Enantioselective Synthesis of Bioactive Molecules Related to Plant Protection and Physiology

Takeshi Kitahara and Hidenori Watanabe

Department of Applied Biological Chemistry, Graduate School of Agricultural and Biological Sciences
The University of Tokyo, [REDACTED]

Abstract: Enantioselective synthesis of bioregulators with remarkable biological activities has been accomplished. The target molecules are plant growth regulators (methyl epijasmonate and analogs, pironetin), plant pathogenic toxins (oxygenated eremophilanes, sorokinianin) and substances related to plant protection (tanabalin; insect antifeedant, mugineic acid and analogs; phytosiderophore).

1. Introduction

Basic research on plant protection and plant physiology is becoming more and more important in order to increase plant-production which is essential for human life and amenity worldwide in the coming 21st century. In this context, we have been studying the synthesis of substances with remarkable bioactivities, such as plant growth regulation, plant nutrition and plant protection, to produce substantial quantities of samples for biological and physiological studies, to evaluate their structure-activity relationships and to create novel useful substances with high activities. We describe herein the enantioselective synthesis of these substances shown in Fig. 1.

Fig. 1 Structures of Our Synthetic Targets

2. Synthesis of Methyl Epijasmonate and Related Analogs

Jasmine oil manufactured from jasmine flowers is a well-known fragrant material for practical use. In 1962, Demole *et al.* identified methyl jasmonate (MJ) **1** as a minor but a key fragrant component of jasmine oil (ref. 1). Later, the corresponding acid analog of **1**, jasmonic acid, was isolated from the culture broth of plant pathogenic fungus, *Lasiodiplodia theobromae*, as a plant growth inhibitor (ref. 2). It was found that methyl jasmonate itself also had similar activity and jasmonate analogs have been postulated as potent plant growth regulators. Thus, the importance of these compounds has been well recognized not only in perfumery industry but also in the field of plant physiology.

In relation to their remarkable biological functions, investigations to detect and isolate these jasmonoids from natural sources have actively been pursued. Those studies have culminated in the characterization of the less stable isomer of **1**, methyl epijasmonate **2**, from the pheromone of the male Oriental fruit moth, *Grapholitha molesta* (ref. 3) and so on. More recently, similar *cis*-analogs, β -D-glucopyranosyltuberonic acid **3** (ref. 4) and its methyl ester **4** (ref. 5) were detected in potato and other related species as tuber-inducing factors. In addition to these glycosides, the aglycone, methyl tuberonate **5**, methyl epijasmonate **2** and other analogs exhibited similar biological activities. Quantitative evaluation of these substances, however, has not been undertaken extensively, because of the shortage of the pure materials.

From these standpoints of view, we synthesized chemically and optically pure jasmonoids not only for practical use but also to provide a biological tool. Here we focus our discussion on the synthesis of a more labile *cis*-series.

Fig. 2 Structures of Jasmonoids

2.1. Synthesis of Both Enantiomers of Methyl Epijasmonate

Enantioselective synthesis of methyl epijasmonate (MEJ) was first reported by Helmchen and coworkers using asymmetric Diels-Alder reaction (ref. 6). Almost at the same time, we succeeded in the efficient synthesis of both enantiomers of MEJ starting from both enantiomers of the known bicyclic lactone **6** which is readily available as a starting material for prostaglandin synthesis. DIBAL reduction of the (-)-lactone, (-)-**6**, was followed by acetal formation and successive epoxidation with MCPBA gave the epoxide **7**. Regiospecific reduction of the oxirane ring and then PDC oxidation gave the ketone **8**, which was converted to the desired ester **9** with an acetate side chain. Stereospecific hydrogenation from the β -face was expected because of the nature of the 2-oxabicyclo[3.3.0]octane system, but this was proved at a later stage. Acid treatment of **9** and the following salt-free Wittig reaction gave the bridged lactone **10** with the desired stereochemistry via concomitant cyclization. The formation of the lactone ring was unambiguous proof of stereospecific hydrogenation from the β -face. The following three-step conversion gave natural (+)-**2** in 26% overall yield through 12 steps. In order to prevent isomerization to the *trans*-isomer during the final oxidation step, we found that two-phase oxidation with chromic acid in ether-water was suitable, giving the pure *cis*-isomer. Starting from the other enantiomer, (+)-**6**, the unnatural antipode (-)-**2** was obtained (ref. 7).

Fig. 3 Synthesis of (+)-Methyl Epijasmonate (Overall 12 steps, 26%)

2.2. Synthesis of Both Enantiomers of Methyl *cis*-(*Z*)-Dehydrojasmonate

Using this strategy, related jasmonate analogs were synthesized with some modification. It was necessary to execute the Wittig reaction of the intermediary hemiacetal at room temperature, because the stable hemiacetal was not so reactive, resulting in the formation of a mixture of *cis*- and *trans*-olefin in the side chain (ca. 9:1). In order to improve this process, we employed a lactone-aldehyde. Thus, in the synthesis of both enantiomers of methyl *cis*-(*Z*)-dehydrojasmonate **11** (ref. 8), the key fragrant substance of an Asian orchid, *Cymbidium goeringii* (ref. 9), lactone thioacetal (–)-**12** was prepared from the acetal **9**. The Wittig reaction of the corresponding aldehyde at $-78^\circ C$ gave phenylselenoolefin **13** and the *cis*-selectivity was shown to be more than 98%. Oxidative elimination of selenide gave the diene lactone **14** and the following conversion furnished the target molecule (+)-**11**. Dess-Martin oxidation was the reagent of choice for the final step giving **11** in excellent yield with no epimerization.

Fig. 4 Synthesis of Methyl *cis*-(*Z*)-Dehydrojasmonate (Overall 15 steps, 17%)

2.3. Synthesis of Methyl Tuberone

We adopted a similar strategy for the synthesis of methyl tuberone **5** using ω -tetrahydropyranoxyporphorane. In this case, however, after oxidation of cyclopentanol, the protecting group of the ω -hydroxyl group had to be removed without epimerization of the *cis*-side chain. Unfortunately, hydrolysis of THP (70% aqueous acetic acid, $50^\circ C$, 60 min) or even 1-ethoxyethyl (70% acetic acid aq., $50^\circ C$, 5 min) caused epimerization to some extent. After several trials, we could optimize the route to the product without any epimerization. The Wittig product **16** was converted to the ω -

trifluoroacetoxycyclopentanol **18** in 5 steps via exchange of the protecting groups. After Dess-Martin oxidation, simple treatment of the ketone **19** with methanol at room temperature without using any base or acid, gave pure methyl tuberonate (+)-**5** via transesterification (refs. 10, 11).

Fig. 5 Synthesis of Methyl Tuberonate (Overall 19 steps, 7%)

2.4. Synthesis of Methyl β -D-Glucopyranosyltuberonate

The intermediate **20** for the synthesis of **5** was glycosylated to give the protected glycoside **21**. In order to synthesize methyl β -D-glucopyranosyltuberonate **4**, it was again necessary to remove the protecting groups of four hydroxyl groups on the glucosyl moiety without epimerization of the α -substituent. We tried to use the protecting method developed for the synthesis of methyl tuberonate (*vide supra*), but in this case, trifluoroacetate was too labile to be retained safely during deprotection and oxidation steps. Selection of dichloroacetate as a protecting group overcame this difficulty and thus, acetyl groups of the glycoside **21** were replaced by dichloroacetyl groups to give the dichloroacetate **23**. Again, simple methanolysis furnished the target glycoside **4** without any epimerization (ref. 11).

Fig. 6 Synthesis of Methyl β -D-Glucopyranosyltuberonate (Overall 21 steps, 6%)

3. Synthesis of Oxygenated Eremophilanes: Phytotoxins

In recent years, highly oxygenated eremophilane sesquiterpenes have been isolated from the microbial world. They possess remarkable bioactivities, such as phytotoxicity (compounds **24**~**28**), plant hormone inhibitor (**30**) and so on (ref. 12). Among them, Sporogen-AO 1 **24** is a microbial hormone with spore-inducing activity to fungus, *Aspergillus oryzae* (ref. 12a), and Bipolaroxin **28** is a host-selective phytotoxin against several weeds (ref. 12e). KM-01 is an inhibitor to brassinosteroids, which are now recognized as the sixth plant hormone (ref. 12g). Being aware of such interesting bioactivities, we have investigated the synthesis of these bioregulators.

Fig. 7 Highly Oxygenated Eremophilanes as Toxins and Inhibitors

3.1. Preparation of a Chiral Building Block by Reduction with Baker's Yeast

In 1985, we succeeded in the efficient preparation of chiral building block **32** with suitable functional groups in the molecule by reduction of the known β -ketoester **31** (ref. 13) with baker's yeast. Optical purity of the resulting hydroxyester **32** was determined as its MTPA ester to be an extremely high 98.6%e.e. This building block is now available in large quantity by simple operation (ref. 14).

Fig. 8 Preparation of a Chiral Building Block by Reduction with Baker's Yeast

3.2. Synthesis of Sporogen-AO 1: Sporogenic Hormone

We reasoned that this building block **32** should be convertible to the properly substituted cyclohexanone **35**, which would give the desired octalone **36** via Robinson annulation. In fact, this was realized via bicycloheptanone **34** prepared from **32** through 5 steps in excellent yield. The presence of the cyclopropane ring in **34** was essential to promote the Mitsunobu reaction smoothly to give the epimer with correct stereochemistry, which on reductive alkylation gave **35** regioselectively. Robinson annulation via regioselective formation of silyl enol ether gave octalone **36**. Thus, without using any blocking group, the octalone system was selectively constructed. Introduction of an acetyl group and a double bond afforded dione **37**. Stereo- and regiospecific epoxidation at the doubly activated olefin and

finally, Peterson-type methylenation gave sporogen-AO 1 **24** (ref. 15).

Fig. 9 Synthesis of (+)-Sporogen-AO 1 (Overall 18 steps, 10%)

Using this strategy, we were able to synthesize phenomenone **25**, gigantene **26** and phaseolinone **27** (ref. 16). Both enantiomers of phaseic acid, a metabolite of abscisic acid, were synthesized using **32** as a single chiral source (ref. 17). Just recently, we also succeeded in the synthesis of dendryphiellin C **29** (ref. 18). The synthesis of bipolaroxin **28** and KM-01 **30** is due to be completed in the near future.

4. Synthesis of Pironetin: Growth Inhibitor

Pironetin (PA-48153C) **38** was isolated from the culture broth of *Streptomyces* sp. NK10958 (ref. 19) or *Streptomyces prunicolor* (ref. 20). It shows interesting bioactivity as a plant growth inhibitor, which might be applicable to the production of dwarf plants; it also contains potent immunosuppressive activity on the responses of both T and B lymphocytes to mitogens. While several syntheses of pironetin **38** have been already reported (ref. 21), we have recently completed its synthesis via a convergent route using our chiral building block **34** (ref. 22). We dissected the molecule at C6-C7 and employed the coupling of epoxide **40** with the dithiane **39**, which would be derivable from **34**.

Fig. 10 Synthesis of Pironetin : Plan

The C1-C6 unit **40** was derived from the known epoxide **41** via opening with acetylenic alanate (ref. 23) and successive epoxide formation. Meanwhile, stereospecific methylation of the ketol **34** and selective reduction gave the desired isomer **43a** after etherification. Stereochemistry was determined by X-ray analysis of the crystalline diol. Oxidation followed by a two-step hydroxylation and then Birch reduction gave the expected ketol **44**. Oxidative cleavage with lead tetraacetate and functional group manipulation afforded the aldehyde **45**, which on Takai reaction (ref. 24) and thioacetalization gave the C7-C14 unit, the dithiane **39**. Coupling reaction of **39** and **40** proceeded smoothly at 0°C in a short time to give the whole skeleton **46**. Prolonged reaction period resulted in extensive decomposition of the product. Cleavage of thioacetal and the following stereoselective reduction by Mori's procedure (ref. 25) gave *anti*-diol **47a** predominantly. Finally, desilylation and oxidation with manganese dioxide afforded pironetin **38** (ref. 22).

Fig. 11 Synthesis of Pironetin (Overall 19 steps, 12.9%)

5. Synthesis of 2'-Deoxymugineic Acid and Related Analogs: Phytosiderophores

Mugineic acid and analogs **48**–**50** are well-known phytosiderophores, which are excreted from the root of grasses (rice, barley, wheat, etc.) under iron-deficient conditions to dissolve and absorb the ferric ion by chelation (ref. 26). Because of such remarkable activity, a number of syntheses have been reported to date (ref. 27). Nevertheless, physiologists still require large quantities of such phytosiderophores for field studies. We wanted to devise a versatile method both for large-scale production and for obtaining various analogs. In every synthesis ever known, reductive amination was employed for connecting the three units. Unstable aldehydes, however, had to be used for those processes and handling of basic intermediates was rather difficult. Our basic plan was to construct the skeleton as stable tripeptides **51**

Fig. 12 Synthesis of Phytosiderophores : Plan

and then to reduce the amide group chemoselectively via thioamide **52** without attacking other functionalities to give the targets **48**–**50**.

Azetidine carboxylate **53** was sequentially condensed with the corresponding amino acid derivatives **54** and **56**, which were derived from natural aspartic acid and malic acid, respectively, to give the desired tripeptide **57**. Although direct borane reduction was not so chemoselective, treatment with Lawesson's reagent afforded thioamide **58** in good yield and successive desulfurization with Raney-nickel followed by deprotection furnished 2'-deoxymugineic acid **49**. This expeditious process efficiently gave the target compound in excellent overall yield 27% through 7 steps (ref. 28). In the same manner, nicotianamine **50** was synthesized. The synthesis of mugineic acid **48** and avenic acid is also forthcoming (ref. 29). Since the azetidine ring and 2'-hydroxyl group of mugineic acid are not essential for the expression of activity, we are attempting to develop large-scale production of simpler analogs according to this scheme.

Fig. 13 Synthesis of 2'-Deoxymugineic acid (Overall 7 steps, 27%)

6. Synthesis of Sorokinianin: Phytotoxin

Sorokinianin **59** was isolated by Nakajima et al. from pathogenic fungus, *Helminthosporium sorokiana*, which infects Australian barley. It shows potent growth inhibition, and the relative stereochemistry was elucidated. Availability of the compound, however, was limited and the absolute configuration was unknown (ref. 30). We noticed its biological activity and decided to synthesize the enantiomer to elucidate the absolute configuration as well as to obtain substantial amount of the material. Its structure is similar to that of helminthosporal, which has already been synthesized (ref. 31), except that it contains an additional three-carbon unit as the hydroxylactone moiety. So, we selected a different and more accessible approach to reach **59**, namely, bicyclic ketone **60**, which should be derived from carvone **61**, was employed as a key intermediate. As shown in Fig. 14, addition of C₁- and the C₃-unit to C6- and C7-position and introduction of oxygen to C8-methylene would afford sorokinianin.

Fig. 14 Synthesis of Sorokinianin : Plan

(R)-(+)-Carvone **61** was converted to ketoaldehyde **62** in three steps, which was treated with a base to equilibrate the mixture giving the desired bicyclic ketol with the equatorial isopropyl group predominantly (4:1). The mixture was separated after silylation to give pure **63**. The minor isomer with

axial substituent was equilibrated by the same base treatment to give more **63**. The Wittig reaction and oxidation of the regenerated hydroxyl group gave the key intermediate **60**. Aldol condensation proceeded stereoselectively to give *exo-erythro* isomer **64** as a major product (100% *exo*-selective; *erythro:threo* at C1'-position=15:1). Addition of one carbon unit, selective ozonolysis and silylation gave lactol-ether **65**. At this point we expected that hydroboration-oxidation should give the desired β -hydroxymethyl group, because the β -face is sterically congested by the lactol-ether ring. Unfortunately, the reaction gave a 1:1 mixture of two isomers, which was separated after oxidation of the lactol to give pure lactone **66**. Hindered borane did not work at all. Hydroxylation of **66** with Davis' reagent afforded sorokinianin **60** exclusively. Protection of the primary OH group was essential for stereospecific hydroxylation. When it was executed without protection, only the epimeric hydroxyl group was introduced to give *epi*-sorokinianin. A plausible mechanism may be that the hydroxide ion deprotonated at the carbon bearing the newly introduced hydroxyl group and then protonation occurred from the less hindered backside. Thus, we succeeded in the synthesis of sorokinianin and the absolute configuration was determined (ref. 32).

Fig. 15 Synthesis of Sorokinianin (Overall 17 steps, 3.4%)

7. Synthesis of Tanabalin: Insect Antifeedant

Tanabalin **67** was isolated from a Brazilian medicinal plant, *Tanacetum balsamita* by Kubo, Kusumi and co-workers and the structure was elucidated unambiguously (ref. 33). This clerodane diterpenoid possesses strong antifeedant activity against a harmful pest, pink boll worm, *Pectinophora*

Fig. 16 Synthesis of Tanabalin : Plan

gossypiella. Our synthetic plan was to employ properly substituted *trans*-octalone **69** as a precursor, to which just addition of a furan ring and functional group modifications should give tanabalinal. The key reaction was how to construct this *trans*-decalin skeleton and we adopted the tandem reaction to obtain the system in a single operation. Basic treatment of the known β -keto ester **71** with iodide **70** should effect initially alkylation (a) and successively intramolecular Robinson-type Michael and aldol reaction (b, c) to give the desired skeleton all at one time. In fact, this was the case under thermodynamic condition and we could complete the synthesis of tanabalinal as follows.

We selected the known δ -lactone (*R*)-**72** as a starting material (ref. 34). Although the known procedures were biochemical transformations, we employed chemical transformation from (*S*)-citronellol via oxidative cleavage to (*R*)-**72**. Sequential alkylation of (*R*)-**72** gave **73** stereospecifically. DIBAL reduction and the successive Horner-Wittig reaction gave the enone **74**, which was converted to the corresponding iodide **70** in three steps. Bromide formation had to be done quickly after liberation of the hydroxyl group by fluoride treatment, or the formation of the substituted tetrahydropyran via cyclization was inevitable. The next tandem reaction was a critical step and the best result was obtained when a mixture of the iodide **70** and β -keto ester **71** was refluxed with sodium methoxide in methanol. The desired *trans*-octalone **69** was obtained as the sole product in 82 % yield. In this tandem reaction, the second step, intramolecular Michael reaction of **75a** to **75b**, determined the stereochemistry of the octalone **69**. As designated like **75t**, maximum overlap between HOMO of enolate and LUMO of enone might be generated when both chains are located at equatorial position, because the bulky prenyl group fixes the molecule by extending to the equatorial position at the transition state.

Fig. 17 Synthesis of (-)-Tanabalinal : Tandem Cyclization

Now, the carbonyl group was reduced and removed by Barton's deoxygenation procedure via thiocarbamate **76**. Acid hydrolysis of acetal and the following DIBAL reduction gave diol **77**. Oxidation with Fetizon reagent directly gave the γ -lactone, which provided aldehyde **78** by careful ozonization. Reaction with 3-furylmagnesium bromide gave a mixture of epimeric alcohols **79** and **80** (1:1) in poor yield. The yield was much improved up to 68% using 3-furyllithium. Finally, acetylation of **79** afforded

(-)-tanabalin, (-)-**67**. The epimer **80** must be convertible to tanabalin by Mitsunobu inversion with acetic acid. The synthesis of this clerodane diterpene was completed in only 18 steps (ref. 35).

Fig. 18 Synthesis of (-)-Tanabalin (Overall 18 steps, 6%)

8. Conclusion

We have been devoted to the synthesis of several bioregulators and related analogs with remarkable biological activities especially with regard to plant growth regulation, nutrition and physiology in optically active forms and have successfully developed general and efficient procedures. Application of these methods to afford substances should help further development of chemical and biological studies in plant physiology.

Acknowledgments: The authors would like to thank all of their co-workers whose names are cited in the references for their devotion to the synthetic work. We are much indebted to the Japanese Ministry of Education, Science, Culture and Sports, Japan Society for the Promotion of Science and T. Hasegawa Co., Ltd. for financial support. Generous gifts of starting materials from Fuji Pharmaceutical Industry Co., Ltd., Shiono Koryo Kaisha Ltd. and Takasago International Corporation are gratefully acknowledged.

References and Notes

- (1) Demole, E.; Lederer, E.; Mercier, D. *Helv. Chim. Acta* **1962**, *45*, 675.
- (2) Aldridge, D.C.; Galt, S.; Giles, D.; Turner, W.B. *J. Chem. Soc., (C)* **1971**, 1623.
- (3) Nishida, R.; Baker, T.C.; Roelofs, W.L. *J. Chem. Ecol.* **1982**, *8*, 947.
- (4) Yoshihara, T.; Omer, E.-S.A.; Koshino, H.; Sakamura, S.; Kikuta, Y.; Koda, Y. *Agric. Biol. Chem.* **1989**, *53*, 2835.
- (5) Matsuura, H.; Yoshihara, T.; Ichihara, A.; Kikuta, Y.; Koda, Y. *Biosci. Biotech. Biochem.* **1989**, *53*, 2835.
- (6) Helmchen, G.; Goeke, A.; Lauer, G.; Urmann, M.; Fries, J. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1024.
- (7) (a) Kitahara, T.; Nishi, T.; Mori, K. *Tetrahedron* **1991**, *47*, 6999. (b) Kitahara, T.; Warita, Y.; Abe, M.; Seya, M.; Takagi, Y.; Mori, K. *Agric. Biol. Chem.* **1991**, *55*, 1013.
- (8) Kitahara, T.; Inoue, M.; Tamogami, S.; Kaiser, R. *Tetrahedron* **1996**, *52*, 1487.

- (9) Kaiser, R. The scent of orchids: Olfactory and chemical investigation, Elsevier, Amsterdam, **1993**, 150-152, 210-212.
- (10) Nishi, T.; Kitahara, T. *Proc. Japan. Acad.* **1995**, 71B, 20.
- (11) Inoue, M.; Kitahara, T. *Tetrahedron* submitted for publication.
- (12) (a) Tanaka, S.; Wada, K.; Marumo, S.; Hattori, H. *Tetrahedron Lett.* **1984**, 25, 5907. Tirilly, Y.; Kloosterman, J.; Sipma, G.; Kettenes-van den Bosch, J.J. *Phytochem.* **1983**, 22, 2082. (b) Riche, C.; Pascard-Billy, C.; Devys, M.; Gaudemer, A.; Barbier, M.; Bousquet, J.F. *Tetrahedron Lett.* **1974**, 2765. Bottalico, A.; Frisullo, S.; Lerario, P.; Randazzo, G.; Capasso, R. *Phytopatho. Medit.* **1982**, 21, 39. (c) Kenfield, D.S.; Bunkers, G.; Wu, Y.-H.; Strobel, G.; Sugawara, F.; Hallock, Y.; Clardy, J. *Experientia* **1989**, 45, 900. (d) Dhar, T.K.; Siddiqui, K.A.I.; Ali, E. *Tetrahedron Lett.* **1982**, 23, 5459. (e) Sugawara, F.; Strobel, G.; Fisher, L.E.; Van Duyne, C.D.; Clardy, J. *Proc. Natl. Acad. Sci. USA* **1985**, 82, 8291. (f) Guerriero, A.; D'Ambrosio, M.; Cuomo, V.; Vanzanella, F.; Pietra, F. *Helv. Chim. Acta* **1989**, 72, 438. (g) Kim, S.-K.; Mizuno, K.; Hatori, M.; Marumo, S. *Tetrahedron Lett.* **1994**, 35, 1731.
- (13) Lukes, R.M.; Poos, G.I.; Sarett, L.H. *J. Am. Chem. Soc.* **1952**, 74, 1401.
- (14) Kitahara, T.; Mori, K. *Tetrahedron Lett.* **1985**, 26, 451.
- (15) Kitahara, T.; Kurata, H.; Mori, K. *Tetrahedron* **1988**, 44, 4339.
- (16) Kitahara, T.; Kiyota, H.; Kurata, H.; Mori, K. *Tetrahedron* **1991**, 47, 1649.
- (17) Kitahara, T.; Touhara, K.; Watanabe, H.; Mori, K. *Tetrahedron* **1989**, 45, 6387.
- (18) Kitahara, T.; Akao, H., manuscript in preparation.
- (19) Kobayashi, S.; Tsuchiya, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Simada, N. *J. Antibiot.* **1994**, 47, 697.
- (20) Yoshida, T.; Koizumi, K.; Kawamura, Y.; Matsumoto, K.; Itazaki, H. *Jpn. Pat. Kokai* **1993**, 5-310726.
- (21) (a) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, 60, 7567. (b) Gurjar, M. K.; Henri Jr., J.T.; Bose, D.S.; Rao, A.V.R. *Tetrahedron Lett.* **1996**, 37, 6615.; Gurjar, M. K.; Chakrabarti, A.; Rao, A.V.R. *Heterocycles* **1997**, 45, 7. (c) Chida, N.; Yoshinaga, M.; Tobe, T. Ogawa, S. *Chem. Commun.* **1997**, 1043.
- (22) Watanabe, H.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **1998**, 39, in press.
- (23) Skrydstrup, T.; Bénéchie, M.; Khoung-Huu, F. *Tetrahedron Lett.* **1990**, 31, 7145.
- (24) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, 108, 7408.
- (25) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, 30, 4386.
- (26) (a) Takagi, S. *Soil Sci. Plant Nutr.* **1976**, 22, 423. (b) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagai, S.; Matsuura, Y.; Kakudo, M. *Proc. Japan. Acad.* **1978**, 54B, 249.
- (27) Shioiri, T.; Hamada, Y.; Matsuura, F. *Tetrahedron* **1995**, 51, 3939. and references cited therein.
- (28) Klair, S.S.; Hindupur, M.R.; Kitahara, T. *Tetrahedron Lett.* **1998**, 39, 89.
- (29) Hindupur, M.R.; Osawa, H.; Kitahara, T. to be submitted.
- (30) Nakajima, H.; Isomi, K.; Hamasaki, T.; Ichinoe, M. *Tetrahedron Lett.* **1994**, 35, 9597.
- (31) Corey, E.J.; Nozoe, S. *J. Am. Chem. Soc.* **1963**, 85, 3527. *ibid.* **1965**, 87, 5728.
- (32) Watanabe, H.; Onoda, T.; Kitahara, T.; Mori, K. *Tetrahedron Lett.* **1997**, 38, 6015.
- (33) Kubo, I.; Jamalamadaka, V.; Kamikawa, T.; Takahashi, K.; Tabata, K.; Kusumi, T. *Chem. Lett.* **1996**, 441.
- (34) (a) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, 44, 111. (b) Poppe, L.; Novák, L.; Kolonitzs, P.; Bata, Á.; Szántay, C. *Tetrahedron* **1988**, 44, 1447.
- (35) Watanabe, H.; Onoda, T.; Kitahara, T. *Tetrahedron Lett.* submitted for publication.

(Received June 26, 1998)