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Chemistry of the Sex Pheromones Produced by Cigarette Beetle(Lacioderma Serricornine F.)

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담배저장해충(Lacioderma Serricornine F.)의 성유인 물질에 관한 고찰

양광규 · 김근수 · 신성철

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초 록

담배저장해충은 숙성된 엽연초에 가장 심각한 해를 끼치는 것으로 알려져 있다. 이 해충의 성유인 물질들 중에서 serricornin이 가장 강한 생리활성을 보여주고 다른 유인물질들은 교접시 이것에 대한 보조역할을 한다. 분광학적인 증거와 합성에 관한 연구로부터 이 화합물의 구조는 (4S, 6S, 7S)-4, 6-dimethyl-7-hydroxynonan-3-one임이 밝혀졌다. 담배저장 해충으로부터 얻어진 성유인 물질들은 모두 polyketide 생합성의 과정에서 생성된다고 제안되었다. 두 가지 nonasymmetric 합성과 열가지 asymmetric 합성이 상세하게 고찰되었다.

1. Introduction

The cigarette beetle(Lacioderma Serricornine F.) is a serious cosmopolitan pest found not only in cured tobacco leaves but also in almost all dried food products. Since the existence of the sex pheromones of female cigarette beetles was reported by Burkholder in 1970,[1] there have been numerous studies. Great interests have been kindled mainly due to the difficulty in detecting the infestation of the pest until its population has increased beyond the economic threshold level because of its clandestine nature as well as the lack of pesticide-dependent control method. In this article, we describe the chemistry of sex pheromones produced by this beetle in detail.

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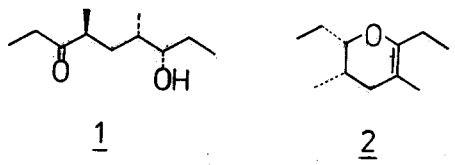
2. Structural elucidation

In 1979, Chuman and his colleagues separated four sexual pheromones(serricornin **1** as a major component, anhydroserricornin **2**, serricorone **3** and serricorole **4**) from the hexane extract of the cigarette beetle.

They assigned 4, 6-dimethyl-7-hydroxynonan-3-one to the structure of serricornin **1** from spectroscopic evidences.[2] This molecule posseses chiral centers at C_4, C_6 and C_7; therefore, eight stereoisomers are possible. Of these eight stereoisomers, natural serricornin was found to have erythro-configuration at vicinal C_6-methyl and hydroxy groups.[3,4,5] Later, the full stereochemistry of serricornin was established to be(4S, 6S, 7S) by several synthetic studies and high resolution pmr spectrum.[6,7,8]



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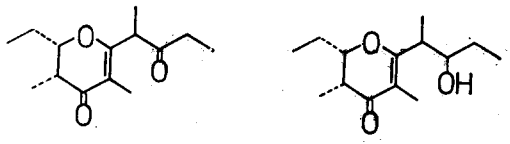

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Fig. 1.

In addition to its stereochemistry, the serricornin molecule is of interest because it can exist in both the acyclie chain and the cyclic hemiketal form. The natural and biologically active isomer SSS shows the complicated pmr and cmr spectra of a binary mixiure of these two forms. From the integral values of the two H-7 signals in the pmr spectrum, the ratio of cyclic hemiketal(SSS-A) to acyclic chain(SSS-B) was determined to be 2.5 : 1, respectively.[7]

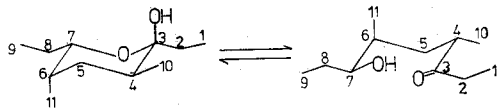


Fig. 2.

The equilibrium between the keto alcohol and the hemiketal forms seems to be closely related to the sex pheromone activity of serricornin. The occurrence and the lack of pheromone activity is dependant on the structural conversion between keto alcohol-hemiketal and anhydroserricornin(Fig. 3)[9].

Spectroscopic evidence and synthetic studies have allowed the elucidation of the structures of serricorone **3** and serricorole **4**.[10] Recently, the absolute configurations of C_2 and C_3 of ser-

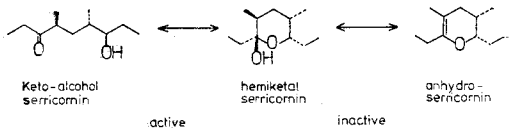


Fig. 3. Structural conversion of the serricornin molecule

ricorone **3** and serricorole **3** were established to be(2S, 3R) by comparing the ORD curves of these compounds with the ORD curve of stegobinone, which was known to be(2S, 3R). By similar means, the configurations at C_2 and C_3 of the anhydroserricornin were proven to be(2S, 3R) in comparison with synthetically prepared anhydroserricornin.[9]

3. Pheromonal activity

Male cigarette bettles show typical responses such as antennal elevation with mesothoracic legs, rapid zigzag locomotion toward the pheromone source, and homosexual mounting. These effects of sex pheromone are evaluated by the behavioral bioassay and the electroantennogram (EGA) experiments on males. Results of these experiments indicated that (S*S*S*)-serricornin **1** elicits the strongest sex pheromonal activity on all parameters.[11,12,13] It has been demonstrated that the high specificity of the stereochemistry-pheromone activity relationship is associated with the configuration at the chiral centers C_6 and C_7 in the serricornin molecule.[12] The (4S, 6S, 7R) isomer of serricornin is known as the inhibitory component conventionally synthesized serricornin product.[14] The importance of C_7 stereochemistry was thus demonstrated.

Serricornone **3** and serricorole **4** can also stimulate sexual activity. These components show somewhat weak biological activity. These pheromonal substances are considered as contributor of the supplementary factors of sexual stimulation in cooperation with serricornin in the copulation of this insect.[9]

The magnitude of pheromonal activity of

anhydroserricornin is 10^{-3} of that of serricornin at its highest, therefore anhydroserricornin is not an important factor. Considering the reversibility of the transformation between serricornin and anhydroserricornin, the latter may be a precursor in biosynthesis or an inactivated form of the former.[9,15] Although these speculations are appealing, no evidence has yet been offered.

4. Relationship between sex pheromonal components and serricornin biosynthesis

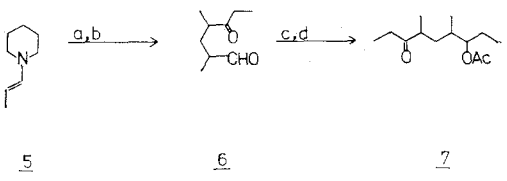
Pheromonal components isolated from cigarette beetles have much similarities with respect to the positions of the functional groups and methyl branches. From these structural similarities it has been suggested that these components may be derived from the corresponding C-11 and C-14 polyketide precursors which are formed by the condensation of four propionate units and five propionate units, respectively.[16]

This hypothesis of polyketide biosynthesis was supported by the biomimetic syntheses of serricorone **3** and stegobinone, which were synthesized via polyketide precursors.[10,17,18,19]

5. Syntheses

In the last decade, a considerable amount of synthetic studies on sex pheromonal components of cigarette beetle have been carried out. Serricornin has been a focus of attention because of its practical value. Although its framework is not intricate in itself, there has been a synthetic problem which must be reckoned with. This problem, which arises from facile epimerization at the C-4 chiral center, could not been conquered until Bartlett and coworkers successfully accomplished the stereoselective synthesis of serricornin.

The Chuman group reported two nonstereochemical methods for synthesis of serricornin. The first(Scheme 1) begins with the alkylation of enamine **5** with an electrophilic olefin.[2] After Grignard reaction and acetylation, serricornin acetate **7** is obtained.

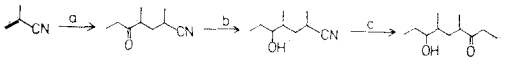


5 6 7

Scheme 1.

reagents: (a) $CH_2=C(CH_3)COCH_2CH_3$, benzene, (b) aq-$(CO_2H)_2$; (c) EtMgBr, ether; (d) Ac_2O, pyridine.

The second synthesis of Chuman (Scheme 2) starts with Micheal addition of diethyl ketone to methacrylonitrile.[20] The ketonitrile **8** is reduced with $NaBH_4$ to obtain the corresponding alcohol **9**. The synthesis of serricornin is completed by the Grignard reaction of **9**.



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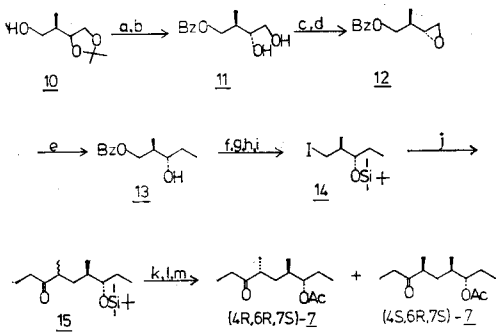
Scheme 2.

reagents: (a) diethyl ketone; (b) $NaBH_4$; (c) EtMgBr, ether.

The first stereocontrolled synthesis of serricornin was introduced by Chuman and coworkers in 1981(Scheme 3).[3] In an attempt to determine the absolute configurations of natural serricornin, they synthesized serricornin, and the stereochemistry at C_6 and C_7 of naturally occurring serricornin was revealed to be (6S, 7S). The 1, 2-acetonide **10** is protected and hydrolyed to obtain 1, 2-diol **11**, which is converted to epoxide **12** via tosylate. The epoxide **12** is treated with lithium dimethylcuprate to give compound **13**. This regiospecific chain elongation is the key step to this synthesis. The compound **13** is converted to protected iodide **14** in four steps. This is alkylated to lithium enolate of diethyl ketone to obtain silylated serricornin **15**. The synthesis is completed by successive deprotection and acetylation to furnish a racemate of (4R, 6R, 7S)-and (4S, 6R, 7S)-acetate. These C-4 epimers are separated by preparative GLC. The completely decoupled cmr spectrum of the syn-

thetic erythro-serricornin acetate was compared with that of the naturally occurring serricornin acetate.



Scheme 3.

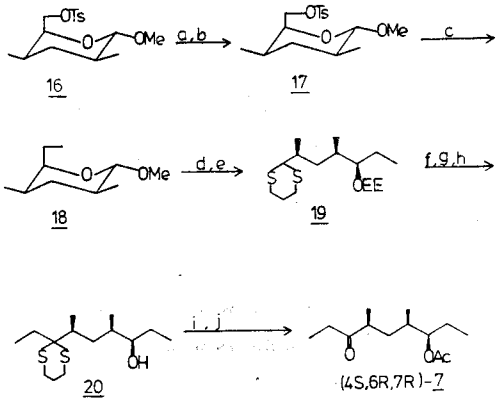
reagents: (a) BnCl, NaH, DMSO; (b) H^+, MeOH; (c) TsCl, pyridine; (d) KOH, MeOH; (e) Me_2 CuLi; (f) $^tBuMe_2SiCl$, imidazole; (g) H_2, Pd-C; (h) TsCl, pyridine; (i) NaI, acetone; (j) LDA, diethyl ketone; (k) acetic acid; (l) acetic anhydride, phridine; (m) prep. GLC.

Mori and Nomi also synthesized (4R, 6R, 7S)- and (4S, 6R, 7S)-serricornin acetate from (2S, 3S)-(+)-β-methylasparatic acid for the purpose of elucidating the configuration at C_6 and C_7 chiral centers.[5] Their result was consistent with the Chuman's disclosure.

In 1982, the absolute stereochemistry of serricornin was firmly established to be (4S, 6S, 7S) from the results of the two different stereoselective syntheses, both by Mori and his group.[4,8] These synthesis are briefly outlined in Scheme 4 and 5, respectively.

The first synthesis begins with the compound **16** derived stereoselectively from glucose in ten steps, and require another ten steps, which leads to (4S, 6R, 7R)-serricornin. By comparing the nmr spectrum of (4S, 6R, 7R)-isomer with that of naturally occurring serricornin, it has been concluded that the synthetic isomer corresponds to the C-4 epimer of the antipode of the natural pheromone. Therefore, the absolute stereochemistry of serricornin must be (4S, 6S, 7S).

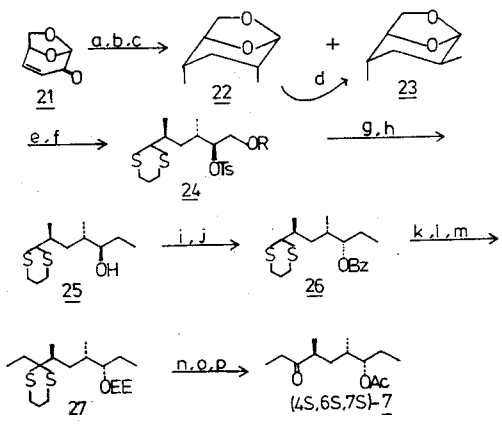
The other synthesis, published in the same year, begins with levoglucosenone **21**. The key steps are the introduction of methyl groups and



Scheme 4.

reagents: (a) Na/liq.-NH_3, NH_4Cl; (b) TsCl, pyridine; (c) Me_2CuLi; (d) 1,3-propanedithiol, BF_3; (e) ethyl vinyl ether, PPTS; (f) n-BuLi, TMEDA; (g) ethyl iodide; (h) PPTS; (i)acetic anhydride, pyridine; (j) $HgCl_2$, $CaCO_3$

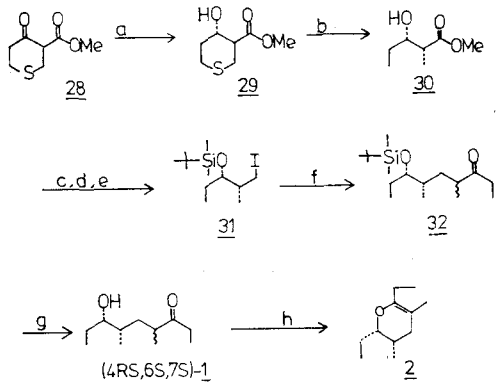
subsequent epimerization at C_2 center. Since the two methyl groups of **22** lie in an unstable 1,3-diaxial relationship, the methyl group adjacent to enolizable acetal(at C_2) is epimerized almost completely. The deacetylated product of the compound (4S, 6S, 7S)-**1** is not only biologically active to the cigarette beetle but also completely consistent with natural serricornin in all respects.



Scheme 5.

reagents: (a) Me_2CuLi; (b) Ph_3PCH_2; (c) H_2, Pd-C; (d) TsOH; (e) 1,3-propanedithiol, BF_3; (f) TsCl, pyridine; (g) KOH, MeOH; (h) Me_2 CuLi; (i) Ph_3P, BzOH; (j) $EtO_2CN{=}NCO_2Et$; (k) KOH, MeOH; (l) α-ethoxyethyl ether, PPTS; (m) BuLi, TMEDA; (n) PPTS; (o) acetic anhydrine; (p) $HgCl_2$-$CaCO_3$.

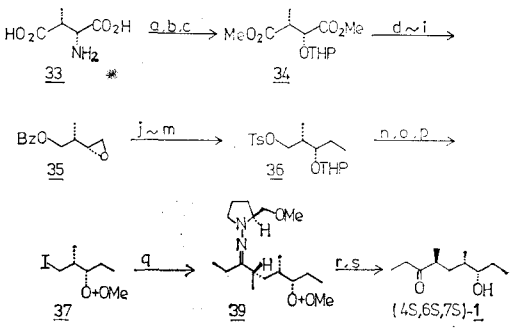
Hofmann and his co-workers reported a synthesis of (4RS, 6S, 7S)-serricornin as a possible precursor to anhydroserricornin **2**(Scheme 6).[21] A noteworthy feature of this synthesis is yeast fermentation to introduce the chirality at C_6 and C_7. Thus, the starting material **28** is fermented by yeast, and the Raney Ni-desulfurization of the resulting β-hydroxyester **29** proceeds without epimerization to give the compound **30** with 98% diastereomeric purity. The protected alcohol is treated with N-methyldicyclohexylcarbodiimidium iodide to obtain silylated iodide **31** as a key intermediate of this work. The iodide **31** is condensed with diethyl ketone and the resulting product **32** is desilylated to give (4RS, 6S, 7S)-serricornin. Overall, dehydrocyclization of this substance provides anhydroserricornin **2** in eight steps.



Scheme 6.

reagents: (a) yeast; (b) Raney Ni; (c) ^{t}BuMe$_2$SiCl, imidazole; (d) DIBAH; (e) N-MDCCI; (f) LDA, diethyl ketone; (g) ^{n}BuN$^+$F$^-$; (h) TsOH.

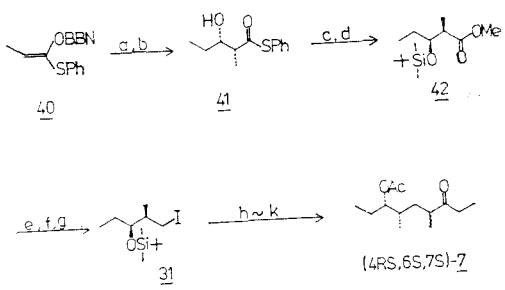
Mori and Nomi have developed a rather long but highly stereoselective synthesis of the natural serricornin, which is summarized in Scheme 7.[6] The starting point is (2R, 3R)-threo-3-methylasparatic acid **33**. The synthesis proceeds through the protected epoxide **35**, which is homologated to the protected tosylate **36**. After iodination, the iodide **37** is alkylated with the hydrazone **38** by the Ender's method[22,23] to give a condensed product **39**. The resulting compound **39** is hydrolyzed to the desired(4S, 6S, 7S)-serricornin.



Scheme 7.

reagents: (a) HNO_2, H_2SO_4; (b) CH_2N_2; (c) DHP, TsOH; (d) LAH; (e) TsOH, MeOH; (f) TsOH, acetone; (g) $NaCH_2COCH_3$, BnCl then H_3O^+; (h) TsCl, pyridine; (i) KOH, MeOH; (j) Me_2CuLi; (k) DHP, TsOH; (l) H_2 Pd-C; (m) TsCl, pyridine; (n) NaI, K_2CO_3; (o) TsOH, MeOH; (p) PPTS, 2-methoxypropene; (q) **38**, LDA; (r) MeI; (s) H_3O^+.

In 1983, Baker and Devlin reported a synthesis summarized in Scheme 8.[24] The important concept of this work is that erythrodisposition of the methyl and hydroxy groups at C_6 and C_7 of the pheromone may be elaborated by kinetically controlled aldol condensation. The synthesis begins with the 9-BBN enolate **40**, which is condensed with propanal to obtain β-hydroxy thiolate **41**. The cross condensed 41 undergoes successive transesterification and protection to give silylated ester **42**. Treatment of **42** with

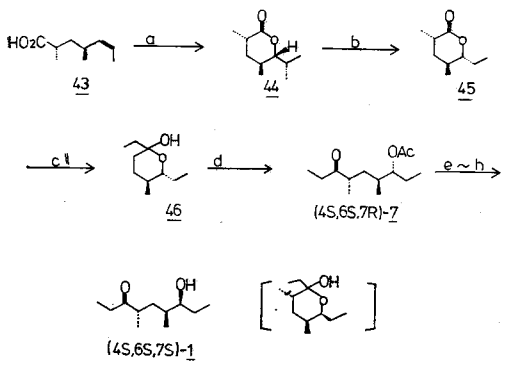


Scheme 8.

reagents: (a) EtCHO; (b) H_2O_2-MeOH; (c) $HgCl_2$-MeOH; (d) ^{t}BuMe$_2$SiCl imidazole; (e) DIBAH; (f) TsCl, Et_3N; (g) NaI, acetone; (h) LDA, HMPA; (i) diethyl ketone; (j) ^{n}Bu$_4$NF; (k) acetic anhydride, pyridine.

DIBAH gives a singly protected alcohol, which is converted to the silylated iodide **31**. The key intermediate **31** is nonstereolectively alkylated to diethyl ketone.

In 1984, Bartlett and his coworkers presented a synthesis of serricornin, which is outlined in Scheme 9.[25] Starting olefinic acid **43** is elaborated via iodolactone **44** to give a simple lactone **45**. This lactone is treated directly with ethylmagnesium bromide to give a hemiketal **46**. The natural serricornin is obtained through ring opening of **46**, protection of ketone, and inversion of the OH group.

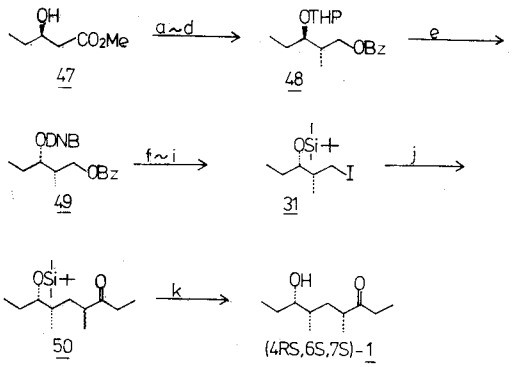


Scheme 9.

reagents: (a) I_2, MeCN; (b) $^nBu_3SnH$; (c) EtMgBr; (d) Acetic anhydride, Pyridine; (e) ethylene glycol then OH^-; (f) MsCl; (g) $Cs(OAc)_2$; (h) H_3O^+.

In the same year, Mori and Watanabe published the synthesis outlined in Scheme 10.[26] This synthesis begins with (R)-3-hydroxypentanoate **47** readily available by microbial β-oxidation of pentanoic acid. Walden inversion of the adduct **48** affords the compound **49**. Again, an intricate sequence of deprotection, protection, and iodination steps leads to the silylated iodide **31**, which is alkylated to diethyl ketone by the previously described method to obtain (4RS, 6S, 7S)-serricornin.

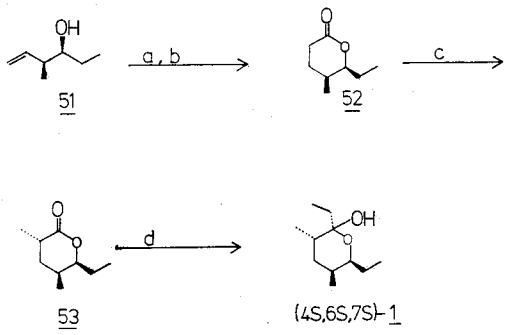
Thereafter, Takeda's group introduced a simple method to stereoselectively synthesize natural (4S, 6S, 7S)-serricornin from **51**(Scheme 11).[27,28] (3S, 4S)-3-Hydroxy-4-methyl-5-hexene



Scheme 10.

reagents: (a) LDA, MeI, HMPA-THF; (b) DHP, PPTS; (c) LAH; (d) BzCl; (e) Walden inversion; (f) aq-KOH then $^tBuMe_2SiCl$; (g) H_2, Pd-C; (h) TsCl; (i) NaI, $NaHCO_3$; (j) diethyl ketone, LDA; (k) aq-acetic acid, THF.

51 undergoes hydroformylation and subsequent oxidation to obtain lactone **52**. The natural serricornin is produced via methylation and Grignard reaction from the lactone **52**.



Scheme 11.

reagents: (a) ^iBuMgCl, Cp_2TiCl_2; (b) CO_2 then HCOOH; (c) MeI, $LiN(SiMe_3)_2$; (d) EtMgBr.

Abstract

Cigarette beetle(Lacioderma serricornine F.) is a serious pest of cured tobacco leaves. Of its pheromonal components, serricornin shows the strongest sexual stimulation. Other substances contribute as the supplementary factors cooperating with this component in the copulation of cigarette beetle. From spectroscopic evidence and synthetic studies, the structure of natural

serricornin has been determined to be (4S, 4S, 7S)-4, 6-dimethyl-7-hydroxynonan-3-one. It has been suggested that the pheromonal components isolated from this beetle may be derived from polyketide biosynthesis. Two nonasymmetric syntheses of serricornin will be reviewed in detail.

References

1. Burkholder, W.E.: "Control of Insect Behavior by Natural Products," p.1. Academic Press, New York (1970).
2. Chuman, T., Kato, K. and Noguchi, M.: Agric. Biol. Chem., 43: 2005(1979).
3. Chuman, T., Kato, K., Noguchi, M., Nomi, H. and Mori, K.: Agric. Biol. Chem., 45: 2019(1981).
4. Mori, K. and Nomi, H.: Tetrahedron Lett., 22: 1127(1981).
5. Mori, M., Chuman, T., Kohno, M., Kato, K., Noguchi, M., Mori, H. and Mori, K.: Tetrahedron Lett., 667(1982).
6. Mori, K. and Nomi, H. Tetrahedron, 38: 3705(1982).
7. Mori, M., Chuman, T. and Kato, K.: Tetrahedron Lett., 25: 2553(1984).
8. Mori, M., Chuman, T., Kato, K. and Mori, K.: Tetrahedron Lett., 23: 4593(1982).
9. Chuman, T., Mochizuki, K., Mori, M., Kohno, M., Kato, K. and Noguchi, M.: J. Chem. Ecol., 11: 417(1985).
10. Chuman, T., Mochizuki, K., Kato, K., Ono, M. and Okubo, A: Agric. Biol. Chem., 47: 1413(1983).
11. Mochizuki, K., Chuman, T., Mori, M., Kohno, M. and Kato, K.: Agric. Biol. Chem., 48: 2833(1984).
12. Chuman, T., Mochizuki, K., Mori, M., Kohno, M., Kato, K., Nomi, H. and Mori, K.: Agric. Biol. Chem., 46: 3109(1982).
13. Mochizuki, K., Mori, M., Chuman, T., Kohno, M., Ohnishi, A. Watanabe, H. and Mori, K.: J. Chem. Ecol., 12: 179(1986).
14. Mori, M., Mochizuki, K., Kohno, M., Chuman, T., Ohinishi, A., Watanabe, HH. and Mori, K.: J. Chem. Ecol., 12:83(1986).
15. Chuman, T.: Nippon Nogeikagaku Kaishi, 58: 1135(1984).
16. Chuman, T.: Yuki Gosei Kagakux Kyokaishi, 39: 1183(1981).
17. Ansell, J.M., Hassner, A. and Burkholder, W.E.: Tetrahedron Lett., 22: 2497(1979).
18. Sakakibare, M. and Mori, K. Tetrahedron Lett., 22: 2401(1979).
19. Ono, M., Onishi, I., Kuwahara, Y., Chuman, T. and Kato, K.: Agric. Biol. Chem., 47: 1933(1983).
20. Ono, M., Onishi, I., Chuman, T., Kohno, M. and Kato, K. Agric. Biol. Chem., 44 2259(1980).
21. Hoffman, R.W., Helbig, W. and Ladner, W.: Tetrahedron Lett., 23: 3479(1982)
22. Enders, D. and Eichenauer, H.: Chem. Ber., 112: 2933(1979).
23. Enders, D. and Eichenauer, H.: Angew. Chem. Int. Ed. Engl., 18: 397(1979).
24. Baker, R. and Devlin, J.A.: J. Chem. Soc., Chem. Commun., 147(1983).
25. Bartlett, P.A., Richardson, D.P. and Myerson, J.: Tetrahedron, 40: 2317(1984).
26. Mori, K. and Watanabe, H.: Tetrahedron, 41: 3423(1985).
27. Kobayashi, Y., Kitano, Y., Takeda, Y. and Sato, F.: Tetrahedron, 42: 2937(1986).
28. Takeda, Y., Kobayashi, Y. and Sato, F.: Chem. Lett., 471(1985).