

# Synthesis and Cytokinin Activity of New Zeatin Derivatives

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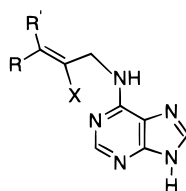
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The analogue of zeatin bearing a vinylic fluorine atom and its geometrical isomer were synthesized. The fluorine atom exerts a favorable influence on cytokinin activity in the fluoro analogue of *cis*-zeatin, but not in the fluoro analogue of zeatin itself. Another series of zeatin derivatives in which the methyl group was replaced by alkyl (ethyl, propyl, and isopropyl), phenyl, and benzyl groups were also obtained. The ethyl analogue was found to be more active than zeatin, while the others were inactive or slightly active.

**Keywords:** Cytokinins; fluoro compounds; synthesis; biological activity

## INTRODUCTION

Zeatin (**1**) and *N*<sup>6</sup>-isopentenyladenine (**2**) are the most



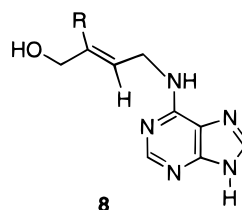
- 1 R = HOCH<sub>2</sub>, R' = Me, X = H
- 2 R = R' = Me, X = H
- 3 R = R' = Me, X = F
- 4 R = CF<sub>3</sub>, R' = Me, X = H
- 5 R = HOCH<sub>2</sub>, R' = Me, X = F
- 6 R = Me, R' = HOCH<sub>2</sub>, X = F
- 7 R = Me, R' = HOCH<sub>2</sub>, X = H

widespread natural plant hormones of the cytokinin family. Except for a series of *N,N'*-disubstituted ureas, the most active cytokinins are *N*<sup>6</sup>-substituted adenines. In this latter class of compounds, studies of structure–activity relationships have demonstrated that optimal cytokinin activity was observed when the *N*<sup>6</sup>-chain contains five or six carbon atoms and bears a double bond in the 2,3-position (Matsubara, 1990). Analogues of zeatin (**1**) have been studied, corresponding to various chain isomerisms (Schmitz et al., 1972), hydroxylation or dihydroxylation (Leonard et al., 1968; Letham, 1973; Van Staden and Drewes, 1982) and hydrogenation (Fujii and Ogawa, 1972) of the double bond, and methylation at the C-1 of the chain (Fujii et al., 1989). However, in zeatin (**1**), neither the influence on the activity of the replacement of the methyl group by other substituents nor that of the replacement of the vinylic proton by halogens has been yet investigated.

We recently synthesized two new derivatives (**3** and **4**) of *N*<sup>6</sup>-isopentenyladenine (**2**), the activities of which were found to be significantly higher than the activity of **2** (Clemenceau et al., 1996). In particular, a near 10-fold increase in activity was observed when the vinylic

hydrogen atom in **2** was substituted for fluorine. Thus, an exceptionally high cytokinin activity was expected for fluorozeatin (**5**), since zeatin (**1**) has been found to be more active than *N*<sup>6</sup>-isopentenyladenine (**2**) in various bioassays (Matsubara, 1990). We describe here the synthesis of this new zeatin analogue and of its geometrical isomer **6** related to *cis*-zeatin (**7**) and the results of their cytokinin bioassays.

We previously described a method of synthesis of zeatin (**1**) (Mornet and Gouin, 1977) which could be used for zeatin analogues where the methyl group is substituted for various other groups. To enrich structure–activity relationships in the zeatin series, we have also synthesized compounds **8a–e** to evaluate their cytokinin activity.



- a R = Et
- b R = Pr
- c R = iPr
- d R = Ph
- e R = Bz

## EXPERIMENTAL PROCEDURES

Melting points were measured with a Reichert Thermovar hotstage apparatus. <sup>1</sup>H NMR spectra were recorded with TMS as an internal standard, at 270 MHz on a JEOL GSX 270 WB spectrometer or at 60 MHz on a Varian EM 360 apparatus. <sup>13</sup>C NMR spectra were obtained from the JEOL spectrometer at 67.9 MHz, and <sup>19</sup>F spectra from the same apparatus at 254.2 MHz, using TMS and CFC<sub>3</sub> as internal standards, respectively. EI mass spectra were recorded with a VG Autospec spectrometer. Microanalyses were obtained from the Service d'Analyses du CNRS (Lyon, France).

**2-Methyl-1-(trityloxy)-2-propene (9).** To a solution of 2-methyl-2-propen-1-ol (11.0 g, 153 mmol), triethylamine (21.6 mL, 153 mmol), and 4-(dimethylamino)pyridine (0.50 g, 4.1 mmol) in dimethylformamide (200 mL) was added trityl chloride (43.4 g, 156 mmol). The reaction mixture was stirred in a nitrogen atmosphere for 24 h. The solution was then diluted with water (350 mL). The white precipitate which was obtained was filtered and extracted with hot cyclohexane (300

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mL). The white crystals obtained on cooling were filtered and dried to give 25.0 g (52%) of compound **9**:  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.51 (s, 3H,  $\text{CH}_3$ ), 3.30 (s, 2H,  $\text{CH}_2\text{O}$ ), 4.72 and 5.04 (2 s,  $2 \times 1\text{H}$ ,  $=\text{CH}_2$ ), 7.01–7.15 and 7.25–7.30 (2 m, 15H, H-phenyl).

**1-Bromo-1-fluoro-2-methyl-2-[(trityloxy)methyl]cyclopropane (10)**. To a mixture of the ethylenic compound **9** (20.0 g, 0.064 mol), benzyltriethylammonium chloride (0.4 g, 0.88 mmol), sodium hydroxide (25 mL of a 50% aqueous solution), and dichloromethane (250 mL) was added dibromofluoromethane (19.2 g, 0.1 mol) dropwise while the solution was stirred. The mixture was heated to reflux with vigorous stirring for 36 h. After cooling, water (1 L) was added, and the solution was extracted with dichloromethane ( $3 \times 100$  mL). The combined organic layers were washed with water and dried over magnesium sulfate. After evaporation of the solvent under low pressure, the residue was chromatographed through a silica gel column with hexane/dichloromethane (8:2) as the eluent. The appropriate fractions were combined and evaporated to leave 19 g of a mixture containing 13.7 g (50%) of **10**, as a mixture of diastereomers, and 5.3 g of the starting compound **9** (according to  $^1\text{H NMR}$  determination). **10** was not further purified:  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90–1.10 and 1.20–1.40 (2 m,  $2 \times 1\text{H}$ ,  $\text{CH}_2$ -ring), 1.34 (d, 3H,  $^4J_{\text{HF}} = 2.1$  Hz,  $\text{CH}_3$ ), 3.06–3.14 (m, 2H,  $\text{CH}_2\text{O}$ ), 7.10–7.30 and 7.41–7.47 (2 m, 15H, H-phenyl).

**N-[(Z)-2-Fluoro-3-methyl-4-(trityloxy)-2-butenyl]phthalimides (11Z and 11E)**. Crude cyclopropane **10** (15 g containing 10.79 g of **10**, 26 mmol) and potassium phthalimide (9 g, 48.6 mmol) were dissolved in dimethylformamide (100 mL). The mixture was heated to 110 °C for 72 h. After cooling, water (200 mL) was added, and the mixture was extracted with dichloromethane ( $3 \times 100$  mL). The combined organic extracts were washed with water (100 mL) and dried over magnesium sulfate. After evaporation of the solvent, the residue was chromatographed through a silica gel column with hexane/ethyl acetate (8:2) as the eluent. Two fractions were isolated which contained respectively the isomers **11Z** and **11E** as major products. After evaporation of the solvents from these fractions, the residues were recrystallized from pentane. Pure **11Z** was obtained as a white powder (6.0 g, 47%): mp 175 °C;  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.96 (d, 3H,  $^4J_{\text{HF}} = 2.8$  Hz,  $\text{CH}_3$ ), 3.73 (d, 2H,  $^4J_{\text{HF}} = 3.3$  Hz,  $\text{CH}_2\text{O}$ ), 4.44 (d, 2H,  $^3J_{\text{HF}} = 20.2$  Hz,  $\text{CH}_2\text{N}$ ), 7.10–7.35 and 7.40–7.50 (2 m, 15H, H-triphenyl), 7.72 and 7.83 (2 m,  $2 \times 2\text{H}$ , H-phthalimide). Elemental analysis found: C, 77.94; H, 5.20; F, 3.74; N, 2.81. Calcd for  $\text{C}_{32}\text{H}_{26}\text{FNO}_3$ : C, 78.19; H, 5.33; F, 3.86; N, 2.85. **11E** was obtained as a white powder containing about 10% of its isomer **11Z** (3.0 g, 23.5%):  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70 (d, 3H,  $^4J_{\text{HF}} = 3.5$  Hz,  $\text{CH}_3$ ), 3.79 (d, 2H,  $^4J_{\text{HF}} = 1.7$  Hz,  $\text{CH}_2\text{O}$ ), 4.20 (d, 2H,  $^3J_{\text{HF}} = 19.7$  Hz,  $\text{CH}_2\text{N}$ ), 7.10–7.30 and 7.40 (2 m, 15H, H-triphenyl), 7.63 and 7.75 (2 m,  $2 \times 2\text{H}$ , H-phthalimide).

**N-[(Z)-2-Fluoro-4-hydroxy-3-methyl-2-butenyl]phthalimide (12Z)**. The phthalimide **11Z** (3.58 g, 7.3 mmol) was dissolved in methanol (100 mL), and *p*-toluenesulfonic acid (1.5 g, 7.5 mmol) was added. The solution was stirred for 48 h at room temperature. The solvent was evaporated, and the residue was chromatographed through a silica gel column with dichloromethane/ethanol (95:5) as the eluent. Evaporation of the appropriate fraction left pure **12Z** as a white powder (1.20 g, 66%): mp 111 °C;  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.96 (d, 3H,  $^4J_{\text{HF}} = 2.8$  Hz,  $\text{CH}_3$ ), 4.22 (d, 2H,  $^4J_{\text{HF}} = 3.1$  Hz,  $\text{CH}_2\text{O}$ ), 4.57 (d, 2H,  $^3J_{\text{HF}} = 20.0$  Hz,  $\text{CH}_2\text{N}$ ), 7.70 and 7.80 (2 m,  $2 \times 2\text{H}$ , H-phthalimide);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  13.3 (d,  $^3J_{\text{CF}} = 4.2$  Hz,  $\text{CH}_3$ ), 35.2 (d,  $^2J_{\text{CF}} = 31.2$  Hz,  $\text{CH}_2\text{N}$ ), 59.7 (d,  $^3J_{\text{CF}} = 10.4$  Hz,  $\text{CH}_2\text{O}$ ), 116.7 (d,  $^2J_{\text{CF}} = 11.4$  Hz,  $\text{C}=\text{CF}$ ), 149.0 (d,  $^1J_{\text{CF}} = 250.0$  Hz,  $=\text{CF}$ ). Elemental analysis found: C, 62.59; H, 4.72; F, 7.54; N, 5.64. Calcd for  $\text{C}_{13}\text{H}_{12}\text{FNO}_3$ : C, 62.65; H, 4.85; F, 7.62; N, 5.62.

**N-[(E)-2-Fluoro-4-hydroxy-3-methyl-2-butenyl]phthalimide (12E)**. This compound was obtained (300 mg, 52%) with the same procedure used for **12Z** from the impure phthalimide **11E** (1.139 g, 2.32 mmol). It was contaminated by a small amount (<10%) of its isomer **12Z**:  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.76 (d, 3H,  $^4J_{\text{HF}} = 3.3$  Hz,  $\text{CH}_3$ ), 4.26 (d, 2H,

$^4J_{\text{HF}} = 1.9$  Hz,  $\text{CH}_2\text{O}$ ), 4.56 (d, 2H,  $^3J_{\text{HF}} = 22.0$  Hz,  $\text{CH}_2\text{N}$ ), 7.73 and 7.84 (2 m, 4H, H-phthalimide);  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  12.3 (d,  $^3J_{\text{CF}} = 7.3$  Hz,  $\text{CH}_3$ ), 36.5 (d,  $^2J_{\text{CF}} = 31.2$  Hz,  $\text{CH}_2\text{N}$ ), 63.9 (d,  $^3J_{\text{CF}} = 8.3$  Hz,  $\text{CH}_2\text{O}$ ), 119.7 (d,  $J = 13.2$  Hz,  $\text{C}=\text{CF}$ ), 152.0 (d,  $^1J_{\text{CF}} = 251.3$  Hz,  $=\text{CF}$ ).

**(Z)-2-Fluoro-4-hydroxy-3-methylbut-2-enylamine (13Z)**. A solution of the phthalimide **12Z** (996 mg, 4 mmol) and 0.25 mL of hydrazine hydrate in methanol (20 mL) was heated to reflux with stirring for 2 h. After cooling, the white precipitate obtained was filtered and washed with water (5 mL). The combined filtrates were evaporated under reduced pressure, and the residue was chromatographed through a silica gel column with dichloromethane/ethanol (95:5) as the eluent. **13Z** was obtained as a yellowish oil and was not further purified (305 mg, 64%):  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70 (d, 3H,  $^4J_{\text{HF}} = 2.8$  Hz,  $\text{CH}_3$ ), 3.4 (d, 2H,  $^3J_{\text{HF}} = 21.6$  Hz,  $\text{CH}_2\text{N}$ ), 4.13 (d, 2H,  $^4J_{\text{HF}} = 3.0$  Hz,  $\text{CH}_2\text{O}$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  13.1 (d,  $^3J_{\text{CF}} = 4.2$  Hz,  $\text{CH}_3$ ), 39.2 (d,  $^2J_{\text{CF}} = 31.1$  Hz,  $\text{CH}_2\text{N}$ ), 59.1 (d,  $^3J_{\text{CF}} = 11.4$  Hz,  $\text{CH}_2\text{O}$ ), 112.7 (d,  $^2J_{\text{CF}} = 14.5$  Hz,  $\text{C}=\text{CF}$ ), 155.4 (d,  $^1J_{\text{CF}} = 253.5$  Hz,  $=\text{CF}$ ).

**(E)-2-Fluoro-4-hydroxy-3-methylbut-2-enylamine (13E)**. This compound was obtained with the same procedure used for **13Z**, from impure **12E** (240 mg, 1 mmol). The product was isolated as a yellowish oil (83 mg, 70%) and was contaminated (<10%) by **13Z**:  $^1\text{H NMR}$  (270 MHz,  $\text{CDCl}_3$ )  $\delta$  1.73 (d, 3H,  $^4J_{\text{HF}} = 3.3$  Hz,  $\text{CH}_3$ ), 3.46 (d, 2H,  $^3J_{\text{HF}} = 22.0$  Hz,  $\text{CH}_2\text{N}$ ), 4.02 (d, 2H,  $^4J_{\text{HF}} = 1.9$  Hz,  $\text{OCH}_2$ );  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ )  $\delta$  12.3 (d,  $^3J_{\text{CF}} = 7.3$  Hz,  $\text{CH}_3$ ), 39.1 (d,  $^2J_{\text{CF}} = 30.1$  Hz,  $\text{CH}_2\text{N}$ ), 61.7 (d,  $^3J_{\text{CF}} = 9.3$  Hz,  $\text{CH}_2\text{O}$ ), 114.3 (d,  $^2J_{\text{CF}} = 14.5$  Hz,  $\text{C}=\text{CF}$ ), 156.6 (d,  $^1J_{\text{CF}} = 250.2$  Hz,  $=\text{CF}$ ).

**6-[(Z)-2-Fluoro-4-hydroxy-3-methylbut-2-enylamino]purine (5)**. The amino alcohol **13Z** (250 mg, 2.1 mmol), 6-chloropurine (320 mg, 2.07 mmol), and triethylamine (0.65 mL) were dissolved in ethanol (20 mL). The solution was heated at 80 °C for 24 h. The solvent was evaporated under reduced pressure, and the residue was recrystallized from water. After filtration and drying at 100 °C under reduced pressure, **5** was obtained as a white powder (350 mg, 74%): mp 223–224 °C;  $^1\text{H NMR}$  (270 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.78 (3H,  $^4J_{\text{HF}} = 2.6$  Hz,  $\text{CH}_3$ ), 3.96 (s, 2H,  $\text{CH}_2\text{O}$ ), 4.41 (d, 2H,  $^3J_{\text{HF}} = 21.0$  Hz,  $\text{CH}_2\text{N}$ ), 4.67 (br s, 1H, OH), 7.80 (br s, 1H, NH), 8.10 and 8.20 (2 s,  $2 \times 1\text{H}$ , 2 and 8H-purine);  $^{19}\text{F NMR}$  (pyridine- $d_5$ )  $\delta$  -115.9 (unresolved peak). Elemental analysis found: C, 50.50; H, 5.10; N, 29.03. Calcd for  $\text{C}_{10}\text{H}_{12}\text{FN}_5\text{O}$ : C, 50.63; H, 5.09; N, 29.05.

**6-[(E)-2-Fluoro-4-hydroxy-3-methylbut-2-enylamino]purine (6)**. It was prepared from the impure amino alcohol **13E** (59.5 mg, 0.5 mmol), with the same procedure used for **5**. The crude product **6** obtained was purified by reversed phase chromatography through a Lichroprep (40–63  $\mu\text{m}$ ) glass column (310  $\times$  25 mm), using water/methanol (70:30) as the eluent. After evaporation of the solvents from the appropriate fractions of the eluent, pure **6** (59 mg, 50%) was obtained as a white powder: mp 220 °C;  $^1\text{H NMR}$  (270 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.63 (d, 3H,  $^4J_{\text{HF}} = 3.20$  Hz,  $\text{CH}_3$ ), 4.08 (d, 2H,  $^4J_{\text{HF}} = 4.23$  Hz,  $\text{CH}_2\text{O}$ ), 4.40 (d, 2H,  $^3J_{\text{HF}} = 20.3$  Hz,  $\text{CH}_2\text{N}$ ), 4.8 (br s, 1H, OH), 7.7 (br s, 1H, NH), 8.12 and 8.19 (2 s,  $2 \times 1\text{H}$ , 2 and 8 H-purine);  $^{19}\text{F NMR}$  (pyridine- $d_5$ )  $\delta$  -113.0 (unresolved peak). Elemental analysis found: C, 50.47; H, 5.11; N, 28.82. Calcd for  $\text{C}_{10}\text{H}_{12}\text{FN}_5\text{O}$ : C, 50.63; H, 5.09; N, 29.05.

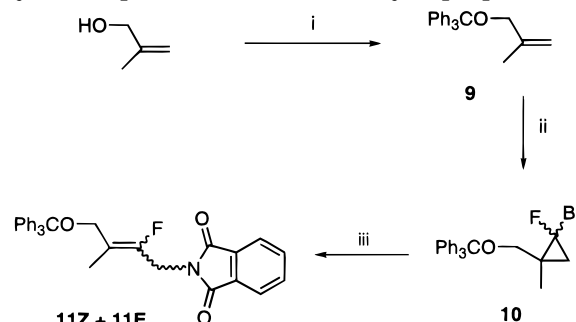
**General Method of Preparation of the 2-Substituted (E)-1-Acetoxy-4-(N-phthalimido)but-2-enes (15a–e)**. Potassium phthalimide (11.1 g, 60 mmol) and a chloroacetate **14** (50 mmol) were stirred overnight in dimethylformamide (100 mL). Water (100 mL) was then added, and the mixture was extracted with diethyl ether ( $3 \times 100$  mL). The combined organic layers were dried over sodium sulfate, and the solvent was evaporated. The residue was recrystallized from petroleum ether or petroleum ether/toluene, leaving white crystals. **15a** (2-ethyl) (13.3 g, 93%): mp 56.5 °C (petroleum ether);  $^1\text{H NMR}$  (60 MHz,  $\text{CCl}_4$ )  $\delta$  1.10 (t, 3H,  $J = 7.5$  Hz,  $\text{CH}_2\text{CH}_3$ ), 2.02 (s, 3H,  $\text{CH}_3\text{C}=\text{O}$ ), 2.28 (q, 2H,  $J = 7.5$  Hz,  $\text{CH}_2\text{CH}_3$ ), 4.25 (d, 2H,  $J = 7.5$  Hz,  $\text{CH}_2\text{N}$ ), 4.47 (s, 2H,  $\text{CH}_2\text{O}$ ), 5.48 (t, 1H,  $J = 7.5$  Hz,  $\text{HC}=\text{C}$ ), 7.60–8.00 (m, 4H, H-phenyl). Elemental analysis found: C, 66.87; H, 5.92; N, 4.63. Calcd for  $\text{C}_{16}\text{H}_{17}$

NO<sub>4</sub>: C, 66.89; H, 5.96; N, 4.88. **15b** (2-propyl) (13.4 g, 89%): mp 72 °C (petroleum ether); <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 1.00 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.20–1.90 (m, 2H, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.02 (s, 3H, CH<sub>3</sub>C=O), 2.30 (t, 2H, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 4.27 (d, 2H, *J* = 7.0 Hz, CH<sub>2</sub>N), 4.43 (s, 2H, CH<sub>2</sub>O), 5.53 (t, 1H, *J* = 7.0 Hz, HC=), 7.50–7.90 (m, 4H, H-phenyl). Elemental analysis found: C, 67.67; H, 6.32; N, 4.54. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub>: C, 67.76; H, 6.36; N, 4.65. **15c** (2-isopropyl) (12.9 g, 86%): mp 56.5 °C (petroleum ether); <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 1.15 [d, 6H, *J* = 7 Hz, (H<sub>3</sub>C)<sub>2</sub>CH], 2.02 (s, 3H, CH<sub>3</sub>C=O), 3.20 [h, 1H, *J* = 7.0 Hz, CH(CH<sub>3</sub>)<sub>2</sub>], 4.30 (d, 2H, *J* = 7.0 Hz, CH<sub>2</sub>N), 4.50 (s, 2H, CH<sub>2</sub>O), 5.47 (t, 1H, *J* = 7.0 Hz, HC=), 7.60–7.90 (m, 4H, H-phenyl). Elemental analysis found: C, 67.59; H, 6.25; N, 4.72. Calcd for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub>: C, 67.76; H, 6.36; N, 4.65. **15d** (2-phenyl) (13.2 g, 79%): mp 87–88 °C (petroleum ether/toluene); <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 1.97 (s, 3H, CH<sub>3</sub>C=O), 4.20 (d, 2H, *J* = 7.0 Hz, CH<sub>2</sub>N), 4.70 (s, 2H, CH<sub>2</sub>O), 5.72 (t, 1H, *J* = 7.0 Hz, HC=), 7.33 (br s, 5H, H-phenyl), 7.60–7.90 (m, 4H, H-phthalimide). Elemental analysis found: C, 71.59; H, 5.02; N, 4.22. Calcd for C<sub>20</sub>H<sub>17</sub>NO<sub>4</sub>: C, 71.63; H, 5.11; N, 4.18. **15e** (2-benzyl) (14.3 g, 82%): mp 103–104 °C (petroleum ether/toluene); <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>) δ 1.95 (s, 3H, CH<sub>3</sub>C=O), 3.67 (s, 2H, CH<sub>2</sub>-benzyl), 4.42 (d, 2H, *J* = 7.0 Hz, CH<sub>2</sub>N), 4.42 (s, 2H, CH<sub>2</sub>O), 5.73 (t, 1H, *J* = 7.0 Hz, HC=), 7.23 (br s, 5H, H-phenyl), 7.60–7.90 (m, 4H, H-phthalimide). Elemental analysis found: C, 72.25; H, 5.40; N, 4.16. Calcd for C<sub>21</sub>H<sub>19</sub>NO<sub>4</sub>: C, 72.19; H, 5.48; N, 4.01.

**General Method of Preparation of the (E)-3-Alkyl(or phenyl)-4-hydroxybut-2-enylamines (16a–e).** A suspension of a phthalimide/ester **15** (10 mmol) and of barium hydroxide octahydrate (9.45 g, 30 mmol) in water (15 mL) was heated to reflux for 3 h. After cooling, the solution was acidified to pH 3. After centrifugation of the mixture, the supernatant was evaporated to dryness under reduced pressure. Recrystallization of the residue in ethanol left a gummy product which was used without further purification, except for **15c** (3-isopropyl), which was obtained as white plates (1.226 g, 69%): mp 70–80 °C dec. Elemental analysis found: C, 47.26; H, 9.14; N, 7.93. Calcd for C<sub>14</sub>H<sub>32</sub>N<sub>2</sub>O<sub>6</sub>S: C, 47.17; H, 9.05; N, 7.86.

**General Method of Preparation of the 6-[(E)-3-Alkyl(or phenyl)-4-hydroxybut-2-enylamino]purines (8a–e).** 6-Chloropurine (154.5 mg, 1 mmol), an amine **16** as the ammonium sulfate (0.75 mmol), and triethylamine (1 mL) were heated in butanol to reflux for 2 h. After cooling, the solvent was evaporated to dryness under reduced pressure, and the residue was recrystallized from water with decolorizing on Darco carbon, leaving white crystals. **8a** (3-ethyl) (82 mg, 35%): mp 174–176 °C; <sup>1</sup>H NMR (270 MHz, DMSO-*d*<sub>6</sub>) δ 0.99 (t, 3H, *J* = 7.0 Hz, CH<sub>3</sub>), 2.13 (q, 2H, *J* = 7.0 Hz, CH<sub>2</sub>CH<sub>3</sub>), 3.84 (br s, 2H, CH<sub>2</sub>O), 4.15 (br s, 2H, CH<sub>2</sub>N), 4.70 (br s, 1H, OH), 5.50 (t, 1H, *J* = 7.0 Hz, =CH), 7.81 (br s, 1H, NH), 8.08–8.17 (2 s, 2 × 1H, 2 and 8-H purine). Elemental analysis found: C, 56.54; H, 6.66; N, 30.12. Calcd for C<sub>11</sub>H<sub>15</sub>N<sub>5</sub>O: C, 56.64; H, 6.48; N, 30.02. **8b** (3-propyl) (148 mg, 60%): mp 129 °C; <sup>1</sup>H NMR (270 MHz, DMSO-*d*<sub>6</sub>) δ 0.89 (t, 3H, *J* = 6.5 Hz, CH<sub>3</sub>), 1.40 (m, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.08 (t, 2H, *J* = 7.5 Hz, CH<sub>2</sub>-CH<sub>2</sub>CH<sub>3</sub>), 3.83 (br s, 2H, CH<sub>2</sub>O), 4.15 (br s, 2H, CH<sub>2</sub>N), 4.70 (m, 1H, OH), 5.54 (t, 1H, *J* = 7.0 Hz, =CH), 7.66 (br s, 1H, NH), 8.09–8.18 (2 s, 2 × 1H, 2 and 8-H purine). Elemental analysis found: C, 58.09; H, 6.86; N, 28.27. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O: C, 58.28; H, 6.93; N, 28.32. **8c** (3-isopropyl) (128 mg, 52%): mp 226 °C; <sup>1</sup>H NMR (270 MHz, DMSO-*d*<sub>6</sub>) δ 1.03 (d, 6H, *J* = 7.1 Hz, 2 CH<sub>3</sub>), 2.94 [h, 1H, *J* = 7.0 Hz, CH(CH<sub>3</sub>)<sub>2</sub>], 3.91 (br s, 2H, CH<sub>2</sub>O), 4.18 (br s, 2H, CH<sub>2</sub>N), 4.59 (br s, 1H, OH), 5.50 (t, 1H, *J* = 7.0 Hz, =CH), 7.73 (br s, 1H, NH), 8.08 and 8.17 (2 s, 2 × 1H, 2 and 8-H purine). Elemental analysis found: C, 57.97; H, 7.15; N, 28.23. Calcd for C<sub>12</sub>H<sub>17</sub>N<sub>5</sub>O: C, 58.28; H, 6.93; N, 28.32. **8d** (3-phenyl) (70 mg, 25%): mp 130 °C; <sup>1</sup>H NMR (270 MHz, DMSO-*d*<sub>6</sub>) δ 4.10 (br s, 2H, CH<sub>2</sub>N), 4.15 (br s, 2H, CH<sub>2</sub>O), 5.0 (br s, 1H, OH), 5.85 (t, 1H, *J* = 7.0 Hz, =CH), 7.25–7.50 (m, 5H, H-phenyl), 8.07 and 8.16 (2 s, 2 × 1H, 2 and 8-H purine). Elemental analysis found: C, 64.31; H, 5.29; N, 25.01. Calcd for C<sub>15</sub>H<sub>16</sub>N<sub>5</sub>O: C, 64.04; H, 5.37; N, 24.89. **8e** (3-benzyl) (207 mg, 70%): mp 217 °C; <sup>1</sup>H NMR (270

### Scheme 1. Synthesis of the Tetrasubstituted Fluorovinyl Compounds **11** from 2-Methyl-2-propen-1-ol



(i) Ph<sub>3</sub>CCl, Et<sub>3</sub>N, DMAP/DMF; (ii) Br<sub>2</sub>FCH, OH<sup>-</sup>, PhCH<sub>2</sub>NEt<sub>3</sub><sup>+</sup>Cl<sup>-</sup>/CH<sub>2</sub>Cl<sub>2</sub>-H<sub>2</sub>O; (iii) K<sup>+</sup> phthalimide/DMF

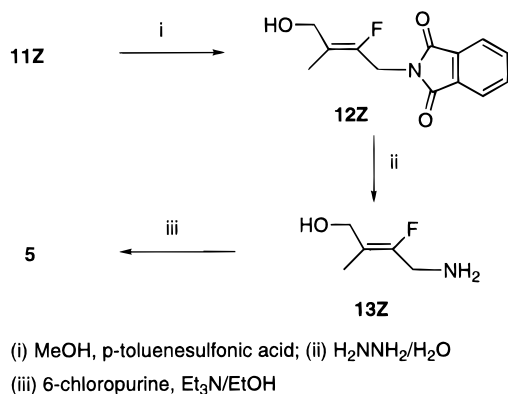
MHz, DMSO-*d*<sub>6</sub>) δ 3.40 (s, 2H, CH<sub>2</sub>-benzyl), 3.72 (br s, 2H, CH<sub>2</sub>O), 4.28 (br s, 2H, CH<sub>2</sub>N), 4.78 (br s, 1H, OH), 5.70 (t, 1H, *J* = 7.0 Hz, =CH), 7.20–7.40 (m, 5H, H-phenyl), 7.80 (br s, 1H, NH), 8.08 and 8.18 (2 s, 2 × 1H, 2 and 8-H purine); HRMS found 295.14177 (M<sup>+</sup>), calcd for C<sub>16</sub>H<sub>17</sub>N<sub>5</sub>O 295.14331.

**Biological Assay.** Compounds **5**, **6**, and **8a–e** were assayed according to the procedure previously described (Clemenceau et al., 1996; Nogue et al., 1995), using zeatin (**1**) and its geometrical isomer *cis*-zeatin (**7**) as reference active compounds.

## RESULTS AND DISCUSSION

**Chemistry.** *Fluorozeatins 5 and 6.* Most of the methods used for obtaining tetrasubstituted fluorovinyl compounds were initially investigated for the synthesis of the trisubstituted analogues. These include condensation of diethyl fluoromalonate with ketones (Kitazume and Ishikawa, 1981), reaction of trifluorovinyl lithium with ketones (Poulter et al., 1977; Normant et al., 1975), Grignard reaction of 1-acyl-1,2-difluoro-2-phenylsulfanylenes (Nakayama et al., 1985), alkylation by alkyl halides of ethyl phenylsulfanylfluoroacetate (Allmendiger, 1991), and Horner–Wadworth–Emmons reaction of a ketone with a 2-(diethylphosphono)-2-fluoroacetate (Massoudi et al., 1983; Etemad-Moghadam and Seyden-Penne, 1985; Machleidt and Weissendorf, 1964), with the corresponding acid (Coutrot and Grison, 1987) or with the corresponding nitrile (Xu and Desmarteau, 1992). The addition of bromofluorocarbene to a double bond, followed by the ring opening of the cyclopropane with the use of a nucleophile (Chau and Schlosser, 1974; Schlosser et al., 1975; Schlosser and Chau, 1975; Müller et al., 1977), was also an efficient method. The nucleophiles used included the diethyl malonate anion, the acetate anion, or toluene. The addition of the carbene was not stereoselective, and a mixture of the two fluoroethylenic compounds was generally obtained at the final step.

We selected this last method as a common source of the two geometrical isomers, for building the skeleton of the aliphatic chain in fluorozeatins **5** and **6** (Scheme 1). We started from 1-hydroxy-2-methyl-2-propene by protecting its alcohol function with the trityl group. The obtained ethylenic compound **9** reacted with the carbene generated from dibromofluoromethane and sodium hydroxide in a phase-transfer conditions reaction. At this step, the cyclopropane **10** which was a mixture of diastereomers, considering the complexity of the NMR signals corresponding to the ring methylene protons, could not be completely separated from the unreacted

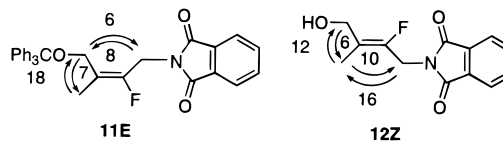
**Scheme 2. Synthesis of Fluorozeatin 5**

starting material **9**. The *R<sub>f</sub>* of this compound in thin-layer chromatography was indeed very close to that of **10** under various conditions of elution. The crude product **10** reacted with potassium phthalimide as a nucleophile, leaving a mixture of the two geometrical isomers **11Z** and **11E**. Pure fluoroethylenic phthalimide **11Z** was isolated by chromatography on silica gel and further recrystallization, but after the same treatment, its isomer **11E** remained contaminated by **11Z**.

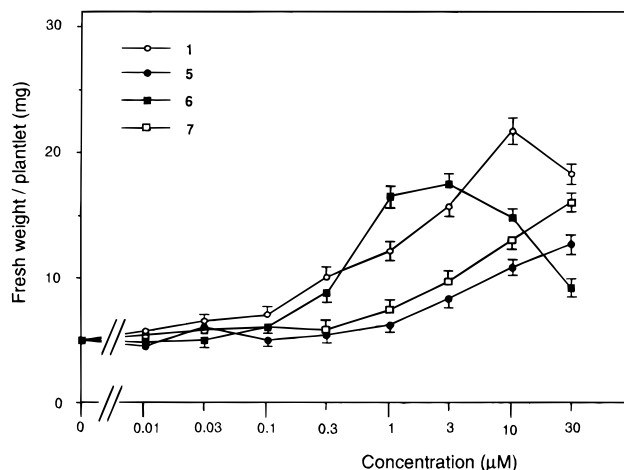
The route from the phthalimide **11Z** to the fluorozeatin **5** is described in Scheme 2. The trityl group was first eliminated by methanolysis in the presence of *p*-toluenesulfonic acid, leading to the phthalimide alcohol **12Z** which further reacted with hydrazine to give the amino alcohol **13Z**. Reaction of this amine with 6-chloropurine in the last step gave finally the expected fluorozeatin **5**. A similar pathway from the impure compound **11E** gave the fluorozeatin **6**, which was separated from a small amount of its isomer **5** by reversed phase chromatography.

The configurations of the ethylenic isomers were checked by NMR spectroscopy. Examination of <sup>1</sup>H NMR data found in the literature for tetrasubstituted ethylenic compounds revealed that the allylic coupling constants <sup>4</sup>*J*<sub>HF</sub> between the vinylic fluorine nucleus and methyl protons followed the rule *J*<sub>trans</sub> < *J*<sub>cis</sub> (Normant et al., 1975; Poulter et al., 1977; Lovey and Pauson, 1982; Coutrot et al., 1987; Abraham and Ellison, 1987). This feature was also found for compounds **5**, **6**, and **11–13**. However, <sup>13</sup>C NMR data, including CF coupling constants, were not available for tetrasubstituted fluoroethylenic compounds. A correlation <sup>3</sup>*J*<sub>cis</sub> < <sup>3</sup>*J*<sub>trans</sub> was found in trisubstituted fluoroethylenes (Bosch et al., 1987), but we did not find a similar sequence with tetrasubstituted compounds **12** and **13**. The <sup>13</sup>C NMR spectra of these compounds showed that <sup>3</sup>*J*<sub>transCH<sub>3</sub>F</sub> (4.2 Hz) was smaller than <sup>3</sup>*J*<sub>cisCH<sub>3</sub>F</sub> (7.3 Hz). Thus, the configurations of the fluoroethylenic compounds were definitely assigned from {<sup>1</sup>H}–<sup>1</sup>H nuclear Overhauser effect studies (NOEDIFF) on final compounds **5** and **6**. Presaturation of the CH<sub>2</sub>O protons led to an enhancement of 7% in **5** and 8% in **6** for the methyl proton signal. However, a 3% enhancement of the CH<sub>2</sub>N signal was observed in **6**, while the expected negative relayed nOe (–3%) appeared for **5** for the same protons. The configurations of the phthalimide ether **11E** and of the phthalimide alcohol **12Z** have been also assigned from nOe studies. The signal enhancements, consistent with the proposed structures, are shown in Figure 1.

**Zeatin Analogues 8a–e.** Zeatin analogues **8a–e** were synthesized using a pathway similar to that used for

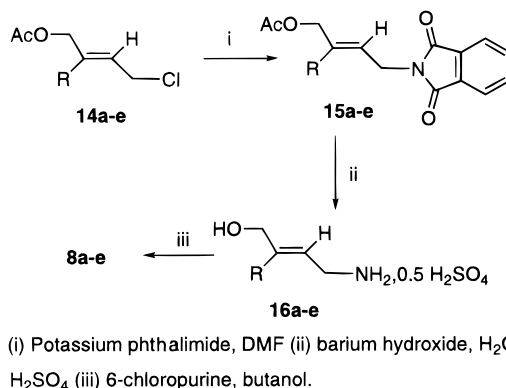


**Figure 1.** Significant nOe enhancements (percentage) observed for **11Z** and **12E**.



**Figure 2.** Cytokinin activity assay. Fresh weight of mutant plantlets of *N. plumbaginifolia* cultured with compounds **5** and **6** at various concentrations. The response is compared to that of zeatin (**1**) and *cis*-zeatin (**7**). Bars indicate standard deviations.

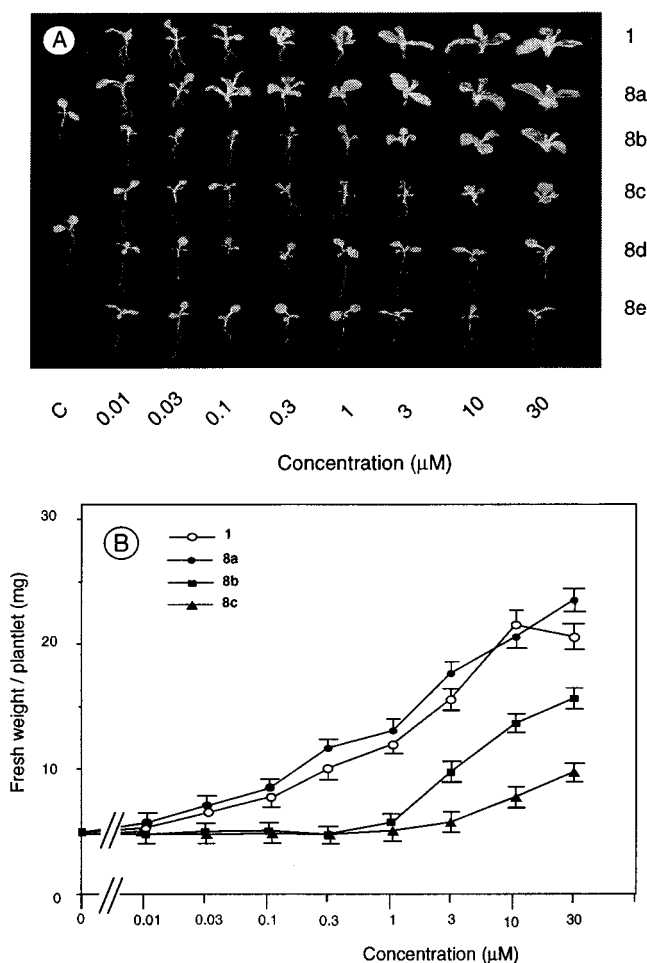
**Scheme 3. Syntheses of Zeatin Analogues 8a–e** (for **8a**, R = Et; for **8b**, R = Pr; for **8c**, R = *i*Pr; for **8d**, R = Ph; and for **8e**, R = Bz)



zeatin (**1**) (Mornet and Gouin, 1977a) from the allylic chlorides **14a–e** (Mornet and Gouin, 1977b) (Scheme 3). Phthalimides **15a–e** were obtained by reaction of these chlorides with potassium phthalimide in dimethylformamide. Hydrolysis of both the phthalimide and the acetate was carried out by heating compounds **15a–e** in an aqueous solution of barium hydroxide. Amino alcohols **16a–e** were isolated as the ammonium sulfates and further reacted with 6-chloropurine to give the expected N<sup>6</sup>-substituted adenines **8a–e**.

**Biological Activity.** The biological properties of zeatin derivatives **5**, **6**, and **8a–e** were evaluated with the same bioassay that was used for the previously studied fluorozeatins (Clemenceau et al., 1996), using mutant plantlets of *Nicotiana plumbaginifolia* (Nogue et al., 1995), which exhibit a characteristic hypertrophy specifically evoked by cytokinins.

The variations of the fresh weight of plantlets versus concentration of fluorozeatins **5** and **6**, and of reference compounds zeatin (**1**) and *cis*-zeatin (**7**), are represented



**Figure 3.** Cytokinin activity assay. (A) Phenotype of mutant plantlets of *N. plumbaginifolia* cultured on compounds **8a–e** at various concentrations. (B) Fresh weight of plantlets cultured on compounds **8a–c** at various concentrations. Bars indicate standard deviations. In both cases, the response is compared to that of zeatin (**1**).

in Figure 2. As observed with other bioassays (Schmitz et al., 1972), *cis*-zeatin was less active than zeatin. Maximal hypertrophy of the plantlets was obtained in the presence of 30 μM *cis*-zeatin. Such a stimulation was already attained in the presence of 3 μM zeatin. On the contrary, the fluoro analogue (**6**) of *cis*-zeatin was more active than zeatin at intermediate concentrations (1 and 3 μM) and at high concentrations (10 and 30 μM), for which a relative inhibition was observed due to a supraoptimal effect. Thus, in this range of concentration, **6** was at least 10-fold more active than *cis*-zeatin (**7**) itself, as previously observed in the case of *N*<sup>6</sup>-isopentenyladenine and of its fluoro analogue (Clemenceau et al., 1996). However, and unexpectedly, such an increase of cytokinin activity was not observed in the case of the fluoro analogue (**5**) of zeatin which appeared to be about 10-fold less active than the parent compound (**1**) over the whole range of concentrations.

Thus, the beneficial effect on cytokinin activity attributed to a vinylic fluorine atom, which we observed in the fluoro analogue of *N*<sup>6</sup>-isopentenyladenine (**3**) (Clemenceau et al., 1996), is confirmed only in the analogue of *cis*-zeatin (**7**). We proposed earlier that the presence of the vinylic fluorine atom in these molecules would render them less sensitive to oxidative cleavage of the aliphatic chain by cytokinin oxidases. However, this would not be the case for the fluoro analogue of

zeatin (**5**). The particular behavior of this compound might be attributed to the existence of an internal hydrogen bond between the fluorine and the OH hydrogen atoms. Examination of a molecular model shows that the loss of side chain planarity which could be detrimental to activity (Hecht et al., 1970) is not observed. Moreover, the model allows the three atoms (F...H–O) to be almost aligned, with a F–O distance (2.26 Å) that is compatible with the existence of a weak but true hydrogen bond (Howard et al., 1996). In this case, the molecule might be forced to adopt a conformation unfavorable to the binding at the cytokinin receptors. However, this hypothesis appears to be improbable if we consider the weak energy expected for such a hydrogen bond. As a comparison, a hydrogen bond energy as weak as 1.48 kcal mol<sup>-1</sup> has been calculated recently for fluoroethylene in water (Howard et al., 1996). One will be able to verify this hypothesis only when receptors to cytokinins are discovered.

Except for the ethyl analogue **8a** (Figure 3A,B) which was as active as zeatin (**1**), zeatin analogues **8a–e** exhibit weaker activity than zeatin (**1**), **8d** and **e** being completely inactive, as seen with the absence of root growth inhibition. In this respect, at the lowest concentrations assayed (i.e. 0.03–0.3 μM), **8a** was slightly more active than zeatin in term of root growth inhibition (Figure 3A). These observations let us suppose that zeatin (**1**) is not the optimal ligand for the cytokinin receptors. In particular, the bulk and hydrophobicity of the chain may be slightly increased in the surroundings of the methyl group for a better fitting. This information may be valuable for further studies of three-dimensional quantitative structure–activity relationships (QSAR).

#### LITERATURE CITED

- Abraham, R. J.; Ellison, S. L. R.; Barfield, M.; Thomas, W. A. An experimental and theoretical investigation of orientational dependence of H-F couplings in fluoro-olefins. *J. Chem. Soc., Perkin Trans. 2* **1987**, 977–985.
- Allmendiger, T. Ethyl phenylsulfinyl fluoroacetate, a new and versatile reagent for the preparation of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated carboxylic acid esters. *Tetrahedron* **1991**, *47*, 4905–4914.
- Bosch, M. P.; Camps, F.; Fabriàs, G.; Guerrero, A. Determination of the stereochemistry of disubstituted fluoroethylenes by <sup>13</sup>C NMR spectroscopy. *Magn. Reson. Chem.* **1987**, *25*, 347–351.
- Chau, L. V.; Schlosser, M. Silberion-induzierte ringöffnung von chlorofluorocyclopropanen (Silver ion induced ring opening of chlorofluorocyclopropanes). *Synthesis* **1974**, 115–116.
- Clemenceau, D.; Cousseau, J.; Martin, V.; Molines, H.; Wakselman, C.; Mornet, R.; Nogue, F.; Laloue, M. Synthesis and cytokinin activity of two fluoro derivatives of *N*<sup>6</sup>-isopentenyladenine. *J. Agric. Food Chem.* **1996**, *44*, 320–323.
- Coutrot, P.; Grison, C.; Sauvêtre, R. 2-Diethoxyphosphoryl alcanoic acid dianions (lithium- $\alpha$ -lithiocarboxylates) [Stereo-selective synthesis of (E)-2-fluoro-2,3-ethylenic esters by Wittig-Horner reaction of methyl (diethylphosphono)-2-fluoroacetate. Comparative study with methyl (diphenylphosphono)-2-fluoroacetate]. *J. Organomet. Chem.* **1987**, *332*, 1–8.
- Etemad-Moghadam, G.; Seyden-Penne, J. Synthèse stéréosélective d'esters  $\alpha,\beta$ -éthyléniques  $\alpha$ -fluorés E par réaction de Wittig-Horner à partir du diéthyl phosphono  $\alpha$ -fluoroacétate de méthyle. Etude comparative avec le diphenyl phosphonoxy  $\alpha$ -fluoroacétate de méthyle. *Bull. Soc. Chim. Fr.* **1985**, 448–454.
- Fujii, T.; Ogawa, N. Absolute configuration of (–)-dihydrozeatin. *Tetrahedron Lett.* **1972**, 3075–3078.

- Fujii, T.; Itaya, T.; Matsubara, S. Purines. XXXIII. Syntheses and cytokinin activities of both enantiomers of 1'-methylzeatin and their 9- $\beta$ -D-ribofuranosides. *Chem. Pharm. Bull.* **1989**, *37*, 1758–1763.
- Hecht, S. M.; Leonard, N. J.; Schmitz, R. Y.; Skoog, F. Cytokinins: influence of side-chain planarity of N<sup>6</sup>-substituted adenines and adenosines on their activity in promoting cell growth. *Phytochemistry* **1970**, *9*, 1907–1913.
- Howard, J. A. K.; Hoy, V. J.; O'Hagan, D.; Smith, G. T. How good is fluorine as a hydrogen bond acceptor? *Tetrahedron* **1996**, *52*, 12613–12622.
- Kitazume, T.; Ishikawa, N. One-pot synthesis of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated esters from chloromalonate ester and carbonyl compounds using "spray-dried" potassium fluoride. *Chem. Lett.* **1981**, 1259–1260.
- Leonard, N. J.; Hecht, S. M.; Skoog, F.; Schmitz, R. Y. Cytokinins: Synthesis and biological activities of related derivatives of 2iP, 3iP, and their ribosides. *Isr. J. Chem.* **1968**, *6*, 539–550.
- Letham, D. S. Cytokinins from Zea Mays. *Phytochemistry* **1973**, *12*, 2445–2455.
- Lovey, A. J.; Pawson, B. A. Fluorinated retinoic acids and their analogues. 3. Synthesis and biological activity of aromatic 6-fluoro analogues. *J. Med. Chem.* **1982**, *25*, 71–75.
- Machleidt, H.; Wessendorf, R. Organische Fluorverbindungen, IV Carbonyl-fluorolefinierungen (Fluoroorganische Verbindungen, IV. Carbonyl fluoroolefinierung). *Liebigs Ann. Chem.* **1964**, *674*, 1–10.
- Massoudi, H. H.; Cantacuzène, D.; Wakselman, C.; Bouthier de la Tour, C. Synthesis of the cis- and trans-isomers of homoaconitic and fluorohomoaconitic acid. *Synthesis* **1983**, 1010–1012.
- Matsubara, S. Structure–activity relationships of cytokinins. *Crit. Rev. Plant Sci.* **1990**, *9*, 17–57.
- Mornet, R.; Guoin, L. Synthèse de l'acétate du chloro-4 méthyl-2 butène-2-ol-1 (E). Nouvelle voie d'accès à la trans-zeatine [Synthesis of (E)-4-chloro-2-methyl-2-butenyl acetate. New access to trans-zeatin]. *Tetrahedron Lett.* **1977a**, 167–168.
- Mornet, R.; Guoin, L. The carbonochloridate cleavage of tertiary amines; a simple step in the preparation of di- and trisubstituted olefinic (allylic) synthons. *Synthesis* **1977b**, 786–787.
- Müller, C.; Stier, F.; Weyerstahl, P. Darstellung, ringöffnungsreaktionen und halogen/lithium-austausch von 1-brom-1-fluorocyclopropanen (Synthesis, ring cleavage, and halogen/lithium exchange of 1-bromo-1-fluorocyclopropanes). *Chem. Ber.* **1977**, *110*, 124–137.
- Nakayama, Y.; Kitazume, T.; Ishikawa, N. Synthesis and 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 of a cytokinin resistant mutant is highly specific and permits a new bioassay. *Plant Growth Regul.* **1995**, *17*, 87–94.
- Normant, J. F.; Foulon, J. P.; Masure, D.; Sauvêtre, R.; Villiéras, J. A new preparation of trifluorovinylolithium. Applications to the syntheses of trifluorovinylalcohols and of  $\alpha$ -fluoro- $\alpha$ -ethylenic acids and derivatives. *Synthesis* **1975**, 122–125.
- Poulter, C. D.; Argyle, J. C.; Mash, E. A. Prenyltransferase. New evidence for an ionization-condensation-elimination mechanism with 2-fluorogeranyl pyrophosphate. *J. Am. Chem. Soc.* **1977**, *99*, 957–959.
- Schlosser, M.; Chau, L. V. Fluororganische synthesen. V. Darstellung und abwandlung von chlorfluorocyclopropanen. Ein gezielter zugang zu fluorallylkoholen (Fluoroorganische synthesen, V. Preparation and transformations of chloro-fluorocyclopropanes. A selective approach to fluoroallylic alcohols). *Helv. Chim. Acta* **1975**, *58*, 2595–2603.
- Schlosser, M.; Spahic, B.; Tarchini, C.; Chau, L. V. Insertion of a carbon atom into olefinic double bonds: synthesis of fluorodienes and fluoroalkenes. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 365–366.
- Schmitz, R. Y.; Skoog, F.; Playtis, A. J.; Leonard, N. J. Cytokinins: Synthesis and biological activity of geometric and position isomers of zeatin. *Plant Physiol.* **1972**, *50*, 702–705.
- Van Staden, J.; Drewes, S. E. 6-(2,3,4-Trihydroxy-3-methylbutylamino)purine, a cytokinin with high biological activity. *Phytochemistry* **1982**, *21*, 1783–1784.
- Xu, Z. Q.; DesMarteau, D. D. A convenient one-pot synthesis of  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated nitriles from diethyl cyanofluoromethanephosphonate. *J. Chem. Soc., Perkin Trans. 1* **1992**, 313–315.

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