), by dipping treatment of rice seedlings, some of them, *e.g.*, compounds **13a** and **13b**, had slightly but unambiguously higher inhibitory activity by foliar application of intact young corn plants, where the hydroxyl group at the C-3 position and the alkyl substituent at the C-2 position seemed to be more suitable than corresponding keto function and alkenyl substituents, respectively. As foliar application is more practical than dipping, this result suggests the existence of compounds more practical than naturally occurring **1b** and **2b**, which should be easily available through synthesis.

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要 約

水稻の幼苗根の成育およびトウモロコシの草丈に対するククルビン酸類縁体の構造活性相関

瀬戸秀春, 禿 康雄, 銭 昭輝, 清水 猛
ククルビン酸のすべての立体異性体および種々の類縁体をラセミ体にて立体選択的に合成し, 構造活性相関の解明ならびに農業上実用可能な植物生長調節剤の探索を目的として, これら化合物について水稻の幼苗根およびトウモロコシの草丈の成長に対する阻害活性を調べた。その結果, 水稻の幼苗根の成長阻害活性を高めるククルビン酸類縁体の化学構造要因として, 1) 1位と2位の置換様式がシスであること, さらに, 2) 3位の水酸基, 3) (*Z*)-2'-petenylあるいはbutyl基に代表される2位のalkenylあるいはalkyl置換基, および, 4) 1位のmethyl acetate置換基が重要であることが解明された。水稻の幼苗根の成長阻害活性において, ククルビン酸類縁体の中で, 相当する3-oxo体である, ジャスモン酸メチルあるいはエピジャスモン酸メチルに勝るものはなかったが, 茎葉処理によるトウモロコシ草丈の成長阻害活性においては, これらの化合物と同等あるいは若干強い活性を示す化合物がいくつか見出された。これにより, より実用的な茎葉処理においては, 3位がケトンであるより水酸基のほうが, また, 2位の置換基がalkenylよりもalkyl基のほうが活性発現に適していると推測された。