Syntheses of *cis*-Zeatin and Its 9-(2-Deoxy-*β*-D-ribofuranosyl) Derivative: A Novel Synthetic Route to the Side Chain at C(6), and Cytokinin Activity

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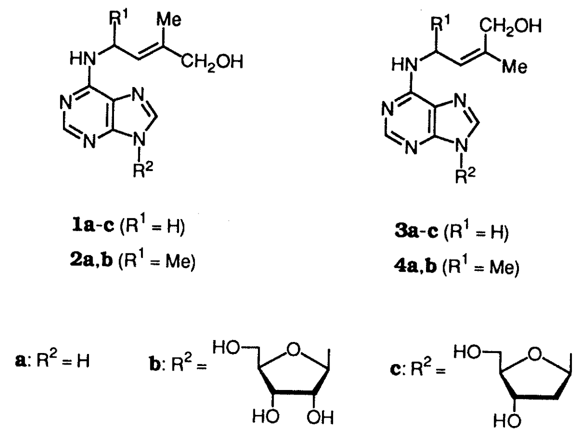
cis-Zeatin (3a) and its 9-(2-deoxy-β-D-ribofuranosyl) derivative (3c) have been synthesized from N-[(1,1-dimethylethoxy)carbonyl]glycine methyl ester (5) in 5 steps by adopting the "α-amino aldehyde/olefination" technology. The new *cis*-zeatin derivative (3c), its *trans* isomer (1c), and known *trans*-zeatin 9-β-D-riboside (1b) were tested for cytokinin activity in the stimulation of chlorophyll biosynthesis in etiolated cucumber cotyledons. The riboside 1b turned out to be the most active cytokinin among them, while the deoxyribosides 1c and 3c showed a marked decrease and a total loss, respectively, of cytokinin activity.

Keywords *cis*-zeatin synthesis; *cis*-zeatin 9-(2-deoxy-*β*-D-ribofuranosyl); *trans*-zeatin 9-*β*-D-ribofuranosyl; *trans*-zeatin 9-(2-deoxy-*β*-D-ribofuranosyl); glycine; *α*-amino aldehyde olefination; *Z* stereoselectivity; diisobutylaluminum hydride reduction; cytokinin activity; chlorophyll biosynthesis stimulation

In 1989, Evidente *et al.*[1] reported the isolation of a new cytokinin from the culture filtrate of *Pseudomonas amygdali*, and its structure was established as 9-(2-deoxy-*β*-D-ribofuranosyl)-*trans*-zeatin (**1c**) by means of chemical synthesis.[1-3] The natural occurrence of both *cis*-zeatin (**3a**) and *trans*-zeatin (**1a**) at the aglycone and the 9-*β*-D-ribofuranoside (**3b** and **1b**) levels[4] suggests that the *cis* isomer (**3c**) of the new cytokinin **1c** may also occur in nature, and the availability of a synthetic reference sample would greatly facilitate the search for this *cis* isomer as a natural product. We therefore investigated the synthesis of **3c** in the present work by adopting the "α-amino aldehyde/olefination" technology, which had been shown by us to be very effective for the construction of the side chains at C(6) of both enantiomers of *trans*-1'-methylzeatin (**2a**) and *cis*-1'-methylzeatin (**4a**), and of their 9-*β*-D-ribofuranosides (**2b** and **4b**)[5,6] and **1c**.[2]



The synthetic route to **3c** started with reduction of the *N*-protected glycine methyl ester **5** with diisobutylaluminum hydride (DIBAH) in CH_2Cl_2–hexane at $-78\,°C$ for 1 h, giving the aldehyde **6** in 67% yield. Olefination of **6** by the Still–Gennari modification[7] [$(CF_3CH_2O)_2P(O)CH(Me)$-CO_2Me, $KN(SiMe_3)_2$, 18-crown-6/MeCN, tetrahydrofuran (THF), $-78\,°C$, 30 min] of the Horner–Wadsworth–Emmons reaction[8] produced the desired (*Z*)-ester **7** and the undesired (*E*)-ester **9** in 58% and 0.5% yields, respectively. On the other hand, Wittig reaction[8] of **6** with methyl 2-

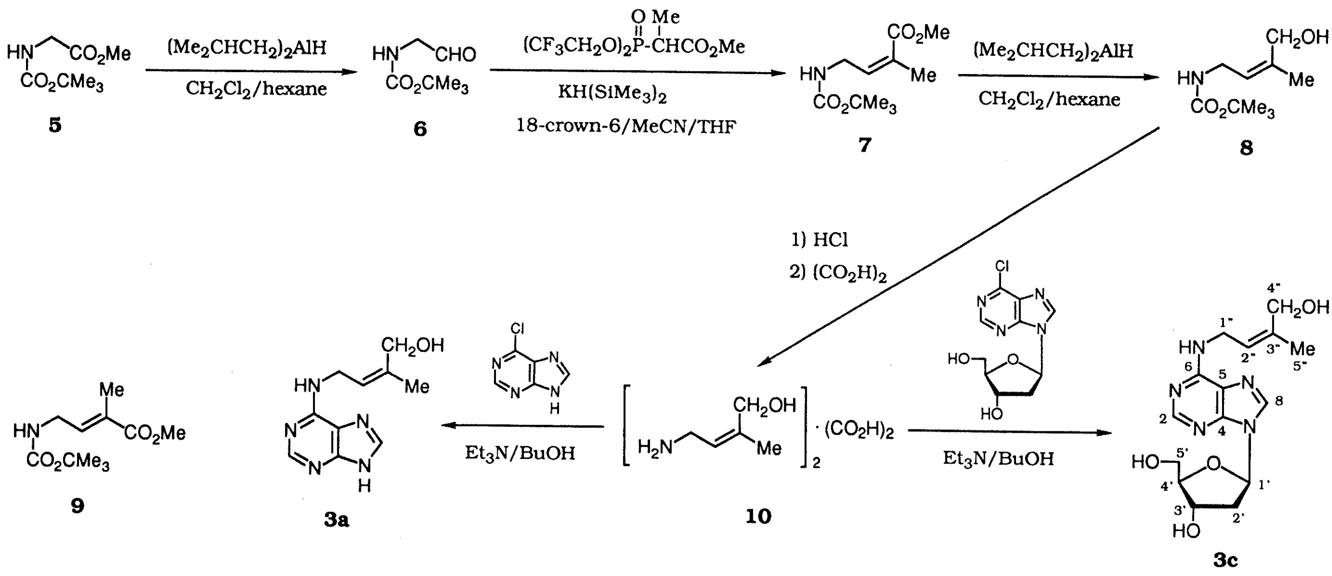


Chart 1

Table I. Cytokinin Activity of 9-(2-Deoxy-β-D-ribofuranosyl)-*cis*-zeatin (**3c**), Its *trans* Isomer (**1c**), and *trans*-Zeatin 9-β-D-Riboside (**1b**) Tested by Cucumber Cotyledon Bioassay

Compound[a]	Averaged chlorophyll yield[b] (% of control)
Control	100.00 a
3c	108.87 aB
1c	164.91 C
1b	217.53 D

a) Solutions of cytokinins were 4.5 μM and contained 0.1% methanol. *b)* Values scored by the same roman letters are not statistically significantly different at the 5% (lower case letters) or at the 1% (capital letters) level in Duncan's multiple range test.

(triphenylphosphoranylidene)propionate according to the literature procedure[2] but with some modification (CH_2Cl_2, room temp., 1 h) gave **7** and **9** in 6% and 74% yields, respectively. On reduction with DIBAH in CH_2Cl_2–hexane at -78 °C for 1 h, the (*Z*)-ester **7** furnished the allyl alcohol **8** in 85% yield. The carbamate **8** was then hydrolyzed with 10% aqueous HCl at room temperature for 1 h, and the resulting amino alcohol was isolated in the form of the oxalate **10** in 85% yield (from **8**).

Finally, coupling of **10** with 6-chloro-9-(2-deoxy-β-D-ribofuranosyl)purine in boiling 1-butanol containing Et_3N for 2.5 h afforded the desired deoxyriboside **3c** in 89% yield as a crystalline solid. In order to confirm the *Z* configuration of **10** and hence that of **3c**, **10** was purinylated with 6-chloropurine under similar conditions to give *cis*-zeatin (**3a**) in 72% yield. The new synthesis of **3a** from **5** through **6**, **7**, **8**, and **10** by taking advantage of the "α-amino aldehyde/olefination" technology represents a convenient alternative to previous synthetic methods.[9-11]

Thus, the total syntheses of natural 9-(2-deoxy-β-D-ribofuranosyl)-*trans*-zeatin (**1c**) and its *cis* isomer (**3c**) have made it possible to obtain sufficient amounts of **1c** and **3c** to test their cytokinin activity, compared to that of *trans*-zeatin 9-β-D-riboside (**1b**), in the stimulation of chlorophyll biosynthesis in etiolated cucumber cotyledons. The activity of the compounds, assayed at a concentration of 4.5 μM, was then evaluated by using Duncan's statistic multiple range test. The results listed in Table I showed that **1c**, compared to **1b** which was the most active cytokinin among the compounds assayed, exhibited a marked decrease in the biosynthesis of chlorophyll, while **3c** was not statistically significantly different from the control. These findings indicate that, in general agreement with previously reported data,[6b,12] both the *trans* stereochemistry of the double bond of the side chain at C(6) and an unaltered ribosyl residue, when it is present, should be two structural features important to stimulating the biosynthesis of chlorophyll in cucumber cotyledones.

Experimental

General Notes All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Thin-layer chromatography (TLC) was conducted on Merck silica gel 60 F_{254} plates (0.25-mm thickness), and spots were detected by means of ultraviolet (UV) absorbance measurement (at 254 nm) and/or by spraying with the standard $KMnO_4$ or I_2–KI reagent. Flash chromatography[13] was carried out by using Merck silica gel 60 (No. 9385). UV spectra were recorded on a Hitachi 320 UV spectrophotometer [on solutions in 95% (v/v) aqueous EtOH, 0.1 N aqueous HCl (pH 1), 0.005 M phosphate buffer (pH 7), and 0.1 N aqueous NaOH (pH 13)]. Infrared (IR) spectra were measured with a JASCO A-202 IR spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 mass spectrometer. ^{1}H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded on either a JEOL JNM-FX-100 (^{1}H 100 MHz), a JEOL JNM-EX-270 (^{1}H 270 MHz, ^{13}C 67.8 MHz), or a JEOL JNM-GSX-500 (^{1}H 500 MHz, ^{13}C 125.65 MHz) instrument. Chemical shifts are reported in δ values relative to Me_4Si. Optical rotations were measured with a JASCO DIP-181 polarimeter using a 1-dm sample tube. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-doublets-of-doublets, s = singlet, sh = shoulder, t = triplet, tq = triplet-of-quartets.

2-Oxoethylcarbamic Acid *tert*-Butyl Ester (6) A stirred solution of **5**[14] (6.87 g, 36 mmol) in dry CH_2Cl_2 (120 ml) was cooled to -78 °C in an atmosphere of N_2, and a 0.95 M solution (76.5 ml, 73 mmol) of DIBAH in hexane was added dropwise over 10 min. After the mixture had been stirred at -78 °C for 1 h, the reaction was quenched by adding 2 N aqueous HCl (36 ml). The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ and then stirred at room temperature for 1.5 h. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2. The CH_2Cl_2 extracts and the above organic layer were combined, washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a colorless oil. The oil was purified by means of flash chromatography[13] [hexane–AcOEt (1 : 1, v/v)] to give **6**[2] (3.89 g, 67%) as a colorless oil, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (NH), 1709 (br, CO's); ^{1}H-NMR (100 MHz, $CDCl_3$) δ: 1.46 (9H, s, CMe_3), 4.06 (2H, d, J = 5 Hz, CH_2), 5.16 (1H, br, NH), 9.65 (1H, s, CHO).

(*Z*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-2-butenoic Acid Methyl Ester (7) and (*E*)-4-[[(1,1-Dimethylethoxy)carbonyl]amino]-2-methyl-2-butenoic Acid Methyl Ester (9) i) *Via* the Still–Gennari Modification of the Horner–Wadsworth–Emmons Reaction: A solution of 18-crown-6–MeCN complex[15] (8.66 g, 25 mmol) and methyl 2-[bis-(2,2,2-trifluoroethoxy)phosphinyl]propionate [$(CF_3CH_2O)_2P(O)CH(Me)CO_2Me$][7] (1.83 g, 5.5 mmol) in dry THF (75 ml) was stirred at -78 °C in an atmosphere of N_2, and a 0.5 M solution (12 ml, 6.0 mmol) of potassium bis(trimethylsilyl)amide [$KN(SiMe_3)_2$] in toluene was added dropwise over 10 min. The mixture was stirred at -78 °C for 25 min, and then a solution of **6** (796 mg, 5.0 mmol) in dry THF (15 ml) was added dropwise over 5 min. After the resulting mixture had been stirred at the same temperature for a further 30 min, the reaction was quenched by adding saturated aqueous NH_4Cl (40 ml). The aqueous layer was separated from the organic layer and extracted with ether (3 × 20 ml). The ethereal extracts and the above organic layer were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a pale yellow oil. The oil was purified by means of flash chromatography[13] [hexane–AcOEt (4 : 1, v/v)] afforded **7** (661 mg, 58%) as a colorless solid. Recrystallization of the solid from hexane yielded an analytical sample as colorless needles, mp 67—67.5 °C; IR ν_{max}^{Nujol} cm^{-1}: 3330 (NH), 1715 (α,β-unsaturated ester CO), 1685 (carbamate CO), 1645 (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45 (9H, s, CMe_3), 1.91 (3H, d, J = 1.5 Hz, CH=C$\underline{Me}$), 3.75 (3H, s, CO_2Me), 4.07 (2H, dd, J = 6 Hz each, NCH_2), 4.89 (1H, br, NH), 6.02 (1H, br, C$\underline{H}$=CMe); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 20.1 (CH=C$\underline{Me}$), 28.4 (C$\underline{Me}_3$), 39.6 (NCH_2), 51.6 (CO$_2\underline{Me}$), 79.4 ($\underline{C}Me_3$), 128.8 (CH=$\underline{C}$Me), 140.6 ($\underline{C}$H=CMe), 156.0 ($\underline{C}O_2CMe_3$), 167.8 ($\underline{C}O_2Me$). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.87; H, 8.50; N, 6.16.

Later fractions in the above chromatography furnished **9**[2] (6 mg, 0.5%) as a colorless solid, mp 54—56 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one obtained by method (ii) described below.

ii) *Via* the Wittig Reaction: A solution of methyl 2-(triphenylphosphoranylidene)propionate[16] (1.15 g, 3.3 mmol) in CH_2Cl_2 (3 ml) was added to a stirred solution of **6** (478 mg, 3.0 mmol) in CH_2Cl_2 (3 ml) over 10 min at 16—18 °C with occasional ice-cooling. The resulting mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The yellow oily residue was extracted with hot hexane (5 × 8 ml). The hexane extracts were combined and concentrated *in vacuo* to leave a slightly yellow solid. The solid was purified by means of flash chromatography[13] using hexane–AcOEt (4 : 1, v/v) as the eluent. Earlier fractions yielded the (*Z*)-isomer (**7**) (44 mg, 6%) as a colorless solid, mp 66—67 °C. This sample was identical (by comparison of the IR spectrum and TLC mobility) with the one prepared by method (i).

Later fractions obtained from the above chromatography gave the (*E*)-isomer (**9**)[2] (508 mg, 74%) as a colorless solid. Recrystallization of the solid from hexane afforded an analytical sample as colorless plates, mp 57—58 °C; IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1713 (α,β-unsaturated ester CO), 1685 (carbamate CO), 1655 (sh) (C=C); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.45 (9H, s, CMe_3), 1.87 (3H, d, J=1 Hz, CH=C<u>Me</u>), 3.74 (3H, s, CO_2Me), 3.90 (2H, br, NCH_2), 4.73 (1H, br, NH), 6.66 (1H, tq, J=6.5, 1 Hz, C<u>H</u>=CMe); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 12.6 (CH=C<u>Me</u>), 28.4 (C<u>Me$_3$</u>), 38.9 (NCH_2), 51.9 (CO_2<u>Me</u>), 79.7 (<u>C</u>Me_3), 129.2 (CH=<u>C</u>Me), 138.3 (<u>C</u>H=CMe), 155.8 (<u>C</u>O_2CMe_3), 168.0 (<u>C</u>O_2Me). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.47; H, 8.58; N, 6.08.

(*Z*)-(4-Hydroxy-3-methyl-2-butenyl)carbamic Acid *tert*-Butyl Ester (8) A stirred solution of **7** (459 mg, 2.0 mmol) in dry CH_2Cl_2 (5 ml) was cooled to −78 °C in an atmosphere of N_2, and a 0.94 M solution (6.4 ml, 6.0 mmol) of DIBAH in hexane was added dropwise over 10 min. After the mixture had been stirred at −78 °C for 1 h, the reaction was quenched by adding a 5 M solution (4 ml) of AcOH in CH_2Cl_2. The resulting mixture was allowed to warm to room temperature, and 10% aqueous tartaric acid (10 ml) and H_2O (10 ml) were added in that order. The aqueous layer was separated from the organic layer and extracted with CH_2Cl_2 (3 × 15 ml). The CH_2Cl_2 extracts and the above organic layer were combined, washed successively with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to leave a colorless oil. Purification of the oil by means of flash chromatography[13] [hexane–AcOEt (3:2, v/v)] gave **8** (342 mg, 85%) as a colorless oil, IR ν_{max}^{film} cm^{-1}: 3350 (NH and OH), 1690 (carbamate CO); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.43 (9H, s, CMe_3), 1.82 (3H, s, CH=C<u>Me</u>), 1.9 (1H, br, OH), 3.72 (2H, d, J=7 Hz, NCH_2), 4.12 (2H, s, C<u>H$_2$</u>OH), 4.74 (1H, br, NH), 5.27 (1H, t, J=7 Hz, C<u>H</u>=CMe).

(*Z*)-4-Amino-2-methyl-2-buten-1-ol Ethanedioate (2:1) (Salt) (10) A mixture of **8** (322 mg, 1.6 mmol) and 10% aqueous HCl (3.2 ml) was stirred at room temperature for 1 h, giving a slightly pinkish solution. The solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (16 ml), and the column was eluted with H_2O. The eluate (75 ml) was concentrated to dryness *in vacuo* to leave a pale yellow oil (158 mg), which was dissolved in EtOH (1.5 ml). The resulting ethanolic solution was exactly neutralized by addition of a solution of oxalic acid (72 mg, 0.8 mmol) in EtOH (0.5 ml) and, if necessary, with Et_3N. The precipitate that resulted was filtered off, washed with EtOH (0.3 ml), and dried to give **10** (199 mg, 85%), mp 180—182 °C. Recrystallization of crude **10** from EtOH–H_2O (10:1, v/v) afforded an analytical sample as colorless scales, mp 183.5—185 °C; IR ν_{max}^{Nujol} cm^{-1}: 3050 (sh) (OH), 1655 (C=C), 1580 (CO_2^-); ^{1}H-NMR (270 MHz, D_2O) δ:[17] 1.83 (3H, s, Me), 3.67 (2H, d, J=7.5 Hz, NCH_2), 4.15 (2H, s, C<u>H$_2$</u>OH), 5.45 (1H, t, J=7.5 Hz, C<u>H</u>=CMe). *Anal.* Calcd for $C_{12}H_{24}N_2O_6$: C, 49.30; H, 8.27; N, 9.58. Found: C, 49.54; H, 8.46; N, 9.66.

(*Z*)-2-Methyl-4-(9*H*-purin-6-ylamino)-2-buten-1-ol (*cis*-Zeatin) (3a) A mixture of **10** (64 mg, 0.22 mmol), 6-chloropurine (62 mg, 0.4 mmol), Et_3N (0.5 ml), and 1-butanol (5 ml) was heated under reflux for 3 h. The reaction mixture was concentrated *in vacuo* to leave a pale yellow oil, which was dissolved in H_2O (1 ml). The resulting aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (4 ml), and the column was eluted with H_2O (50 ml). The eluate was concentrated *in vacuo*, and the residual solid (82 mg) was recrystallized from EtOH (1 ml), giving a first crop (46 mg) of **3a**. A second crop (17 mg) was obtained by concentration of the mother liquor from the above recrystallization under reduced pressure and subsequent purification of the residue by flash chromatography[13] [AcOEt–EtOH (4:1, v/v)]. The total yield of **3a** was 63 mg (72%). Further recrystallization of crude **3a** from EtOH yielded an analytical sample as colorless prisms, mp 212—214 °C (lit. mp 206—208 °C[9a]; mp 209 °C[9b]); MS *m/z*: 219 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 269 nm (ε 19100); $\lambda_{max}^{H_2O}$ (pH 1) 274 (18000); $\lambda_{max}^{H_2O}$ (pH 7) 269 (19300); $\lambda_{max}^{H_2O}$ (pH 13) 275 (18600), 283 (sh) (14300); ^{1}H-NMR [500 MHz, $(CD_3)_2SO$] δ: 1.71 (3H, s, Me), 4.04 (2H, s, C<u>H$_2$</u>OH), 4.12 (2H, br, NCH_2), 4.73 (1H, br, OH), 5.35 (1H, t, J=6.5 Hz, C<u>H</u>=CMe), 7.60 (1H, br, N<u>H</u>CH_2), 8.08 and 8.17 (1H each, s, purine protons), 12.88 [1H, br, N(9)H]. *Anal.* Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.94. Found: C, 54.59; H, 6.04; N, 31.91. This sample was identical [by mixture melting point test and comparison of the IR (Nujol) and ^{1}H-NMR spectra and TLC mobility (in four solvent systems)] with authentic *cis*-zeatin (Sigma Chemical Co.).

(*Z*)-*N*-(4-Hydroxy-3-methyl-2-butenyl)-2′-deoxyadenosine [9-(2-Deoxy-β-D-ribofuranosyl)-*cis*-zeatin] (3c) A stirred solution of **10** (64 mg, 0.22 mmol) and 6-chloro-9-(2-deoxy-β-D-ribofuranosyl)purine[18] (108 mg, 0.4 mmol) in 1-butanol (5 ml) containing Et_3N (0.5 ml) was heated under reflux for 2.5 h. The reaction mixture was concentrated *in vacuo* to leave a slightly yellow oil, which was dissolved in H_2O (1 ml). The aqueous solution was passed through a column of Amberlite IRA-402 (HCO_3^-) (4 ml), and the column was eluted with H_2O (50 ml). The eluate was concentrated *in vacuo*, and the residual oil was purified by flash chromatography[13] [AcOEt–EtOH (4:1, v/v)] to give **3c** (119 mg, 89%) as a colorless solid, mp 139—141 °C. Recrystallization of the solid from MeCN–EtOH (10:1, v/v) yielded an analytical sample as colorless needles, mp 142.5—143.5 °C; $[\alpha]_D^{22}$ −20.4° (c=0.322, EtOH); MS *m/z*: 335 (M^+); UV $\lambda_{max}^{95\%\,EtOH}$ 269 nm (ε 19700); $\lambda_{max}^{H_2O}$ (pH 1) unstable; $\lambda_{max}^{H_2O}$ (pH 7) 269 (20500); $\lambda_{max}^{H_2O}$ (pH 13) 269 (20400); ^{1}H-NMR (500 MHz, CD_3OD) δ: 1.82 [3H, d, J=1 Hz, C(5″)-H's], 2.39 (1H, ddd, J=13.5, 6, 2.5 Hz) and 2.80 (1H, ddd, J=13.5, 8, 6 Hz) [C(2′)-H's], 3.74 and 3.84 [1H each, dd, J=12.5, 3 Hz, C(5′)-H's], 4.07 [1H, ddd, J=3 Hz each, C(4′)-H], 4.20 [2H, s, C(4″)-H's], 4.25 [2H, br, C(1″)-H's], 4.57 [1H, ddd, J=6, 3, 2.5 Hz, C(3′)-H], 5.47 [1H, tq, J=7, 1 Hz, C(2″)-H], 6.41 [1H, dd, J=8, 6 Hz, C(1′)-H], 8.20 and 8.25 (1H each, s, purine protons)[19]; ^{13}C-NMR (125.65 MHz, CD_3OD) δ: 21.7 [C(5″)], 38.9 [C(1″)], 41.6 [C(2′)], 61.7 [C(4″)], 63.6 [C(5′)], 73.0 [C(3′)], 87.2 [C(1′)], 89.9 [C(4′)], 121.3 [C(5)], 124.3 [C(2″)], 140.0 [C(3″)], 140.9 [C(8)], 149.1 [C(4)], 153.3 [C(2)], 155.9 [C(6)].[19] *Anal.* Calcd for $C_{15}H_{21}N_5O_4$: C, 53.72; H, 6.31; N, 20.88. Found: C, 53.48; H, 6.46; N, 20.85.

Bioassay Procedure The cytokinin activities (*i.e.*, stimulation of chlorophyll biosynthesis) of compounds **3c**, **1c**, and **1b** were tested in the cucumber cotyledon bioassay as described by Fletcher *et al.*,[20] with some minor modifications. The results are given in Table I.

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