Synthesis and Cytokinin Activity of Two Fluoro Derivatives of N^6-Isopentenyladenine

Denis Clemenceau,† Jack Cousseau,† Valérie Martin,‡ Huguette Molines,‡ Claude Wakselman,‡ René Mornet,*,† Fabien Nogue,§ and Michel Laloue§

Laboratoire d'Ingénierie Moléculaire et Matériaux Organiques, Faculté des Sciences, 2 Boulevard Lavoisier, 49045 Angers Cedex, France, CERCOA, 2 à 8 rue Henry Dunant, 94320 Thiais, France, and Laboratoire de Biologie Cellulaire, INRA, Route de St Cyr, 78026 Versailles, France

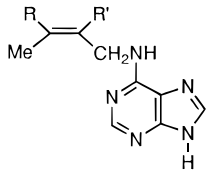
Two derivatives of N^6-isopentenyladenine, **3** and **4**, bearing either a vinylic fluorine atom or a trifluoromethyl group, were easily synthesized from known fluorinated precursors. Both derivatives **3** and **4** were found to be more active, as cytokinins, than the parent compounds zeatin (**1**) and N^6-isopentenyladenine (**2**).

Keywords: *Cytokinins; fluoro compounds; biological activity*

INTRODUCTION

Cytokinins, a family of plant hormones, have been the subject of numerous chemical studies (Koshimizu and Iwamura, 1986; Mok and Mok, 1994). Except for a series of *N*,*N*′-disubstituted ureas, most of the synthetic analogues of the natural cytokinins zeatin (**1**) and N^6-isopentenyladenine (**2**) are N^6-substituted adenines. Studies of structure−activity relationships for cytokinins in the adenine series have shown that the N^6-chain should contain no more than five or six carbon atoms for optimal activity (Matsubara, 1990).

Cytokinins, associated with auxins, another family of hormones, are essential in culture media used for *in vitro* cultures of plant cells and tissues, especially to induce bud formation. Synthetic cytokinins such as 6-benzylaminopurine or kinetin (Miller et al., 1956), both adenine derivatives, and the two ureas CPPU (Takahashi et al., 1978) and thidiazuron (Mok et al., 1982), are generally used for this purpose rather than zeatin (**1**) or N^6-isopentenyladenine (**2**) because they are less prone to metabolization in plant cells. One of the main pathways for degradation of the natural cytokinins **1** and **2** is the oxidation of the N^6-chain, giving adenine



1 R = $HOCH_2$, R' = H
2 R = Me, R' = H
3 R = Me, R' = F
4 R = CF_3, R' = H

and the corresponding aldehyde, through a hypothetic intermediate imine (Laloue and Fox, 1985). This reaction is catalyzed by cytokinin oxidases (Whitty and Hall, 1974; Mc Gaw and Horgan, 1983; Chatfield and Amstrong, 1986; Laloue and Fox, 1989).

No fluorinated derivatives of the natural cytokinins have been synthesized so far, and as the biological activity of a compound may be dramatically changed by replacement of an appropriate hydrogen atom by a fluorine atom (Filler and Kobayashi, 1982; Welsh, 1987; McCarthy et al., 1991), we have therefore prepared and studied the fluoro derivatives **3** and **4** of N^6-isopentenyladenine (**2**). These compounds were found to be more active as cytokinins than the natural analogues **1** and **2**.

EXPERIMENTAL PROCEDURES

Melting points have been taken on a Mettler FP 61 or a Reichert Thermovar hotstage apparatus. ^{1}H NMR spectra were recorded with TMS as internal standard at 270 MHz on a JEOL GSX 270 WB spectrometer or at 200 MHz on a Bruker AC 200 apparatus. ^{13}C NMR spectra were obtained from the JEOL spectrometer at 68.5 MHz and ^{19}F NMR spectra from the Brucker spectrometer at 188.13 MHz using $CFCl_3$ as reference. IR spectra were recorded on a Perkin-Elmer 1420 or 841 spectrometer and UV spectra on a Perkin-Elmer Lambda 2 spectrometer. Elemental analyses were obtained from the Service d'Analyses du CNRS, Lyon, France, or from the Service Central d'Analyses de l'Université Paris VI.

2-Fluoro-3-methylbut-2-en-1-ol (7). *Preparation Using $LiAlH_4$.* To a stirred suspension of $LiAlH_4$ (0.80 g, 21 mmol) in 50 mL of anhydrous diethyl ether, kept at 0 °C under nitrogen, was added the ester **6** (Machleidt and Wessendorf, 1963) (3.10 g, 21.2 mmol) in an anhydrous diethyl ether solution (10 mL). After 1 h, water was added dropwise until a white suspension was obtained. This suspension was filtered under reduced pressure, and the solvents were evaporated from the filtrate. The residue was distilled under reduced pressure to give **7** (1.48 g, 68%): bp 61 °C/20 Torr [lit. (Bessiere et al., 1977; Le Van and Schlosser, 1974) 60−63 °C/17 Torr]; IR (film) ν_{max} 3352, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 1.67 and 1.68 (2 s, 2 × 3H, 2 CH_3), 1.92 (s, 1H, OH), 4.22 (d, 2H, $^3J_{HF}$ = 22.6 Hz, CH_2O); ^{19}F NMR ($CDCl_3$) δ −121.90 (t × septuplet, $^3J_{HF}$ = 23.0 Hz, $^4J_{HF}$ = 3.1 Hz); ^{13}C NMR ($CDCl_3$) δ 15.70 (d, $^3J_{CF}$ = 8 Hz, CH_3), 17.40 (d, $^3J_{CF}$ = 5 Hz, CH_3), 57.98 (d, $^2J_{CF}$ = 31 Hz, OCH_2), 112.28 (d, $^2J_{CF}$ = 17 Hz, =C), 152.50 (d, $^1J_{CF}$ = 241 Hz, =CF).

Preparation Using Diisobutylaluminum Hydride. To a stirred solution of **6** (2.30 g, 15.8 mmol) in 50 mL of anhydrous diethyl ether, cooled to 0 °C under nitrogen, was added through a syringe a 1 M dichloromethane solution of diisobutylaluminum hydride (34.8 mL, 34.8 mmol). After 2 h at 0 °C, 6.73 g (20.9 mmol) of Na_2SO_4·$10H_2O$ was added, and stirring was kept on for 0.5 h. The suspension was filtered under reduced pressure, and the solvent was evaporated from the filtrate. The residue was distilled to give **7** (1.15 g, 70%).

2-Fluoro-3-methylbut-2-enylammonium Chloride (5a). To a stirred solution of the alcohol **7** (1.70 g, 16.3 mmol) in 10

* Author to whom correspondence should be addressed (e-mail rene.mornet@univ-angers.fr).

† Laboratoire d'Ingénierie Moléculaire et Matériaux Organiques.

‡ CERCOA.

§ INRA.

0021-8561/96/1444-0320$12.00/0

mL of THF, at room temperature, were added 19.5 mL of a 1 M solution of HN_3 in benzene (19.5 mmol) and isopropyl azodicarboxylate (3.60 g, 17.9 mmol) in 10 mL of THF. Then triphenylphosphine (9.4 g, 35.8 mmol) in 60 mL of THF was slowly added, while the temperature rose to 30 °C. The mixture was left at room temperature for 1 h, then heated, and kept at 50 °C for 3 h. The solvents were evaporated, and the residue was dissolved in 80 mL of dichloromethane. The solution was transferred into a separatory funnel, and 80 mL of a 1 M HCl solution was added. After decantation, the aqueous layer was collected, and the organic layer was extracted by 2 × 20 mL of the HCl solution. The gathered aqueous solutions were evaporated at 40 °C under reduced pressure. The residue was dissolved in 20 mL of a methanol−diethyl ether mixture (50:50). Addition of diethyl ether allowed the ammonium salt **5a** to precipitate. Filtration gave a white powder (1.54 g, 68%): mp 129 °C (dec); ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.64 (d, 3H, $^4J_{HF}$ = 3.3 Hz, CH_3), 1.67 (d, 3H, $^4J_{HF}$ = 2.8 Hz, CH_3), 3.66 (d, 2H, $^3J_{HF}$ = 22.1 Hz, CH_2), 8.54 (br s, 3H, NH_3^+); ^{19}F NMR (DMSO) δ −116.84 (t × septuplet, $^3J_{HF}$ = 22 Hz, $^4J_{HF}$ = 3.2 Hz); ^{13}C NMR (DMSO) δ 15.68 (d, $^3J_{CF}$ = 8 Hz, CH_3), 17.37 (d, $^3J_{CF}$ = 5 Hz, CH_3), 35.65 (d, $^2J_{CF}$ = 31 Hz, CH_2N), 115.08 (d, $^2J_{CF}$ = 16 Hz, =C), 147.06 (d, $^1J_{CF}$ = 240 Hz, =CF); HRMS found 103.0794 (M − HCl)$^+$, $C_5H_{10}FN$ requires 103.07972.

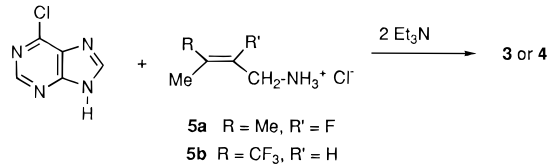
6-(2-Fluoro-3-methylbut-2-enylamino)purine (3). In 10 mL of ethanol were added 6-chloropurine (0.453 g, 2.93 mmol), the salt **5a** (0.389 g, 2.79 mmol), and 1 mL of triethylamine. The mixture was heated at reflux for 24 h. The solvent was evaporated, and the crude residue was chromatographed through a silica column (eluent chloroform−ethanol 9:1). The solid resulting from the fractions containing **3** was recrystallized from ethanol to give a white powder (0.465 g, 76%): mp 259 °C; ^{1}H NMR (DMSO-d_6) δ 1.59 (d, 3H, $^4J_{HF}$ = 3.3 Hz, CH_3), 1.74 (d, 3H, $^4J_{HF}$ = 2.6 Hz, CH_3), 4.34 (d, 2H, $^3J_{HF}$ = 18 Hz, CH_2N), 8.1 and 8.2 (2 s, 2 × 1H, 2 and 8 H-purine), 7.53−7.94 (m, 1H, NH); ^{19}F NMR (DMSO) δ −116.31 (unresolved peak); ^{13}C NMR (DMSO) δ 15.68 (d, $^3J_{CF}$ = 8 Hz, CH_3), 17.28 (d, $^3J_{CF}$ = 5 Hz, CH_3), 36.42 (d, $^2J_{CF}$ = 38 Hz, CH_2N), 109.01 (d, $^2J_{CF}$ = 12 Hz, =C), 128.51, 129.24, 132.66, 138.97, 152.17 (C-purine), 151.1 (d, $^1J_{CF}$ = 242 Hz, =CF); UV (EtOH) λ_{max} 267 nm (ϵ_{max} = 21 800); HRMS found 221.1087, $C_{10}H_{12}N_5F$ requires 221.10767. Elemental analysis found: C, 53.97; H, 5.60; F, 8.18. Calcd for $C_{10}H_{12}N_5F$: C, 54.29; H, 5.47; F, 8.59.

***N*-[(*E*)-3-(Trifluoromethyl)but-2-enyl]phthalimide (9).** *From (E)-1-Bromo-3-(trifluoromethyl)but-2-ene* (**8**) *(Martin et al., 1993).* A mixture of **8** (3.5 g, 17.3 mmol), dry potassium carbonate (0.986 g, 7.14 mmol), and phthalimide (2.1 g, 14.3 mmol) was heated at 120 °C with stirring for 4 h. The mixture was then cooled, and water (10 mL) was added. The solid that precipitated was filtered, washed with water (2 × l0 mL) and methanol (10 mL), and recrystallized from methanol to give the expected phthalimide **9** as white crystals (2.79 g, 72%): mp 199 °C; ^{1}H NMR ($CDC1_3$, 200 MHz) δ 1.91 (s, 3H, CH_3), 5.82 (d, 2H, J = 6.8 Hz, CH_2), 6.04 (br t, 1H, J = 6.8 Hz, =CH), 7.64−7.81 (m, 4H, H-phenyl); ^{19}F NMR ($CDCl_3$) δ −70 (s); IR (CCl_4) ν_{max} 2910, 2840, 1760, 1710, 1600 cm^{-1}. Elemental analysis found: C, 57.89; H, 3.77. Calcd for $C_{13}H_{10}F_3NO_2$: C, 57.99; H, 3.74.

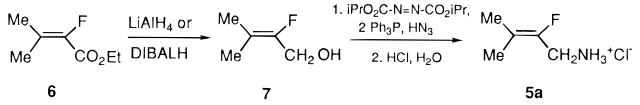
From (E)-3-(Trifluoromethyl)but-2-en-1-ol (**10**). Diethyl azodicarboxylate (1.6 g, 10.7 mmol) was slowly added to a stirred mixture of triphenylphosphine (2.8 g, 10.7 mmol) and potassium phthalimide (1.57 g, 10.7 mmol) in THF (15 mL), at 0 °C. (*E*)-3-(Trifluoromethyl)but-2-en-1-ol **(10)** (Kaminski et al., 1989) (1 g, 7.14 mmol) was then added dropwise and the mixture stirred at room temperature for 30 min. After cooling and the addition of water (10 mL), the mixture was acidified with 3 M HCl and extracted with ether (3 × 20 mL). The organic layers were dried over magnesium sulfate. After filtration, the solvent was evaporated under vacuum (20 Torr). The solid was recrystallized from a small amount of warm methanol to give **9** (1.08 g, 56%).

(*E*)-3-(Trifluoromethyl)but-2-enylammonium Chloride (5b). A mixture of **9** (2.79 g, 10.4 mmol) and hydrazine hydrate (0.625 g, 12.5 mmol) in methanol (50 mL) was heated at reflux for 2 h. A white gelatinous precipitate was formed.

Scheme 1. General Method of Preparation of N^6-Substituted Adenines Used for Obtaining the Fluorocytokinins 3 and 4



Scheme 2. Synthesis of the Amine Salt 5a



After cooling, 10 mL of 3 M HCl solution was added, and the mixture was heated at reflux for 1 h. The mixture was cooled, and solid phthalylhydrazide was removed by filtration and washed with water (2 × l0 mL). The filtrate was extracted with ether (3 × 50 mL). The aqueous layer was neutralized with aqueous sodium hydroxide (2 M) and extracted with diethyl ether (3 × 30 mL). The organic layer was dried over magnesium sulfate. After filtration, the ethereal layer was saturated with anhydrous hydrogen chloride. The mixture was filtered to give **5b** as white crystals (1.09 g, 60%): mp 200 °C (dec); ^{1}H NMR (CD_3OD, 200 MHz) δ 1.82 (s, 3H, CH_3), 3.67 (d, 2H, J = 6.8 Hz, CH_2), 4.82 (s, 3H, NH_3^+), 6.11 (br t, 1H, J = 6.8 Hz, =CH); ^{19}F NMR (CD_3OD) δ −70.83 (s); IR ν_{max} 3400, 3000, 1600 cm^{-1}. Elemental analysis found: C, 34.75; H, 5.15; N, 7.88. Calcd for $C_5H_9F_3ClN$: C, 34.20; H, 5.17; N, 7.98.

(*E*)-6-[3-(Trifluoromethyl)but-2-enylamino]purine (4) was prepared according to the same method as **3**, from 6-chloropurine (154.5 mg, 1 mmol), **5b** (194 mg, 1.1 mmol), and triethylamine (253 mg, 2.5 mmol). The crude solid obtained was recrystallized from water−ethanol, giving white crystals of **4** (130 mg, 50%): mp 227 °C; ^{1}H NMR (DMSO-d_6, 270 MHz) δ 1.89 (s, 3H, CH_3), 4.25 (m, 2H, CH_2), 6.24 (t, 1H, J = 5.4 Hz, =CH), 7.98 (m, 1H, NH), 8.12 and 8.21 (2 s, 2 × 1H, 2 and 8-H purine). Elemental analysis found: C, 46.52; H, 3.88; F, 21.85; N, 27.02. Calcd for $C_{10}H_{10}F_3N_5$: C, 46.70; H, 3.92; F, 22.16; N, 27.23.

Biological Assay. About 50 surface-sterilized seeds of mutant zea 1−64 of *Nicotiana plumbaginifolia* were sown in 9-cm Petri dishes containing 15 mL of B medium (Bourgin et al., 1979). The compounds to be assayed were added to the autoclaved cooling medium from 30 mM stock solutions in DMSO. Petri dishes were placed in a growth chamber with a long daylight regime (16 h of light at 25 °C, 6 h of darkness at 23 °C). The fresh weight of 20 plantlets was measured after 3 weeks of growth. Similar results were obtained in two separate experiments.

RESULTS AND DISCUSSION

Chemistry. Both N^6-substituted adenines **3** and **4** were prepared according to the classical method (Leonard, 1974) which consists of heating to reflux 6-chloropurine with the corresponding amines in ethanol. Here, the amines were generated from their hydrochlorides **5a,b** by the action of triethylamine, used in excess for further neutralization of the hydrochloric acid produced in the reaction (Scheme 1).

The amine salt **5a** was prepared from the ester **6** (Machleidt and Wessendorf, 1963) (Scheme 2). This compound was reduced either by lithium aluminum hydride or by diisobutylaluminum hydride to give the alcohol **7** in about 70% yield. This alcohol **7**, which has been previously prepared according to other methods (Nakayama et al., 1985; Bessiere et al., 1977; Le Van and Schlosser, 1974), was transformed into **5a** through a one-pot procedure (Fabiano et al., 1987). It was first

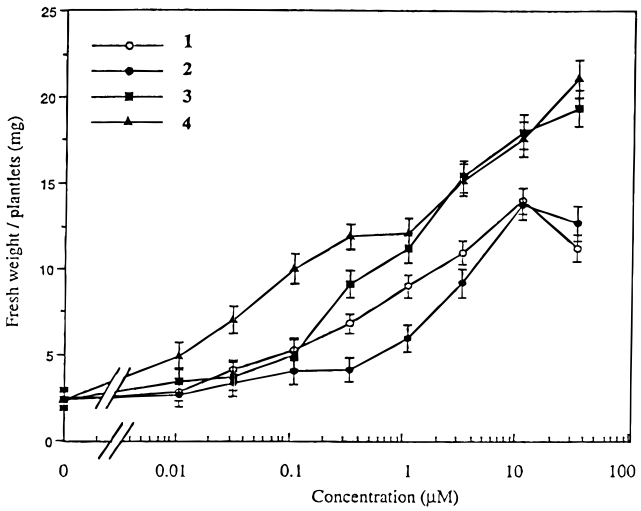
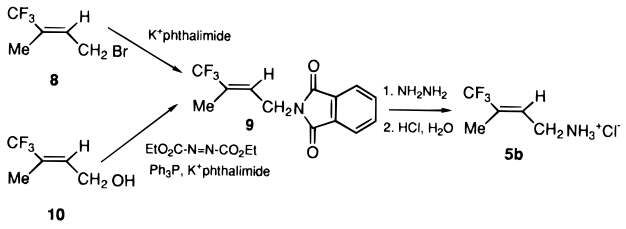


Figure 1. Cytokinin activity assay: fresh weight of mutant plantlets of *N. plumbaginifolia* cultured on variable concentrations of tested compounds **3** and **4**. The response is compared to that of zeatin (**1**) and N^6-isopentenyladenine (**2**). Bars indicate standard deviation.

Scheme 3. Synthesis of the Amine Salt 5b



converted into an azide via a Mitsunobu reaction, followed by an *in situ* Staudinger reaction between this azide and a second equivalent of triphenylphosphine. The subsequent acid hydrolysis with aqueous HCl of the resulting nonisolated iminophosphorane afforded **5a** in 68% yield.

The amine salt **5b** was easily obtained through a Gabriel reaction involving the bromide **8** (Martin et al., 1993). The intermediate phthalimide **9** was also prepared by using the Mitsunobu procedure from the alcohol **10** (Kaminski et al., 1989) (Scheme 3).

Biological Activity. The biological properties of the fluorocytokinins **3** and **4** were evaluated in an assay using mutant plantlets of *N. plumbaginifolia* (Nogue et al., 1995), which exhibit a characteristic hypertrophy specially evoked by cytokinins. This assay has been recognized to give similar results to cellular division tests with tobacco cells or callus. Cytokinin activity was expressed as the fresh weight increase of the plantlets *vs* concentration of cytokinins (Figure 1). Zeatin (**1**) and N^6-isopentenyladenine (**2**) were used as reference compounds.

As shown in Figure 1, both compounds **3** and **4** were found to be more active than N^6-isopentenyladenine (**2**) and zeatin (**1**). Compound **4** exhibited the highest activity, especially at low concentration range, since a significant stimulation of plantlet growth (4-fold) was achieved in the presence of 0.1 μM of **4**, as compared to 0.3, 1, and 3 μM for **3**, **1**, and **2**, respectively. At concentrations above 1 μM, **3** and **4** are equally active and more than 3 times more active than the parent compounds **1** and **2**. Thus, it is clear that the fluorine vinylic atom in **3** and the trifluoromethyl group in **4** exert beneficial effects on activity in these compounds. These effects may be related to a better fitting in the hypothetical cytokinins receptor(s). However, fluorine atoms may have sufficient effects to inhibit or slow down the oxidative cleavage of the aliphatic chain by cytokinin oxidases in **3** and **4**, to give either competitive inhibitors of these enzymes or long-lived cytokinins, respectively. Further biochemical works will be necessary to verify these hypotheses. In particular, purification of wheat germ cytokinin oxidase (Laloue and Fox, 1989) is in progress. It should allow us to study its interactions with the fluorocytokinins **3** and **4**.

ACKNOWLEDGMENT

We thank Dr. Marc Tordeux (CERCOA) for fruitful discussions about syntheses.

LITERATURE CITED

Bessiere, Y.; Savary, D. N. H.; Schlosser, M. Solvolytic ring-opening of alkoxychlorofluoro-cyclopropanes; a ready access to fluorinated α,β-unsaturated aldehydes and ketones. *Helv. Chim. Acta* **1977**, *60*, 1739−1746.

Bourgin, J. P.; Chupeau, Y.; Missonier, C. Plant regeneration from mesophyll protoplasts of several *Nicotiana* species. *Physiol. Plant.* **1979**, *45*, 288−292.

Chatfield, J. M.; Amstrong, D. J. Regulation of cytokinin oxidase activity in callus tissues of *Phaseolus vulgaris* L. cv Great Northern. *Plant Physiol.* **1986**, *80*, 493−499.

Fabiano, E.; Golding, B. T.; Sadeghi, M. M. A simple conversion of alcohols into amines. *Synthesis* **1987**, 190−192.

Filler, R.; Kobayashi, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982; Chapter 1.

Kaminski, J. J.; Solomon, D. M.; Conn, D. J.; Wong, S. C.; Chiu, P. J. S.; Massa, T.; Siegel, M. I.; Watnick, A. S. Antiinflammatory activity of a series of substituted 2,3-dihydro-6-hydroxypyrimido[2,1-*f*]purine-4,8(1*H*,9*H*)-diones. *J. Med. Chem.* **1989**, *32*, 1118−1127.

Koshimizu, K.; Iwamura, I. Cytokinins. In *The Chemistry of Plant Hormones*; Takahashi, N., Ed.; CRC Press: Boca Raton, FL, 1986; Chapter 4.

Laloue, M.; Fox, J. E. Characterization of an imine intermediate in the degradation of isopentenylated cytokinins by a cytokinin oxidase from wheat. *Abstracts of Papers*, 12th International Conference on Plant Growth Substances, Heidelberg; International Plant Growth Substances Association: Heidelberg, 1985; p 23.

Laloue, M.; Fox, J. E. Cytokinin oxidase from wheat. Partial purification and general properties. *Plant Physiol.* **1989**, *90*, 899.

Leonard, N. J. Chemistry of cytokinins. In *The Chemistry and Biochemistry of Plant Hormones*; Runeckles, V. C., Sondheimer, E., Walton, D. C., Eds.; Academic Press: New York, 1974; p 27.

Le Van, C.; Schlosser, M. Silver ion-induced ring-opening of chlorofluorocyclopropanes. *Synthesis* **1974**, 115−116.

Machleidt, H.; Wessendorf, W. Organische fluorverbindungen, IV. Carbonyl-fluorolefinierungen (Fluoroorganic compounds, IV. Fluoroethylenic compounds from reaction of carbonyl groups). *Liebigs Ann. Chem.* **1963**, *674*, 1−10.

Martin, V.; Molines, H.; Wakselman, C. 1-Bromo-3-trifluoromethylbut-2-ene: synthesis and electrophilic reactivity. *J. Fluorine Chem.* **1993**, *62*, 63−68.

Matsubara S. Structure-activity relationships of cytokinins. *Crit. Rev. Plant Sci.* **1990**, *9*, 17−57.

McCarthy, J. R.; Matthews, D. P.; Stemerick, D. M.; Huber, E. W.; Bey, P.; Lippert, B. J.; Snyder, R. D.; Sunkara, P. S. Stereospecific methods to E and Z terminal fluoro olefins and its application to the synthesis of 2′-deoxy-2′-fluoromethylene nucleosides as potential inhibitors of ribonucleoside diphosphate reductase. *J. Am. Chem. Soc.* **1991**, *113*, 7439−7440.

McGaw, B. A.; Horgan, R. Cytokinin oxidase from *Zea mays* kernels and *Vinca rosea* crown-gall tissue. *Planta* **1983**, *159*, 30−37.

Miller, C. O.; Skoog, F.; Okumura, F. S.; Von Saltza, M. H.; Strong, F. M. Isolation, structure and synthesis of kinetin, a substance promoting cell division. *J. Am. Chem. Soc.* **1956**, *78*, 1375−1380.

Mok, D. W. S.; Mok, M. C. In *Cytokinins, Chemistry, Activity, and Function*; CRC Press: Boca Raton, FL, 1994; pp 15−55.

Mok, M. C.; Mok, D. W. S.; Amstrong, D. J.; Shudo, K.; Isogai, Y.; Okamoto, T. Cytokinin activity of *N*-phenyl-*N*′-1,2,3-thiadiazol-5-ylurea (thidiazuron). *Phytochemistry* **1982**, *21*, 1509−1511.

Nakayama, Y.; Kitazume, T.; Ishikawa, N. Synthesis of useful building blocks for monofluorinated compounds derived from trifluoroethene. *J. Fluorine Chem.* **1985**, *29*, 445−458.

Nogue, F.; Jullien, M.; Mornet, R.; Laloue, M. The response to cytokinins of a cytokinin resistant mutant is highly specific and permits a new bioassay. *Plant Growth Regul.* **1995**, *17*, 87−99.

Takahashi, S.; Shudo, K.; Okamoto, T.; Yamada, K.; Isogai, Y. Cytokinin activity of *N*-phenyl-*N*′-(4-pyridyl)urea derivatives. *Phytochemistry* **1978**, *17*, 1201−1207.

Welch, J. T. Advances in the preparation of biologically active organofluorine compounds. *Tetrahedron* **1987**, *43*, 3123−3197.

Whitty, C. D.; Hall, R. H. Cytokinin oxidase in *Zea mays*. *Can. J. Biochem.* **1974**, *52*, 789−799.

Received for review February 22, 1995. Revised manuscript received October 4, 1995. Accepted October 24, 1995.[⊗]

JF9501148

[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1995.