Note

(±)-Methyl 11-Fluorojasmonate as a Designed Antimetabolite of Methyl Jasmonate: Synthesis and Plant Growth Regulatory Activity

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INTRODUCTION

Jasmonoids have been found to play important roles in plant growth regulation.1 Recent development of industrial production of (±)-methyl jasmonate (MJA, 1) from Nippon Zeon Co., Ltd. made it possible to use MJA as a practical plant growth regulator.2 We have been studying new jasmonoid analogs to develop more active compounds.3 We took notice of the hypothesis that the metabolic inactivation pathway of MJA begins with hydroxylation at 11- or 12-position (11:12 = ca. 9/1). This hypothesis was supported by the metabolic experimental result of [2-14C]-9, 10-dihydrojasmonic acid.4 Furthermore, methyl 11-hydroxy- (11-OH-MJA, 2)5 and 12-hydroxyjasmonates (12-OH-MJA, 3)6 were reported to be inactive for some plant growth inhibition tests.8 So we supposed that blocking at 11-position would increase the plant hormonal activities of MJA. Previously, we reported that the growth inhibitory activity on rice seedlings of methyl 12,12,12-trifluorojasmonate (12-F3-MJA, 4), which was designed for antimetabolite for 12-hydroxylation, was stronger than that of MJA.3a Continuing this study, we designed 11-fluoro analog of MJA (11-F-MJA, 5) as antimetabolite for 11-position. Substitution by one fluorine atom would also repress the stereochemical change around this position. In this paper, synthesis and some plant growth regulatory activities of 5 are described.

RESULTS AND DISCUSSION

1. Synthesis

We used the intermediate of our synthesis of (±)-methyl 12-hydroxyjasmonate (methyl trans-tuberonate (3)).9 7-Anti-propargynorbornenol ethoxyethyl (EE) ether (6) was coupled with acetaldehyde to give alcohol 7. The hydroxy group of 7 was converted to fluorne group with diethylaminosulfur trifluoride (DAST)10 to afford fluorne compound 8. The EE group was deprotected (9) and the resulting hydroxy group was oxidized to give ketone 10. Baeyer-Villiger oxidation of 10 gave an inseparable mixture (6:1) of 11 and its 3-oxa-isomer (12). This mixture was treated with NaOMe in MeOH to give methyl ester 13. Undesired regioisomer was separated with silica gel column chromatography. Dess-Martin oxidation of 13 gave 14. Finally, hydrogenation of the triple bond of 14 to Z-double bond gave 5. The trans/cis ratio was >99:1 from 1H NMR analysis. The total yield was 1.6% in eight steps from 6.

2. Bioassays

Plant growth regulatory activities of 11-F-MJA (5) were assessed in the growth of rice seedlings and the germination of radish seeds.30 (±)-Methyl jasmonate (1) free from epimer was prepared by treatment of commercial MJA (Zeppin®) with DBU. Fig. 1 showed the result for the growth of rice seedlings. The growth inhibitory activity of 11-F-MJA was about 10 times weaker than that of MJA. 11-F-MJA was also less active in the growth of the germinating radish. In this case, the growth promoting effect was observed at lower concentration (Fig. 2). Suppose that the substitution by one fluorine atom did not change so much the degree of absorption to the plant body, the C-F bond was recognized not as C-H mimic but as C-OH mimic. Generally, a C-F bond seems to be a stereochemical mimic of a C-H bond, however in some cases, it works as a C-OH mimic as in the case of 3-deoxy-3-fluorothymidine.11 It seemed that the electronic nature of the C-F bond of 5, which resembles a C-O bond rather than a C-H bond, would be predominant. The observation that the growth of the radish roots were promoted by 5 also supported this assumption: the similar effect was observed for 12-hydroxyjasmonic acid, though no such effect for the corresponding 11-OH derivative was reported.3b Consequently, 11-F-MJA (5) acted as 11-OH-MJA mimic. Considering that 12-F3-MJA (4) was as active as MJA (1) in these bioassays, it was confirmed that the C-H bonds at 11-position influenced the plant growth regulatory activities of MJA.

EXPERIMENTAL

1. General

1H NMR spectra; a Varian Gemini 2000. Mass spectra; a Jeol JMS-700. Column chromatography; Merck silica gel 60 (70-230 mesh).

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Scheme 1  Plausible metabolic inactivation pathway of methyl jasmonate and designed antimetabolites.

Scheme 2  Synthesis of methyl 11-fluorojasmonate.

a) n-BuLi, THF, HMPA, then acetaldehyde (70%).
b) DAST, Et₃N, CH₂Cl₂ (36%).
c) TsOH, MeOH (57%).
d) Dess-Martin periodinane, CH₂Cl₂ (66%).
e) MCPBA, K₂CO₃, NaHCO₃, CHCl₃ (11/12 = 6/1).
f) NaOMe, MeOH (85%, 2 steps).
g) Dess-Martin periodinane, CH₂Cl₂ (72%).
h) H₂, Lindlar cat., MeOH (28%).

Fig. 1  The effects of methyl 11-fluorojasmonate (5, □) and methyl jasmonate (1, •) on the growth of the rice seedlings (*Oryza sativa* cv. Sasaminori). The length of the second leaf sheath was measured after incubated for 6 days.

Fig. 2  The effects of methyl 11-fluorojasmonate (5, □) and methyl jasmonate (1, •) on the root elongation of germinating radish seeds (*Raphanus sativus* cv. Sakuranbo). The length of the root was measured after incubated for 5 days.
2. **Synthesis of Compounds**

2.1 (1*S,2*S,4*S,7*S*)-2-[(1RS)-1-Ethoxylethyl] oxy-7-[(4RS)-4-hydroxy-2-pentynyl] bicyclo[2.2.1] heptane (7)

To a solution of 6 (3.00 g, 13.5 mmol) in THF (30 ml) was added dropwise n-BuLi (1.6 M, 9.3 ml, 15 mmol) at -78°C under nitrogen. The mixture was warmed to -30°C and to this was added HMPA (3 ml) and stirred for 1 hr, then to this was added acetaldehyde (2 ml). This mixture was stirred for further 2 hr while the temperature was gradually raised to 20°C. The reaction was quenched with a sat. aq. NH4Cl soln. and extracted with ether. The extract was washed with a sat. aq. NaHCO3 soln. and brine, dried (MgSO4) and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave 7 (2.45 g, 9.21 mmol) as a colorless oil. 1H NMR δ (300 MHz): 1.05-1.12 (2H, m), 1.20 and 1.21 (total 3H, each t, J=7.1Hz, CH3CH2), 1.29 and 1.30 (total 3H, each d, J=5.2 Hz, CH3CH2), 1.42 (3H, d, J=6.6 Hz, CH3OCH2), 1.45-1.75 (6H, m), 2.08 (1H, m), 2.11-2.18 (3H, m), 3.44 (1H, m, 2-H), 3.57-3.71 (2H, m, CH2O), 4.51 (1H, m, CHOH), 4.67 and 4.70 (total 1H, q, J=5.2Hz, O-CH-O). EIMS m/z: 241 (M+), 221 (M+-HF).

2.2 (1*S,2*S,4*S,7*S*)-2-[(1RS)-1-Ethoxylethyl] oxy-7-[(4RS)-4-fluoro-2-pentynyl] bicyclo[2.2.1] heptane (8)

To a solution of DAST (1.2ml, 9.2mmol), Et3N (3.9 ml, 27mmol) in CH2Cl2 (40 ml) was added 7 (2.45g, 9.21mmol) and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (15:1) gave 8 (0.89 g, 3.33 mmol, 36%) as a colorless oil. 1H NMR δ (300 MHz): 1.01-1.12 (2H, m), 1.20 and 1.21 (total 3H, each t, J=7.1 Hz, CH3CH2), 1.26 (1H, m), 1.29 and 1.30 (total 3H, each d, J=5.2 Hz, CH3CH2), 1.55 (3H, dd, J=22.5, 6.3 Hz, CH3CHF), 1.4-1.65 (4H, m), 2.08 (1H, m), 2.13-2.18 (3H, m), 3.41-3.50 (1H, m, 2-H), 3.58-3.71 (2H, m, CH2O), 4.67 and 4.70 (total 1H, q, J=5.2 Hz, CH3CHF), 5.22 (1H, dtq, J=48.6, 6.6, 1.7 Hz, CH2F). EIMS m/z: 202 (M+-EtOH-HF), 176 (M+-EtOCH=CH2-HF). HREIMS m/z (M++H-H2O): Found, 220.1096; Calcd. for C13H18O3, 220.1099.

2.6 Methyl (1S*,2S*,3S*)-2-[[4RS]-4-fluoro-2-pentynyl]-3-oxocyclopentanecacate (14)

In the same manner as that described in Ref. 9, this mixture gave 13 (273 mg, 1.13 mmol, 85%, 2 steps) as a colorless oil. 1H NMR δ (300 MHz): 1.53 (3H, dd, J=22.5, 6.6 Hz, CH3), 1.64 (1H, m), 1.8-2.2 (3H, m), 2.34 (1H, dd, J=15.5, 8.2 Hz), 2.46 (1H, m), 2.57 (1H, dd, J=15.5, 5.5 Hz), 3.68 (3H, s, OMe), 4.04 (1H, dt, J=6.3, 5.3 Hz, 2CH3), 5.21 (1H, dqq, J=48.6, 6.6, 1.6 Hz, CHF). EIMS m/z: 241 (M*), 221 (M*+HF). HREIMS m/z (M*): Found, 222.1253; Calcd. for C13H18FO3, 222.1256.

2.7 Methyl (1S*,2S*)-2-[[4RS]-4-fluoro-2-penteny]-3-oxocyclopentanecacate (5)

A suspension of 14 (161 mg, 0.67 mmol), Lindlar catalyst (15 mg) in MeOH (3 ml) was stirred under hydrogen atmosphere at 20°C for 12 hr. The catalyst was then filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (15:1) gave 5 (51 mg, 0.21 mmol, 28%) as a pale yellow oil. 1H NMR δ (300 MHz): 1.36-1.42 (3H, dt, J=23.6, 6.3 Hz, CH3CHF), 1.48 (1H, m), 1.95 (1H, m), 2.1-2.2-2.5 (5H, m), 2.65 (1H, m), 3.7 (3H, s, OMe), 5.32-5.47 (1H, m, CH=F), 5.48-5.62 (2H, m, CH=CH), FABMS m/z: 223 (M*+H-HF). HREIMS m/z (M*): Found, 222.1258; Calcd. for C13H18O3, 222.1256.

2. Synthesis of Compounds

2.1 (1*S,2*S,4*S,7*S*)-2-[(1RS)-1-Ethoxylethyl] oxy-7-[(4RS)-4-hydroxy-2-pentynyl] bicyclo[2.2.1] heptane (7)

In the same manner as that described in Ref. 9, 8 (832 mg, 3.10 mmol) gave 9 (347 mg, 1.77 mmol, 57%) as a colorless oil. 1H NMR δ (300 MHz): 1.02-1.10 (2H, m), 1.35-1.6 (3H, m), 1.56 (3H, dd, J=22.5, 6.3 Hz, CH3), 1.73 (1H, dd, J=13.2, 7.1 Hz), 2.0 (1H, pseudo d, J=3.5 Hz), 2.08-2.14 (1H, m), 2.15-2.20 (3H, m), 3.78 (1H, pseudo d, J=7.6 Hz, 2-H), 5.22 (1H, dqt, J=48.6, 6.6, 1.7 Hz, CHF).

EIMS m/z: 176 (M+-HF). HREIMS m/z (M+-HF): Found, 176.1196; Calcd. for C13H16O, 176.1201.

2.4 (1*S,4*S,7*S*)-7-[(4RS)-4-Fluoro-2-pentynyl] bicyclo[2.2.1] heptan-2-one (10)

In the same manner as that described in Ref. 9, 9 (325 mg, 1.66 mmol) gave 10 (276 mg, 1.42 mmol, 66%) as a colorless oil. 1H NMR δ ppm (300 MHz): 1.4-1.6 (2H, m), 1.56 (3H, dd, J=22.5, 6.3 Hz, CH3), 1.75-2.0 (3H, m), 2.15-2.4 (4H, m), 2.52-2.56 (2H, m), 5.22 (1H, dqt, J=48.6, 6.6, 1.7 Hz, CHF). EIMS m/z: 194 (M*), 174 (M*-HF). HREIMS m/z (M*): Found, 194.1108; Calcd. for C12H15OF, 194.1107.

3. Bioassay

3.1 Rice seeding assay

The growth regulatory effect on rice seedling growth was carried out in the same manner as described previously20a

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*Note: The page contains technical and chemical information related to the synthesis of compounds, including various spectroscopic data, reactions, and yields. The content is typical of a scientific research paper, focusing on the preparation and characterization of organic compounds.*
under non-sterile conditions. A group of ten rice seedlings (Oryza sativa cv. Sasaminori) that had been germinated in water at 30°C for 3 days was transplanted to a test tube (36×100 mm) with 7 ml of 0.7% agar medium and this was incubated for 6 days at 25°C under fluorescent light (1700 cd·sr·m⁻²). Then the lengths of the second leaf sheaths were measured on two replicates.

3.2 Radish germination assay
The growth regulatory effect on germination of radish (Raphanus sativus cv. Sakuranbo) seeds was tested according to the above mentioned lettuce assay. A group of 30 radish seeds was placed in a 8.5 cm Petri dish with 0.7% agar medium and this was incubated for 5 days at 25°C under fluorescent light (1700 cd·sr·m⁻²). Then the germination rate was measured on two replicates.

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REFERENCES

要約
(±)- Jasmon酸メチルの抗代謝アナログとして設計した 11-フルオロジャスモン酸メチルの合成と植物成長調節活性

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佐藤 靖, 折谷隆之

ジャスモン酸メチルは植物の成長抑制に働くアブセンジ酸様の植物ホルモン様物質である。その代謝不活性化は11 位炭素は12 位の水酸化から始まるも推定されている。実際、単離成は合成された11-(12)および12-水酸化体は不活性である。この代謝をブロックし、より高活性なアナログを開発する目的で、11位のモノフルオロ置換体を設計した。

合成（ラセミ体）は、既に報告した12-OH 体の合成経路に準じ、ノルボルネンを出発原料として用いて行った。鍵段階のフッ素化反応には DAST を用いた。

イネ芽生えの第二葉伸長長阻害試験では、このアナログはジャスモン酸メチルの約10 分の1 の活性であった。ハツカダイ コン芽生えの根伸長阻害試験でも活性は弱かったが、低濃度では逆に伸長を促進した。12-OH 体も同様の効果を示すことが知られている。これらの結果から、導入したC-F 結合は、望むC-H 結合のミミックではなく、C-OH 結合のミミックとして働き、活性が低下したものと考えた。