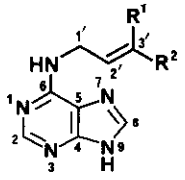
SYNTHESES OF (1'R)-1'-METHYL-cis-ZEATIN AND ITS 9-β-D-RIBOFURANOSIDE

Tozo Fujii,* Masashi Ohba, and Miwa Sakari

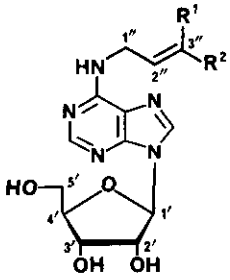
Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi, Kanazawa 920, Japan

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

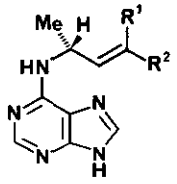
Naturally occurring cytokinins, a group of N^6-substituted adenines and their derivatives inducing cell division in certain plant tissue cultures, comprise trans-zeatin (Ia) which is often referred to as zeatin, cis-zeatin (Ib), and their 9-β-D-ribofuranosides (IIa and IIb).[1] The recent isolation of (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 synthesis[4]



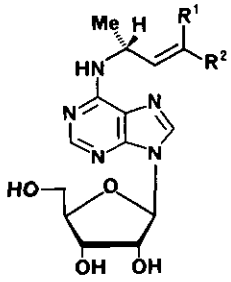
Ia,b



IIa,b



IIIa,b

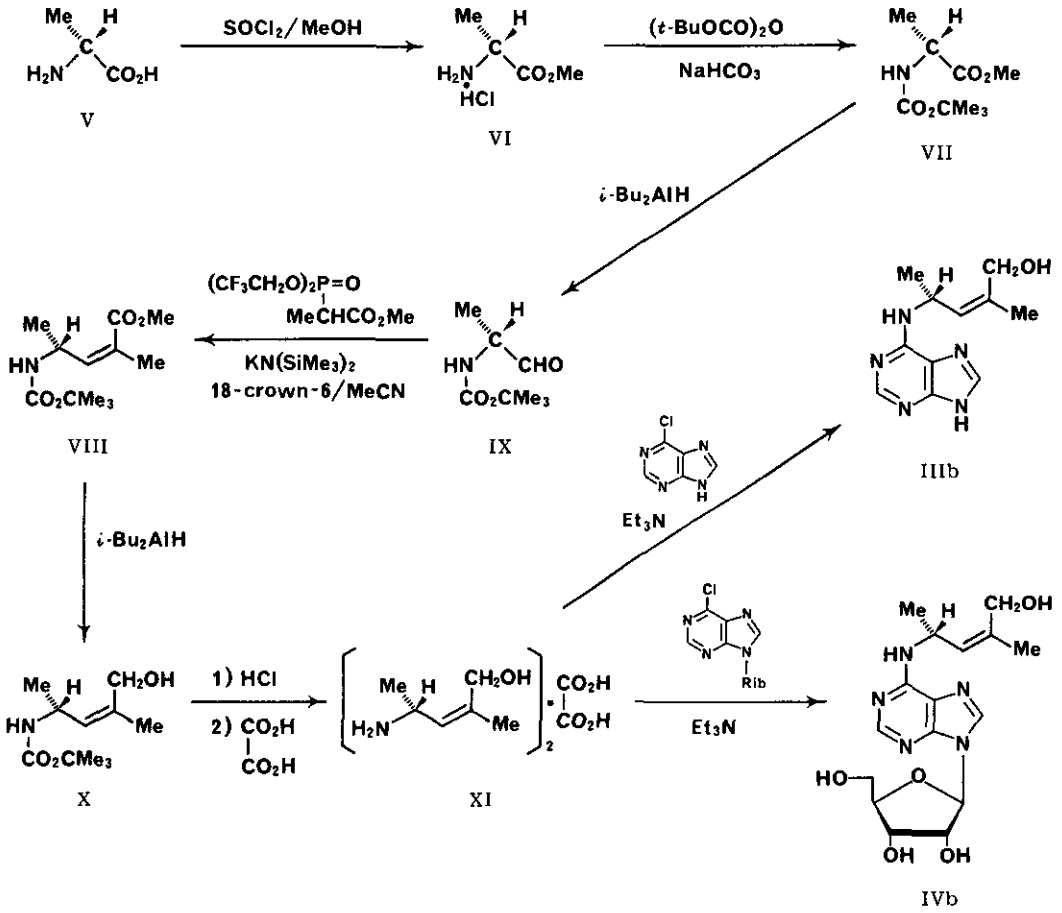


IVa,b

a: R^1 = Me; R^2 = CH_2OH b: R^1 = CH_2OH; R^2 = 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 VI[6] according to the previously reported procedure. Conversion of VII into the (+)-aldehyde IX [66% yield; $[\alpha]_D^{22}$ +35.2° (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 modification[9] [$(CF_3CH_2O)_2P(O)CH(Me)CO_2Me$, $KN(SiMe_3)_2$, 18-crown-6/MeCN, tetrahydrofuran, −78°C, 30 min] of the Horner–Emmons reaction, affording a 99 : 1 mixture[10] of the (Z)-isomer VIII and its (E)-isomer[4] in 68% yield, from which VIII [mp 54–54.5°C; $[\alpha]_D^{22}$ −71.7° (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 formed[9] 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° (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°C (dec.); $[\alpha]_D^{23}$ −10.1° (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°C; $[\alpha]_D^{22}$ −128° (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-ribofuranosylpurine[12] produced the target riboside IVb [mp 206.5–207.5°C; $[\alpha]_D^{23}$ −131° (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.

ACKNOWLEDGMENT

Financial support provided by the Japan Research Foundation for Optically Active Compounds is deeply appreciated.

REFERENCES

1. For reviews, see (a) K. Koshimizu and H. Iwamura, Nippon Nogeikagaku Kaishi, 1978, 52, R49; (b) S. Matsubara, Phytochemistry, 1980, 19, 2239; (c) D. S. Letham and L. M. S. Palni, Ann. Rev. Plant Physiol., 1983, 34, 163.
2. A. Evidente, G. Surico, N. S. Iacobellis, and G. Randazzo, Phytochemistry, 1986, 25, 525.

3. G. Surico, A. Evidente, N. S. Iacobellis, and G. Randazzo, Phytochemistry, 1985, 24, 1499.
4. T. Itaya, T. Fujii, A. Evidente, G. Randazzo, G. Surico, and N. S. Iacobellis, Tetrahedron Lett., 1986, 27, 6349.
5. (a) D. S. Tarbell, Y. Yamamoto, and B. M. Pope, Proc. Natl. Acad. Sci. U. S. A., 1972, 69, 730; (b) N. J. Miles, P. G. Sammes, P. D. Kennewell, and R. Westwood, J. Chem. Soc., Perkin Trans. 1, 1985, 2299.
6. (a) M. Brenner and W. Huber, Helv. Chim. Acta, 1953, 36, 1109; (b) M. Zaoral, J. Kolc, F. Korenczki, V. P. Černěckij, and F. Šorm, Collect. Czech. Chem. Commun., 1967, 32, 843 (Chem. Abstr., 1967, 66, 86016g).
7. Lit.[4] $[\alpha]_D^{18}$ +35.2° (c 1.00, MeOH).
8. (a) G. Stork and E. Nakamura, J. Am. Chem. Soc., 1983, 105, 5510; (b) T. Moriwake, S. Hamano, D. Miki, S. Saito, and S. Torii, Chem. Lett., 1986, 815; (c) T. Shono and N. Kise, ibid., 1987, 697.
9. W. C. Still and C. Gennari, Tetrahedron Lett., 1983, 24, 4405.
10. Determined by high-performance liquid chromatographic analysis [Waters ALC/GPC 204 liquid chromatograph, Hibar column LiChrosorb Si 60 (5 μm), hexane–AcOEt (7 : 1, v/v), 470 p.s.i., 0.8 ml/min].
11. The assigned structures of all new compounds were supported by elemental analyses and satisfactory spectral data.
12. J. Žemlička and F. Šorm, Collect. Czech. Chem. Commun., 1965, 30, 1880.
13. (a) N. J. Leonard, A. J. Playtis, F. Skoog, and R. Y. Schmitz, J. Am. Chem. Soc., 1971, 93, 3056; (b) H. J. Vreman, R. Y. Schmitz, F. Skoog, A. J. Playtis, C. R. Frihart, and N. J. Leonard, Phytochemistry, 1974, 13, 31; (c) E. Scarbrough, D. J. Armstrong, F. Skoog, C. R. Frihart, and N. J. Leonard, Proc. Natl. Acad. Sci. U. S. A., 1973, 70, 3825.

Received, 16th May, 1988