

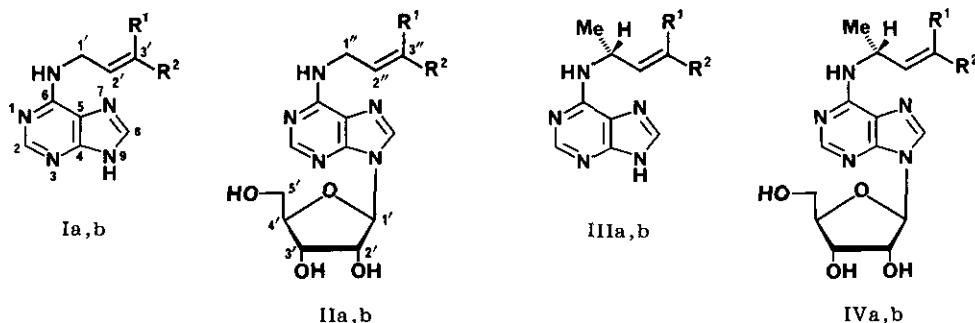
SYNTHESES OF (1'R)-1'-METHYL-cis-ZEATIN AND ITS 9-β-D-RIBOFURANOSIDE

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Abstract — The *cis* isomers IIIb and IVb of the recently isolated cytokinins (1'R)-1'-methylzeatin (IIIa) and (1'R)-1'-methylzeatin 9-β-D-ribose (IVa) have been synthesized from D-alanine (V) through the intermediates VI, VII, IX, VIII, X, and XI.

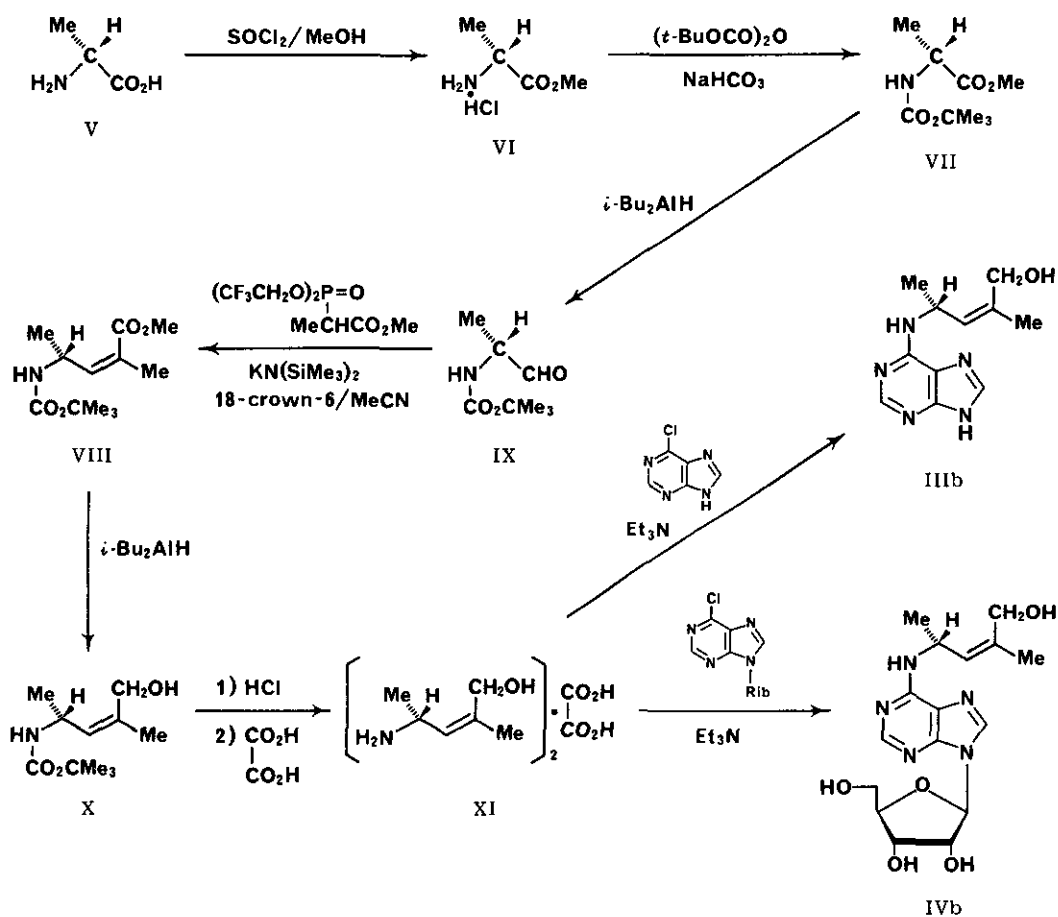
Naturally occurring cytokinins, a group of N⁶-substituted adenines and their derivatives inducing cell division in certain plant tissue cultures, comprise *trans*-zeatin (Ia) which is often referred to as zeatin, *cis*-zeatin (Ib), and their 9-β-D-ribofuranosides (IIa and IIb).¹ The recent isolation of (1'R)-1'-methylzeatin (IIIa)² and its 9-β-D-ribofuranoside (IVa)³ from the culture filtrate of *Pseudomonas syringae* pv. *savastanoi* and the establishment of their structures by synthesis⁴



a: R¹ = Me; R² = CH₂OH b: R¹ = CH₂OH; R² = Me

brought an addition of two new members to this group. The occurrence of both the *cis* and *trans* isomers in the zeatin series suggests that the *cis* isomers of IIIa and IVa may also occur in nature, and the availability of synthetic samples would greatly facilitate the search for these *cis* isomers as natural products. This led us to synthesize (1'R)-1'-methyl-*cis*-zeatin (IIIb) and (1'R)-1'-methyl-*cis*-zeatin 9-β-D-ribofuranoside (IVb) in the present study.

The synthetic route started with N-(*tert*-butoxycarbonyl)-D-alanine methyl ester



(VII),⁵ which was prepared from D-alanine (V) through VI⁶ according to the previously reported procedure. Conversion of VII into the (+)-aldehyde IX [66% yield; $[\alpha]_{\text{D}}^{22} +35.2^\circ$ (c 1.00, MeOH)⁷] was effected by diisobutylaluminum hydride (DIBAH) reduction (CH_2Cl_2 -hexane, -78°C , 1 h), a method known to reduce *N*-alkoxycarbonyl α -amino acid esters to the corresponding aldehydes without accompanying racemization.⁸ The (+)-aldehyde IX was then subjected to the Still-Gennari modification⁹ [$(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}(\text{Me})\text{CO}_2\text{Me}$, $\text{KN}(\text{SiMe}_3)_2$, 18-crown-6/MeCN, tetrahydrofuran, -78°C , 30 min] of the Horner-Emmons reaction, affording a 99 : 1 mixture¹⁰ of the (*Z*)-isomer VIII and its (*E*)-isomer⁴ in 68% yield, from which VIII [mp $54\text{--}54.5^\circ\text{C}$; $[\alpha]_{\text{D}}^{22} -71.7^\circ$ (c 1.03, MeOH)]¹¹ was isolated in 61% yield by recrystallization (from hexane). The assignment of geometry in VIII was based on the facts that it was the major isomer formed⁹ and that its olefinic proton [δ 5.80 (dq, J = 8.5 and 1.5 Hz)] resonated in CDCl_3 at higher

field than that [δ 6.53 (dq, $J = 8.5$ and 1.5 Hz)]⁴ of the (E)-isomer.

Reduction of the (-)-(Z)-ester VIII with DIBAH (CH_2Cl_2 -hexane, -78°C , 45 min) gave the (-)-allylic alcohol X [92% yield; mp 67.5°C ; $[\alpha]_D^{24} -3.3^\circ$ (c 1.00, MeOH)], which was then hydrolyzed with 10% aqueous HCl (room temp., 1 h). The resulting amino alcohol hydrochloride was first treated with Amberlite IRA-402 (HCO_3^-), and the free base that formed was converted into the (-)-oxalate XI [88% yield from X; mp $199-199.5^\circ\text{C}$ (dec.); $[\alpha]_D^{23} -10.1^\circ$ (c 0.458, MeOH)] by treating it with oxalic acid in EtOH.

Condensation of XI with 6-chloropurine in boiling 1-butanol containing Et_3N for 3.5 h furnished (1'R)-1'-methyl-cis-zeatin (IIIb) [mp $182-183.5^\circ\text{C}$; $[\alpha]_D^{22} -128^\circ$ (c 0.117, EtOH); cd (c 5.93×10^{-5} M, MeOH) $[\theta]^{18}$ (nm): -26100 (272) (neg. max.), $+57700$ (215) (pos. max.)] in 75% yield. A similar condensation of XI with 6-chloro-9- β -D-ribofuranosylpurine¹² produced the target riboside IVb [mp $206.5-207.5^\circ\text{C}$; $[\alpha]_D^{23} -131^\circ$ (c 0.156, MeOH); cd (c 3.46×10^{-5} M, MeOH) $[\theta]^{18} -29500$ (275) (neg. max.), $+54300$ (218) (pos. max.)] in 96% yield.

In summary, the cis isomers (IIIb and IVb) of the recently isolated cytokinins IIIa and IVa are now available by the seven-step syntheses described above. It is known that the trans forms (Ia and IIa) in the zeatin series are more active than the corresponding cis forms (Ib and IIb) in the standard tobacco callus bioassay for cytokinin activity.^{1b,13} A comparative study of the cytokinin activities of both geometrical isomers of (1'R)-1'-methylzeatin at the aglycone (IIIa,b) and the glycoside (IVa,b) levels will be made by Prof. S. Matsubara at Kyoto Prefectural University in order to check the validity of such trans-cis activity relationship.

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