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SYNTHESES AND ABSOLUTE CONFIGURATIONS OF THE CYTOKININS 1'-METHYLZEATIN AND ITS 9-RIBOSIDE †

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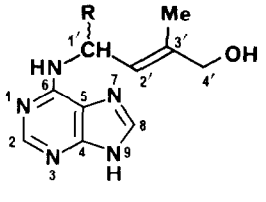
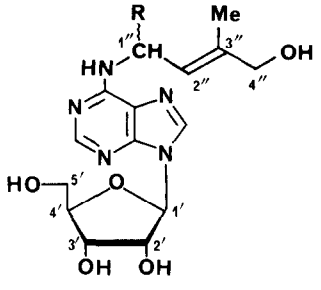
Abstract — On the basis of the chiral syntheses of (1'*R*)-I and (1'*S*)-I and of their 9-ribosides (1"*R*)-III and (1"*S*)-III from *D*- and *L*-alanines, the structures of the cytokinins 1'-methylzeatin and its 9-riboside have been established to be (1'*R*)-I and (1"*R*)-III.

In quite recent papers,[1,2] some of us reported the isolation of two new cytokinins from the culture filtrate of *Pseudomonas syringae* pv. *savastanoi* and proposed the gross structures I[1] and III[2] for them on the basis of spectroscopic data and comparison with related adenine derivatives including the known cytokinins[3] zeatin (II) and its 9-riboside (IV). The new cytokinins, 1'-methylzeatin (I) and its 9-β-*D*-ribofuranosyl derivative (III), are unique in that their N^6-substituents consist of a branched allyl alcoholic C_6 unit with an asymmetric center adjacent to N^6. However, the absolute configuration at the asymmetric center remained undetermined for both compounds. In this communication, we wish to record the results of our synthetic work, which permit the assignment of the absolute stereoformulas (1'*R*)-I and (1"*R*)-III to these cytokinins.

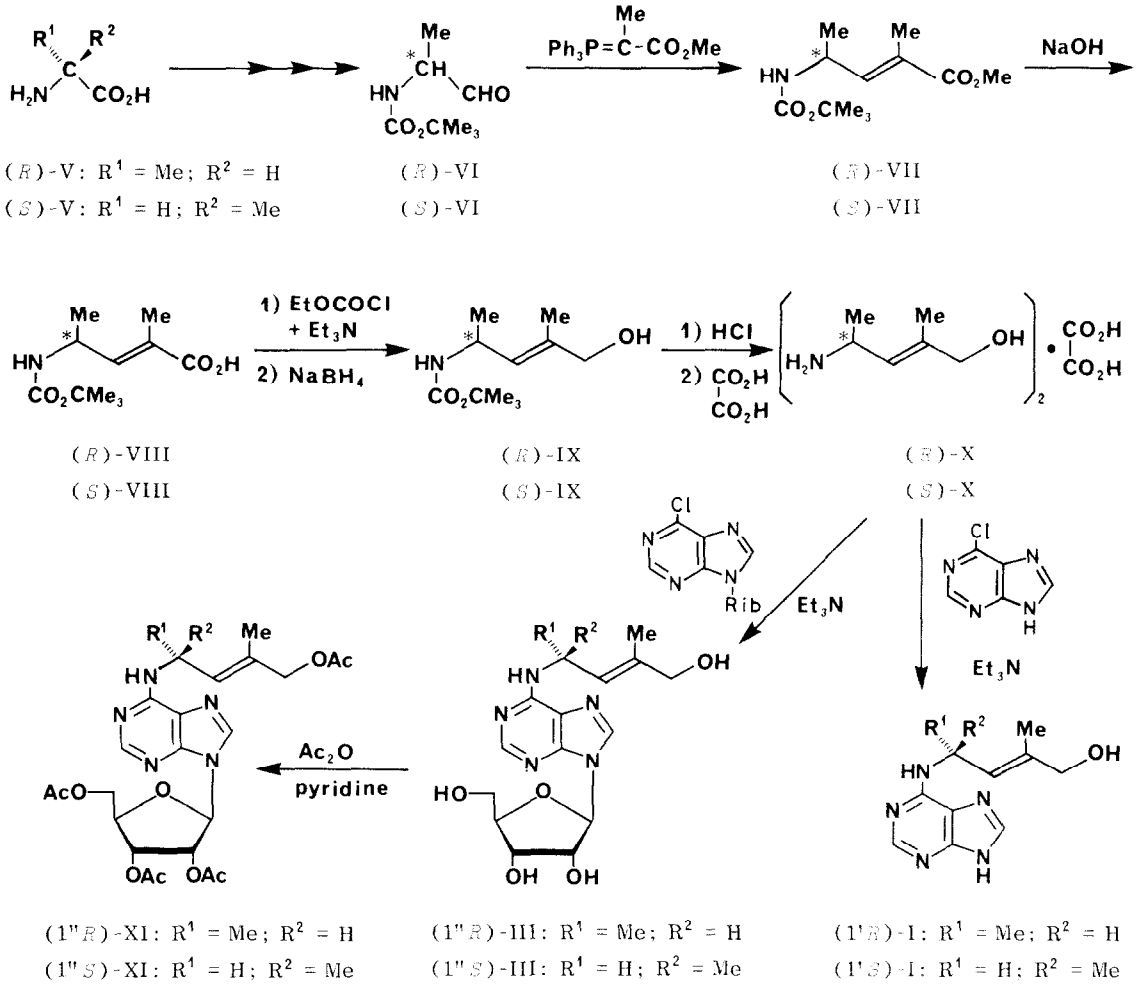


I: R = Me
II: R = H



III: R = Me
IV: R = H

†Dedicated to Emeritus Professor Dr. Shigehiko Sugasawa (University of Tokyo) on the occasion of his 88th birthday, with gratitude for the inspiration, both human and scientific, that he has always provided.



(*R*)-V: R^1 = Me; R^2 = H
(*S*)-V: R^1 = H; R^2 = Me

(*R*)-VI
(*S*)-VI

(*R*)-VII
(*S*)-VII

(*R*)-VIII
(*S*)-VIII

(*R*)-IX
(*S*)-IX

(*R*)-X
(*S*)-X

(1"*R*)-XI: R^1 = Me; R^2 = H
(1"*S*)-XI: R^1 = H; R^2 = Me

(1"*R*)-III: R^1 = Me; R^2 = H
(1"*S*)-III: R^1 = H; R^2 = Me

(1'*R*)-I: R^1 = Me; R^2 = H
(1'*S*)-I: R^1 = H; R^2 = Me

Prior to the present study, the synthetic route from *L*-alanine [(*S*)-V] to the (−)-aldehyde (*S*)-VI had already been established by Shioiri's group.[4] Therefore, the (+)-aldehyde (*R*)-VI (mp 90–91°C; $[\alpha]_D^{18}$ +35.2°)[5] was similarly prepared from *D*-alanine [(*R*)-V] in 71% overall yield. Wittig reaction of (*R*)-VI with methyl 2-(triphenylphosphoranylidene)propionate[6] (CH_2Cl_2, 22°C, 1 h) gave a 95 : 5 mixture of (*R*)-VII and its (*Z*)-isomer in 98% yield, from which (*R*)-VII (mp 79–80°C; $[\alpha]_D^{15}$ +14.4°) was isolated in 88% yield by recrystallization (from hexane). The assignment of geometry in (*R*)-VII is based on the facts that it is the major isomer formed[7] and that its olefinic proton [δ 6.53 (dq, J = 8.5 and 1.5 Hz)] resonated in $CDCl_3$ at lower field than that [δ 5.83 (br d, J = 8 Hz)] of the minor isomer. Hydrolysis of (*R*)-VII with 2 *N* aq. NaOH (MeOH, 30°C, 3 h) afforded (*R*)-VIII [mp 123–124°C; $[\alpha]_D^{26}$ +4.7° (*c* 1.02)] in 99% yield. The next step, selective reduction of the carboxy group to the hydroxymethyl group, was achieved by application of the literature procedure:[8]

(1) acylation with ethyl chloroformate and Et_3N (THF, −10 – −5°C, 30 min) and (2) $NaBH_4$ reduction (aq. THF, room temp., 3 h) to produce (*R*)-IX (89% yield; $[\alpha]_D^{16}$ +0.1°). The carbamate (*R*)-IX was hydrolyzed with 10% aq. HCl (room temp., 1 h), and the amino alcohol hydrochloride that formed was converted via the free base [Amberlite IRA-402 (HCO_3^-)] into the (−)-oxalate (*R*)-X [79% yield from (*R*)-IX; mp 222–223°C (dec.); $[\alpha]_D^{18}$ −5.2°]. A parallel series of conversions starting with (*S*)-VI[4] yielded (*S*)-X ($[\alpha]_D^{17}$ +5.3°).[9]

Condensation of 6-chloropurine with (*R*)-X in boiling 1-butanol containing Et_3N for 10 h afforded the (−)-base (1'*R*)-I [mp 201–202°C; $[\alpha]_D^{26}$ −109° (*c* 0.153, EtOH); CD (*c* 2.71 × 10^{-5} *M*, MeOH) $[\theta]^{25}$ (nm): −20300 (273) (neg. max.), +61300 (214) (pos. max.)] in 70% yield. A similar condensation with (*S*)-X gave the (+)-enantiomer (1'*S*)-I [$[\alpha]_D^{26}$ +103° (*c* 0.137, EtOH); CD (*c* 2.89 × 10^{-5} *M*, MeOH) $[\theta]^{25}$ (nm): +19700 (273) (pos. max.), −59900 (214) (neg. max.)] in 70% yield. Of the two optical isomers, (1'*R*)-I was identical with natural 1'-methylzeatin[1] by comparison of their chiroptical properties, mass, UV, and ^1H and ^{13}C NMR spectra, and TLC mobilities.

The syntheses of the corresponding 9-ribosides were effected by condensations of 6-chloro-9-β-D-ribofuranosylpurine[10] with (*R*)-X and with (*S*)-X (1-butanol, Et_3N, reflux, 8 h), giving (1"*R*)-III [mp 130–132°C (hemihydrate); $[\alpha]_D^{14}$ −117° (*c* 0.102); CD (*c* 5.20 × 10^{-5} *M*, MeOH) $[\theta]^{25}$ (nm): −24300 (277) (neg. max.), +50400 (217) (pos. max.)] and (1"*S*)-III [glass; $[\alpha]_D^{18}$ −2.2° (*c* 0.500); CD (*c* 2.88 × 10^{-5} *M*, MeOH) $[\theta]^{25}$ (nm): +15800 (275) (pos. max.), −47100 (216) (neg. max.)] in 88% and 89% yields, respectively. The two nucleosides on acetylation (Ac_2O, pyridine) provided the tetra-*O*-acetyl derivatives (1"*R*)-XI [95% yield; $[\alpha]_D^{14}$ −54.3° (*c* 0.500, $CHCl_3$)] and (1"*S*)-XI [80% yield; $[\alpha]_D^{15}$ −3.5° (*c* 0.82, $CHCl_3$)]. Although mass, UV, and ^1H and ^{13}C NMR spectroscopies and TLC of these synthetic III and XI did not permit the identification with those of natural origin, comparison of their chiroptical properties clearly indicated that the synthetic (1"*R*)-III is identical with natural 1'-methylzeatin 9-riboside [CD (*c* 2.45 × 10^{-5} *M*, MeOH) $[\theta]^{25}$ (nm): −16900 (277) (neg. max.), +38800 (217) (pos. max.)].

The above results unequivocally established the absolute configurations of the new cytokinins as (1'*R*)-I and (1"*R*)-III. Comparison of the cytokinin activities of zeatin (II) and both enantiomers of 1'-methylzeatin at the aglycone and the glycoside levels would be of great interest.

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