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Chemistry and biology of oxygen heterocycles as insect pheromones are reviewed referring to *exo*-brevicomin, disparlure, japonilure and olean. Synthesis of koninginin A, a microbial metabolite, is discussed. Two azetidine alkaloids, penaresidin A and penazetidine A, were synthesized.

J. Heterocyclic Chem., **33**, 1497 (1996).

Introduction.

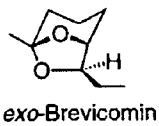
New heterocyclic bioregulators and semiochemicals are discovered every year. Due to the advances in analytical techniques, their gross structures can be elucidated even with μg quantities of the naturally occurring materials. Assignment of the absolute configuration to these rare natural products is not an easy task. Their enantioselective synthesis is quite often the only rational way to determine the absolute stereochemistry, especially when the natural products are oils and therefore unsuitable for X-ray studies. My works in pheromone chemistry gave many examples of stereochemical assignments by synthesis.

Another important role of the enantioselective synthesis of bioregulators and semiochemicals is to provide samples for further biological studies. Of utmost importance is the fact that synthesis can give us not only the naturally occurring enantiomer but also its antipode and stereoisomer(s). Synthesis gives us the chance to clarify the stereochemistry-bioactivity relationships among bioactive natural products.

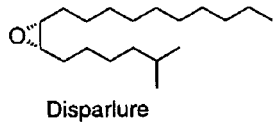
In this lecture, I will first review my work in pheromone chemistry. Stereochemistry-bioactivity relationships among insect pheromones will be reviewed referring to oxygen heterocycles such as *exo*-brevicomin, disparlure, japonilure and olean. Secondly, synthesis of a microbial metabolite koninginin A will be reported. Our synthesis clarified the absolute configuration of koninginin A as depicted in Figure 1. Thirdly, Synthesis of two azetidine alkaloids, penaresidin A and penazetidine A, will be reported. These are marine natural products with interesting bioactivities.

ENANTIOSELECTIVE SYNTHESIS OF HETEROCYCLIC BIOREGULATORS AND SEMIOCHEMICALS

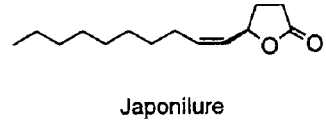
1. Insect Pheromone



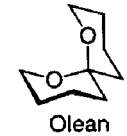
exo-Brevicomin



Disparlure

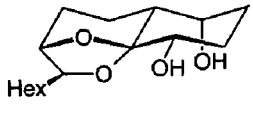


Japonilure

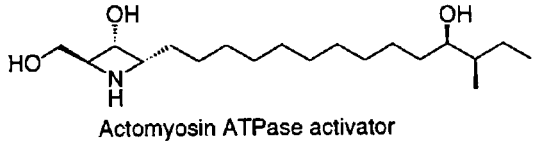


Olean

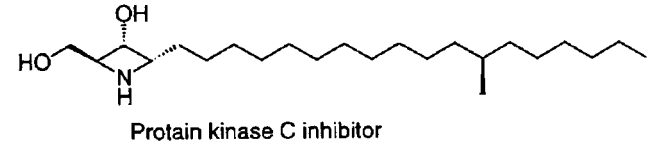
2. Koninginin A



3. Penaresidin A and Penazetidine A

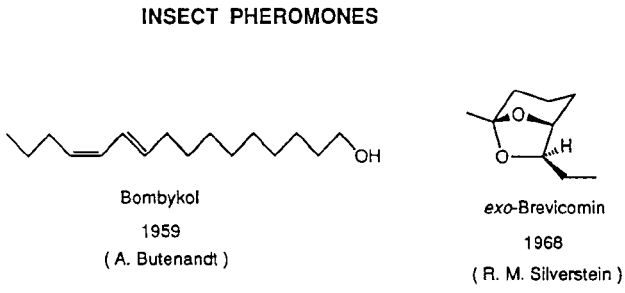


Actomyosin ATPase activator



Protain kinase C inhibitor

Figure 1

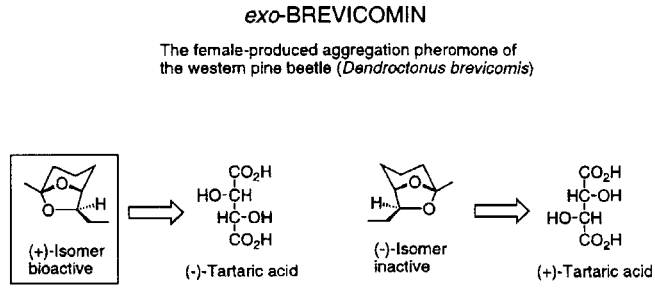


Reviews on Pheromone Synthesis :

K. Mori, *Tetrahedron*, **45**, 3233–3298 (1989).

K. Mori, in J. ApSimon (ed.), *The Total Synthesis of Natural Products*,
Vol. 4, pp. 1–183 (1981), John Wiley, New York.
Vol. 9, pp. 1–534 (1992), John Wiley, New York.

Figure 2

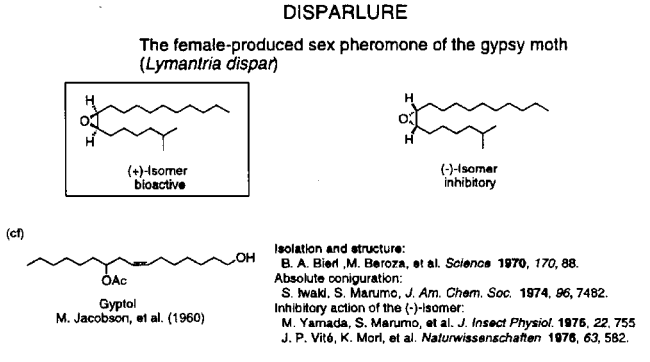


Isolation and structure:
R. M. Silverstein, et al., *Science*, **1968**, *159*, 873.
Synthesis of the enantiomers:
K. Mori, *Tetrahedron*, **1974**, *30*, 4223.
Only the (+)-isomer is bioactivive:
D. L. Wood, K. Mori, et al., *Science*, **1976**, *192*, 896.

Figure 3

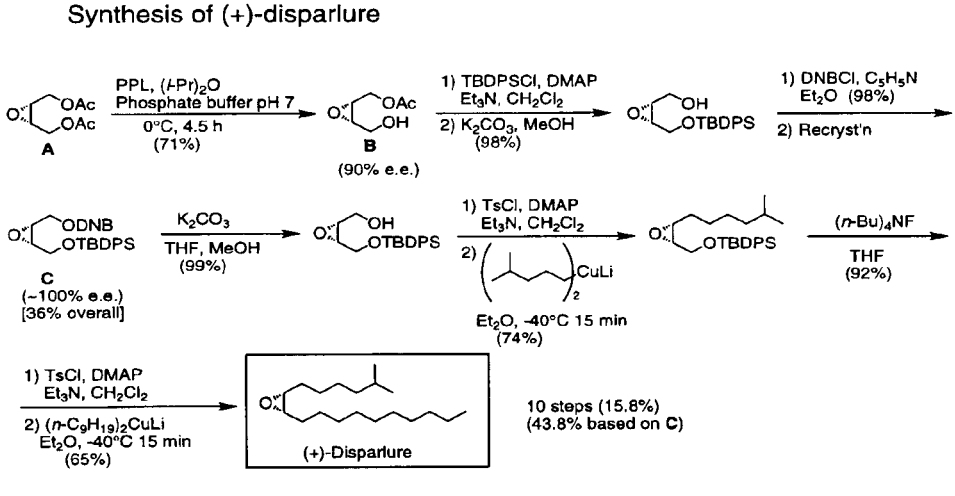
Insect Pheromones.

As shown in Figure 2, Butenandt isolated and identified the first insect pheromone bombykol in 1959. This silk moth pheromone is an achiral diene alcohol. In 1968, Silverstein isolated *exo*-brevicomin as the aggregation pheromone of the western pine beetle. This is a chiral compound. In the case of chiral natural products like *exo*-brevicomin, we have to establish their absolute configuration, and then there arises two questions: (1) Are natural products enantiomerically pure ? and (2) How is the relationship between stereochemistry and bioactivity ?



Isolation and structure:
B. A. Bierl ,M. Beroza, et al. *Science* **1970**, *170*, 88.
Absolute coniguration:
S. Iwaki, S. Marumo, *J. Am. Chem. Soc.* **1974**, *96*, 7482.
Inhibitory action of the (-)-isomer:
M. Yamada, S. Marumo, et al. *J. Insect Physiol.* **1975**, *22*, 755
J. P. Vité, K. Mori, et al. *Naturwissenschaften* **1976**, *63*, 582.

Figure 4



J.-L. Brevet, K. Mori, *Synthesis*, **1992**, 1007

Figure 5

In 1974, I synthesized the enantiomers of *exo*-brevicomin. It then became clear that only the (+)-isomer is bioactive (Figure 3). Accordingly, the natural product must be the (+)-isomer.

Disparlure is the female-produced sex pheromone of the gypsy moth (Figure 4). In 1960, Jacobson claimed the pheromone to be gyptol, but it was untrue. Then in 1970 Beroza isolated and identified the pheromone as disparlure. Marumo's synthesis as well as ours revealed that the natural and bioactive enantiomer is the (+)-isomer, while the (-)-isomer is inhibitory against the pheromone action. To be practically useful as pheromone traps, one must prepare enantiomerically pure disparlure. Figure 5 illustrates our 1992 synthesis of (+)-disparlure. Enzymatic asymmetric hydrolysis of the *meso*-diacetate **A** with pig pancreatic lipase to give the monoacetate **B** was followed by purification of the crystalline **C** to give eventually enantiomerically pure (+)-disparlure.

Japonilure is the female-produced sex pheromone of the japanese beetle (Figure 6). Tumlinson and his coworkers isolated this pheromone in 1977. They synthesized racemic japonilure, which was totally inactive. They then synthesized the enantiomers of japonilure and found only the (*R*)-isomer to be bioactive. The (*S*)-isomer is a very strong pheromone inhibitor. Accordingly, the racemic pheromone was totally inactive, and even a sample with 90% e.e. was only 1/3 as active as the pure (*R*)-isomer. In the Tumlinson synthesis of japonilure, the key reaction was the Wittig reaction employing the lactonic aldehyde which was apt to racemize. The resulting product therefore sometimes happened to be far less bioactive than the pure pheromone.

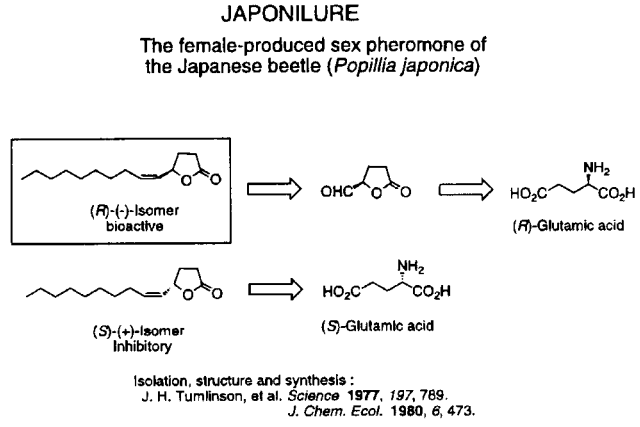


Figure 6

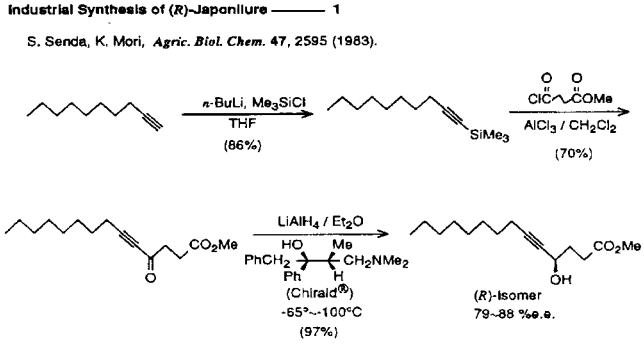


Figure 7

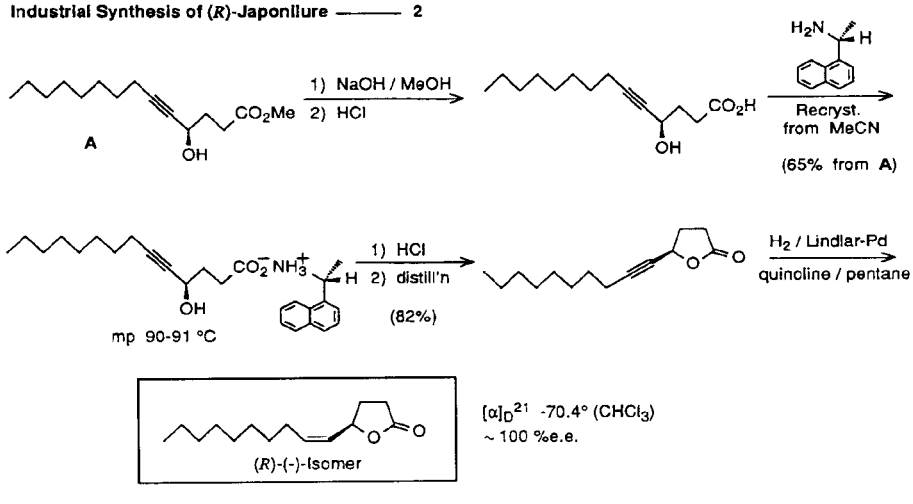


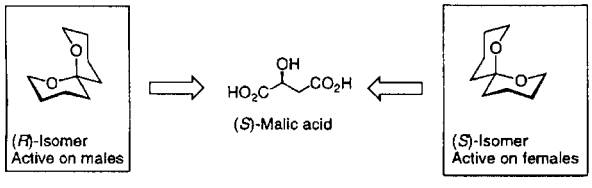
Figure 8

We developed an industrial asymmetric synthesis of japonilure in 1983 (Figures 7 and 8), which yielded the enantiomerically pure pheromone. By starting from 1-decyne, an acetylenic keto ester was prepared, which was reduced with lithium aluminum hydride in the presence of Chirald® (Darvon alcohol) to give the (*R*)-hydroxy ester of 79~88% e.e. Fortunately, the (*R*)-1-(1-naphthyl)ethylamine salt of the corresponding hydroxy acid could readily be purified by recrystallization. Acidification of the salt furnished an acetylenic lactone, which was hydrogenated to give enantiomerically pure japonilure. Our product was as active as the natural japonilure itself.

Olean is the female-produced sex pheromone of the olive fruit fly (Figure 9). It was isolated and identified in 1980 by Baker, Francke and their coworkers. In 1985, we synthesized both the enantiomers of olean by starting from (*S*)-malic acid. Haniotakis's bioassay in Greece revealed that (*R*)-olean is active on males, while the (*S*)-isomer is active on females. The female insect produces racemic olean. This is an efficient way to excite both males and the female herself by her pheromone.

OLEAN

The female-produced sex pheromone of the olive fruit fly (*Bactrocera oleae*)



Isolation and structure:
R. Baker, W. Francke, et al., *J. Chem. Soc., Chem. Commun.*, **1980**, 52.
Synthesis of the enantiomers:
K. Mori, T. Uematsu, H. Watanabe, *Tetrahedron*, **1985**, *41*, 2751, 3663.
Bioactivity:
G. Haniotakis, W. Francke, K. Mori, H. Redlich, V. Schurig, *J. Chem. Ecol.*, **1990**, *16*, 429.

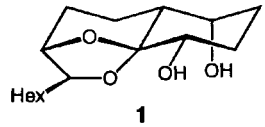
Figure 9

Our synthetic works in pheromone chemistry clarified the absolute configuration of many pheromones, showed that the natural pheromone is sometimes enantiomerically pure, but sometimes enantiomerically impure and can even be a racemate. The relationship between absolute configuration and bioactivity is rather complicated in the case of insect pheromones.

Koninginin A.

(-)-Koninginin A was isolated in 1989 by Cutler and his coworkers as a metabolite of the soil microorganism *Trichoderma koningii* (Figure 10). It inhibits the growth of etiolated wheat coleoptiles. In 1991, Ghisalberti also isolated it as an antibiotic produced by *Trichoderma harzianum*. The gross structure of koninginin A was proposed by Cutler. Its relative stereochemistry was subsequently proposed by Ghisalberti on the basis of extensive ^{1}H-NMR studies.

(–)-KONINGININ A



1

Isolation and structure elucidation:
(1) H. G. Cutler et al., *Agric. Biol. Chem.*, **1989**, *53*, 2605-2611. Growth inhibition of etiolated wheat coleoptiles; produced by the soil microorganism *Trichoderma koningii*.
(2) E. L. Ghisalberti et al., *J. Nat. Prod.*, **1991**, *54*, 396-402. Antifungal agent against the take-all fungus *Gaeumannomyces graminis* var. *tritici*; produced by *Trichoderma harzianum*.

Relative stereochemistry: Ghisalberti (1991)

Absolute stereochemistry: Unknown

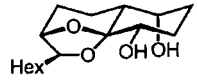
Synthesis of (±)-koninginin A:
K. Mori and K. Abe, *Polish J. Chem.*, **1994**, *68*, 2255-2263.

Synthesis of (-)-koninginin A:
K. Mori and K. Abe, *Liebigs Ann. Chem.*, **1995**, 943-948.

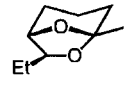
Figure 10

In 1994, we published a synthesis of (±)-koninginin A, and confirmed the correctness of the proposed relative stereochemistry. The absolute configuration of (-)-koninginin A was determined as depicted in **1** (Figure 10) by its enantioselective synthesis, which will be detailed in the present lecture. In planning the synthesis, we had to decide which of the enantiomers should be synthesized. My previous works in pheromone chemistry indicate that (-)-*exo*-brevicomin and (-)-frontalin possess the absolute configuration as shown in Figure 11.

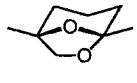
HYPOTHESIS ON THE ABSOLUTE CONFIGURATION OF (–)-KONINGININ A



(–)-Koninginin A (**1**)



(–)-*exo*-Brevicomin
K. Mori, *Tetrahedron*, **1974**, *30*, 4223-4227.



(–)-Frontalin
K. Mori, *Tetrahedron*, **1975**, *31*, 1381-1384.

Figure 11

Because the naturally occurring koninginin A is levorotatory, it probably possesses the absolute configuration similar to these levorotatory acetal pheromones. Accordingly, **1** should be synthesized.

RETROSYNTHETIC ANALYSIS OF (–)-KONINGININ A

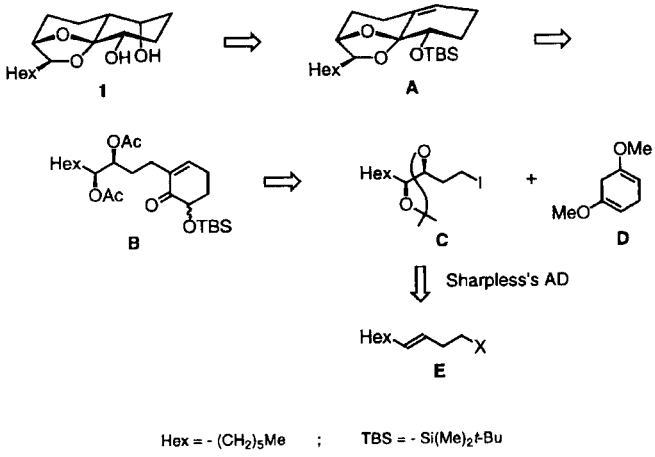


Figure 12

Figure 12 shows our retrosynthetic analysis of (-)-koninginin A. The strategy is to fix the stereochemistry of the acetal portion of the molecule first, and then to adjust the stereochemistry of the cyclohexane portion. Thus the unsaturated acetal **A** is considered to be the appropriate precursor. The acetal **A** can be obtained from cyclohexenone **B** by removal of the acetal protective groups and acetalization of the resulting keto diol. The intermediate **B** may be prepared from **C** and **D** in a few steps. The synthesis of **C** is feasible by the Sharpless asymmetric dihydroxylation of the olefin **E**.

SYNTHESIS–1

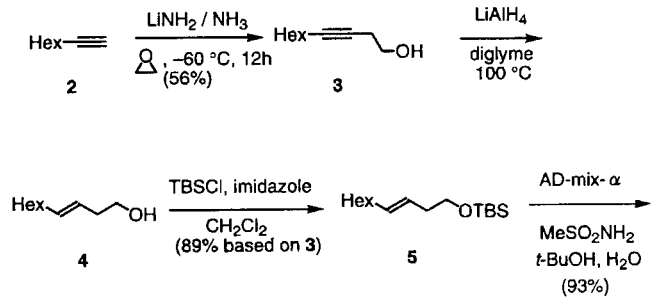
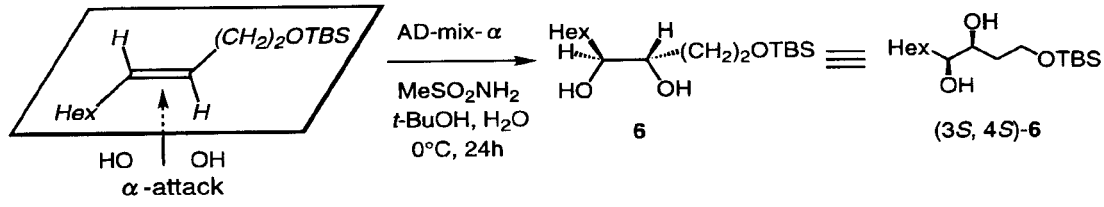


Figure 13

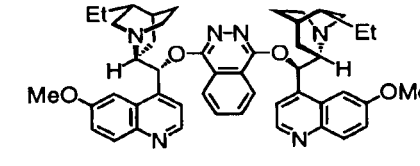
As shown in Figure 13, the synthesis started from 1-octyne (**2**), whose chain-elongation gave 3-decyn-1-ol (**3**). This was reduced with lithium aluminum hydride to give (*E*)-3-decen-1-ol (**4**), which was converted to the corresponding TBS ether (**5**). This olefin **5** was submitted to the Sharpless asymmetric dihydroxy-

SYNTHESIS–2

Asymmetric dihydroxylation
K. B. Sharpless et al., *J. Org. Chem.*, **1992**, *57*, 2768-2771.



AD-mix-α (1kg)
= $(DHQ)_2$-PHAL (5.52g)
+ $K_2OsO_2(OH)_4$ (0.52g)
+ $K_3Fe(CN)_6$ (700g)
+ K_2CO_3 (294g)



$(DHQ)_2$-PHAL
Ligand used in AD-mix-α

Figure 14

lation reaction to give the optically active diol in 93% yield. The olefin **5** can be dihydroxylated on the α-side by employing AD-mix α. According to the general scheme shown in Figure 14, the resulting optically active diol must be (3*S*,4*S*)-**6**. In order to determine the enantiomeric purity of the diol **6**, it was converted to the corresponding bis-3,5-dinitrobenzoate **7** and analyzed by HPLC employing Chiralcel® OD-H as the stationary phase (Figure 15). The enantiomeric excess of crude **7** was 90.6%. Its recrystallization from diisopropyl ether yielded enantiomerically pure **7**. Hydrolysis of **7** gave pure **6**. The diol **6** was then converted to the corresponding acetonide, and its TBS protective group was removed to give the alcohol **8**. The corresponding iodide **9** was prepared by treatment of **8** with iodine and triphenylphosphine. We thus obtained the enantiomerically pure building block **C** required for the construction of the acetal portion of the target molecule.

SYNTHESIS–3

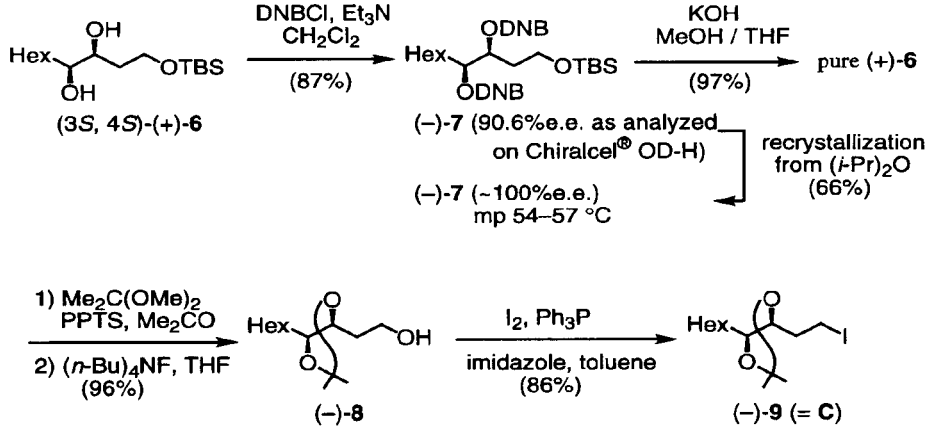


Figure 15

SYNTHESIS–4

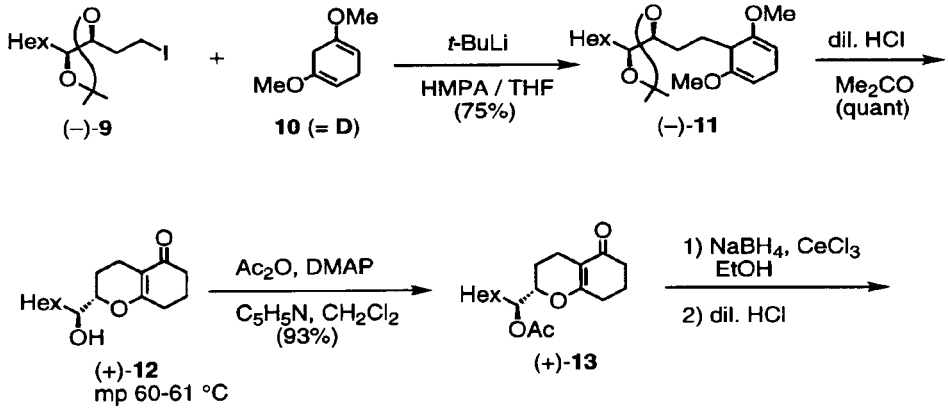


Figure 16

Alkylation of the anion generated from **10** with **9** yielded **11** as shown in Figure 16. Treatment of **11** with dilute hydrochloric acid gave crystalline **12**. The hydroxy group of **12** was then protected as its acetate. The resulting acetoxy ketone **13** was reduced with sodium borohydride in the presence of cerium chloride, and the product was treated with dilute hydrochloric acid. As shown in Figure 17, the product was a mixture of two monoacetates **14a** and **b**, which was acetylated to give the diacetate **15**. Treatment of **15** with TBS triflate and triethylamine gave

SYNTHESIS–5

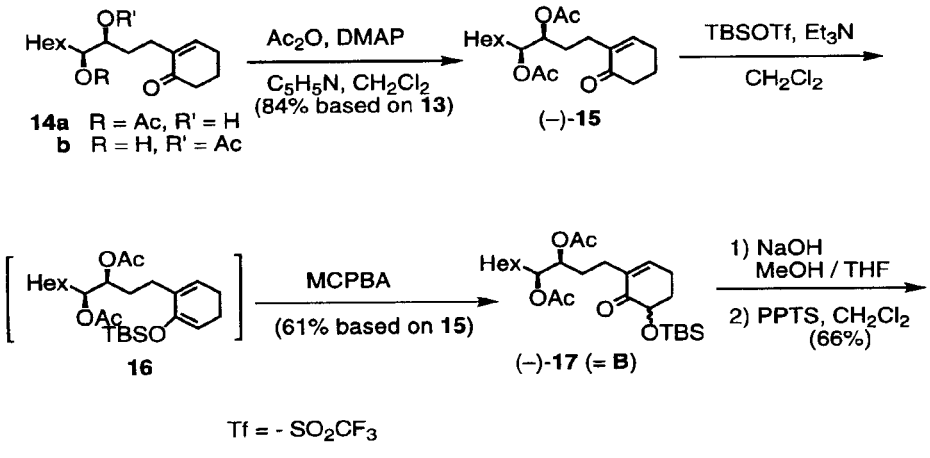


Figure 17

SYNTHESIS–6

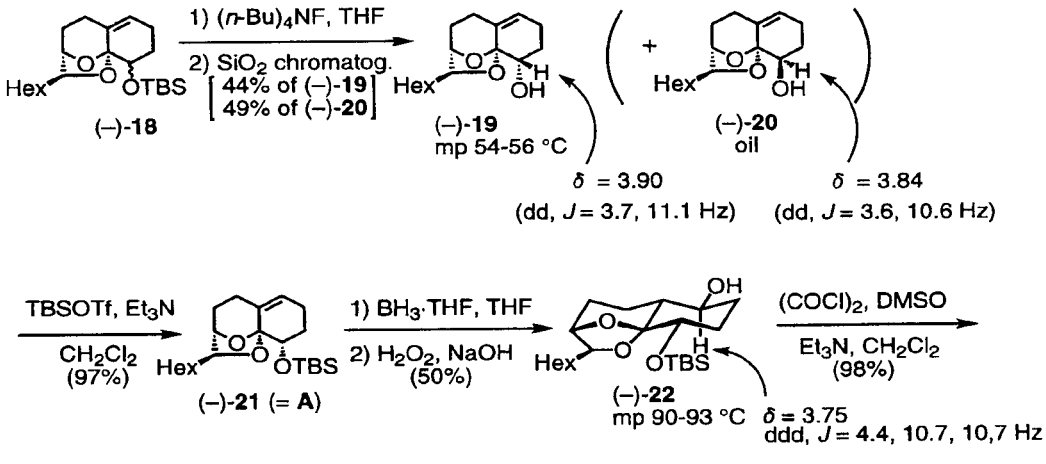


Figure 18

the silyl enol ether **16**, which was immediately oxidized with *m*-chloroperbenzoic acid (MCPBA) to furnish **17** as a stereoisomeric mixture.

The next step was the construction of the intramolecular acetal linkage. Thus, the acetyl protective groups of **17** were removed with sodium hydroxide, and the acetal ring was closed by treatment with PPTS in dichloromethane to give the product **18** (Figure 18) in 66% yield. The product **18** was treated with tetra-(*n*-butyl)ammonium fluoride, and purified by silica gel chromatography to give crystalline **19** and oily **20**. The former was later converted to (-)-koninginin A. Reprotection of the hydroxy group of **19** as TBS ether to give **21** was followed by hydroboration-oxidation of the double bond of **21** from the less-hindered β-side to give **22** as crystals. The equatorial and β-orientation of the hydroxy group of **22** was assigned on the basis of the ^{1}H-NMR analysis (Figure 18). The alcohol **22** was then oxidized under the Swern conditions to give the ketone **23** (Figure 19) in 98% yield. Reduction of **23** with lithium aluminum hydride gave the desired α-axial alcohol **24**, whose TBS protective group was removed to furnish crystalline (-)-koninginin A (**1**). The overall yield of **1** was 0.72% based on 1-octyne (22 steps). The absolute configuration of (-)-koninginin A was thus established as 2*S*,3*S*,5a*R*,6*R*,9*S*,9a*R* as depicted in the formula.

Figure 20 shows the 300 MHz ^{1}H-NMR spectrum of our synthetic koninginin A and the published one of the natural product isolated by Cutler *et al.* The ^{13}C-NMR spectrum of our synthetic koninginin A and the published spectrum of the natural product are show in Figure 21. The spectra of the synthetic (-)-**1** were in good accord with those of the natural product.

Penaresidin A.

Penaresidin A (**1**) and B (**2**) are two sphingosine-derived azetidine alkaloids isolated as potent ATPase activators (Figure 22). In 1991, Kobayashi *et al.* isolated **1** and **2**, and the structures including the relative stereochemistry of the azetidine portion were proposed on the basis of the detailed ^{1}H-NMR analysis of the mixture of the corresponding tetraacetyl derivatives. We became interested in the unique structure and bioactivity of penaresidin A, and began our synthetic study.

Figure 23 shows the retrosynthetic analysis of penaresidin A. We thought that the azetidine portion of penaresidin A might be constructed by treatment of a phytosphingosine derivative **A** with a base. Reduction of **B** gives a phytosphingosine-type compound. The epoxide **B** can be prepared by the epoxidation of a sphingosine derivative **C**. Synthesis of **C** is feasible by the coupling of the two building blocks **D** and **F**. The aldehyde **D** is a well known building block in sphingosine synthesis, and can be prepared from (*S*)-serine (**E**) according to Garner. The side-chain portion **F** can be prepared from **G** and **H**. The epoxide **H** is derivable from (*S*)-isoleucine (**I**).

SYNTHESIS–7

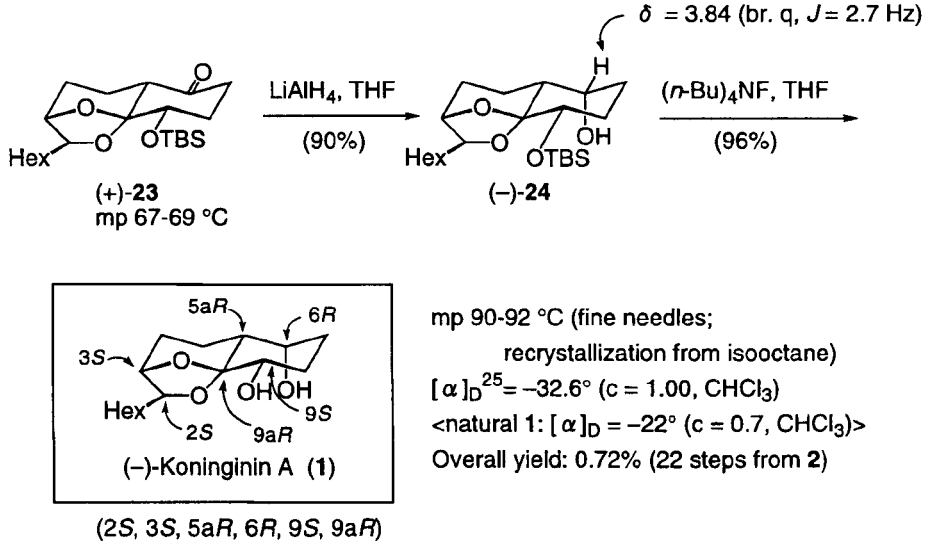
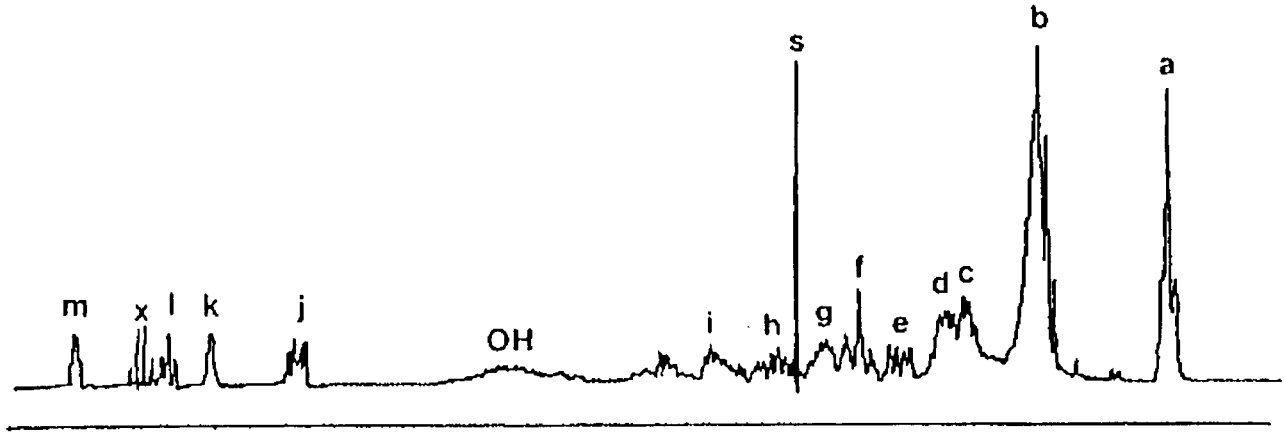


Figure 19

^{1}H-NMR Spectra of (–)-Koninginin A (**1**)

Natural (–)-**1**



Synthetic (–)-**1**)

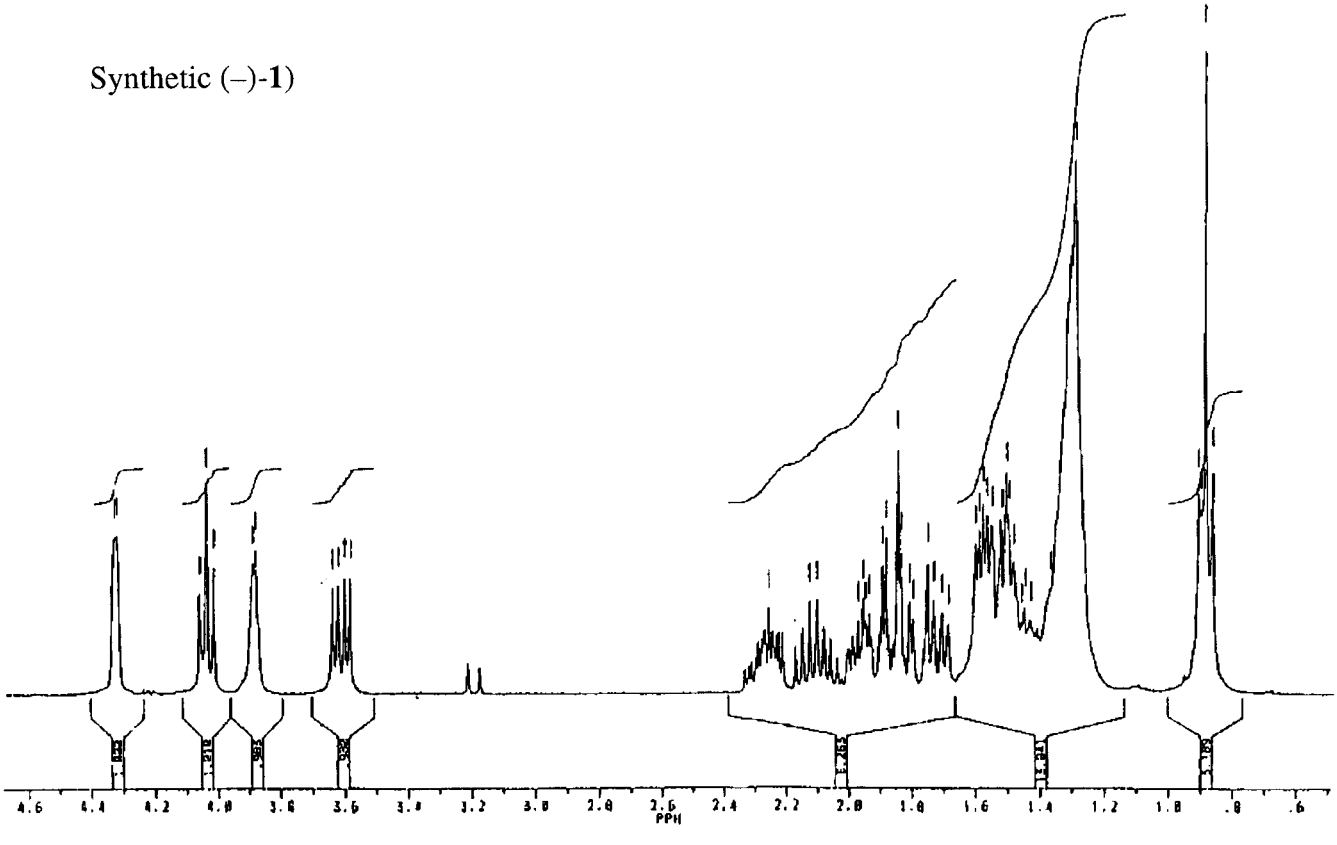
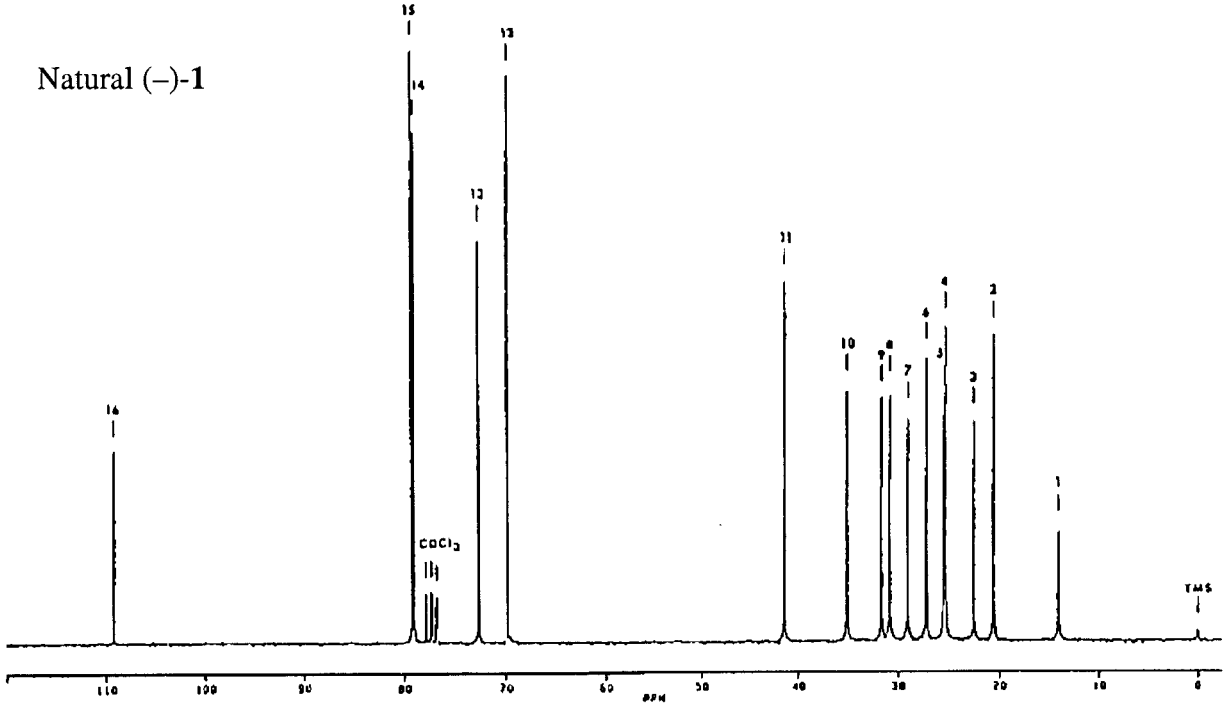


Figure 20

^{13}C-NMR Spectra of (–)-Koninginin A (**1**)



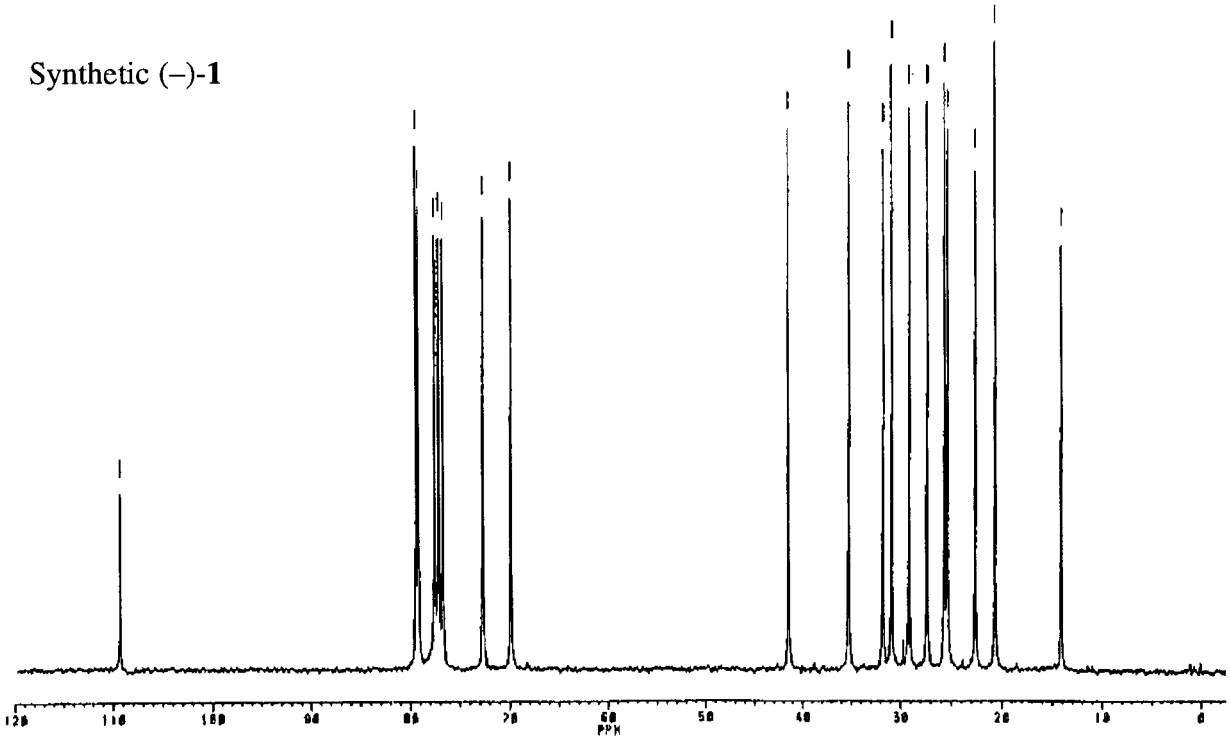
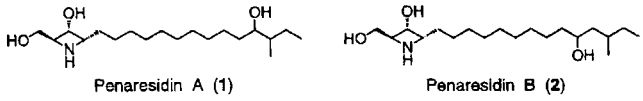


Figure 21

Penaresidin A and B



A mixture of the tetraacetate of A and B = dextrorotatory

Isolation and structure elucidation :
J. Kobayashi, J.-f. Cheng, M. Ishibashi, M. R. Wälchli, S. Yamamura and Y. Ohizumi,
J. Chem. Soc. Perkin Trans. 1, **1991**, 1135-1137.
Actomyosin ATPase activator isolated from the Okinawan marine sponge *Penares* sp.

Relative stereochemistry of the azetidine portion : Kobayashi (1991)

Absolute stereochemistry : unknown

Figure 22

Synthesis-1

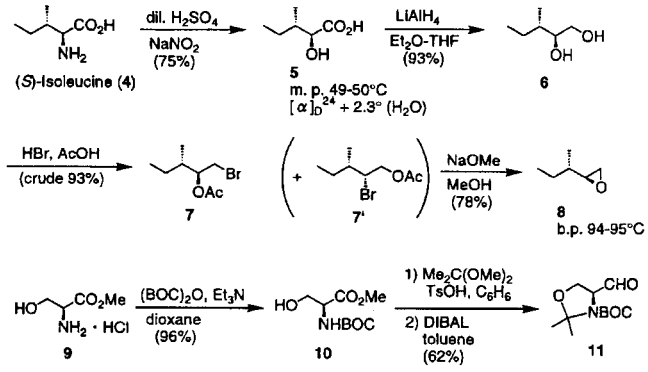


Figure 24

Preparation of the chiral building blocks **8** and **11** is summarized in Figure 24. Deamination of (*S*)-isoleucine (**4**) with nitrous acid yielded hydroxy acid **5** with retention of configuration. Reduction of **5** with lithium aluminum hydride afforded diol **6**, which was treated with hydrogen bromide in acetic acid to give a mixture of two acetoxy bromides, **7** and **7'**. Treatment of the mixture with sodium methoxide in methanol furnished the epoxide **8** as a volatile oil. We then prepared the aldehyde **11** according to the method of Garner. (*S*)-Serine methyl ester hydrochloride (**9**) was converted to *t*-butoxycarbonyl (BOC) serine methyl ester **10**. Treatment of **10** with 2,2-dimethoxypropane followed by DIBAL gave the aldehyde **11**.

Figure 25 shows the preparation of the sphingosine derivatives **16** and **17**. The epoxide **8** was treated with the anion derived from 1-decyne in the presence of boron trifluoride to give the acetylenic alcohol **12**. This was submitted to the acetylene zipper reaction to give **13**. After protecting the hydroxy group of **13** as TBS ether, the resulting **14** was treated with *n*-butyllithium followed by the aldehyde **11** to effect the coupling of the two parts of the target molecule, yielding **15**. Lithium-ethylamine reduction of **15** converted the triple bond to (*E*)-double bond and removed the protective group to give a sphingosine derivative **16**. The amino group of **16** was then tosylated to yield the corresponding *p*-toluenesulfonamide **17**. The next step was the epoxidation of **17** (Figure 26). Treatment of **17** with MCPBA in hexane yielded a mixture of two epoxides **18** and **19**. The desired epoxide **18** was

Retrosynthetic Analysis of Penaresidin A

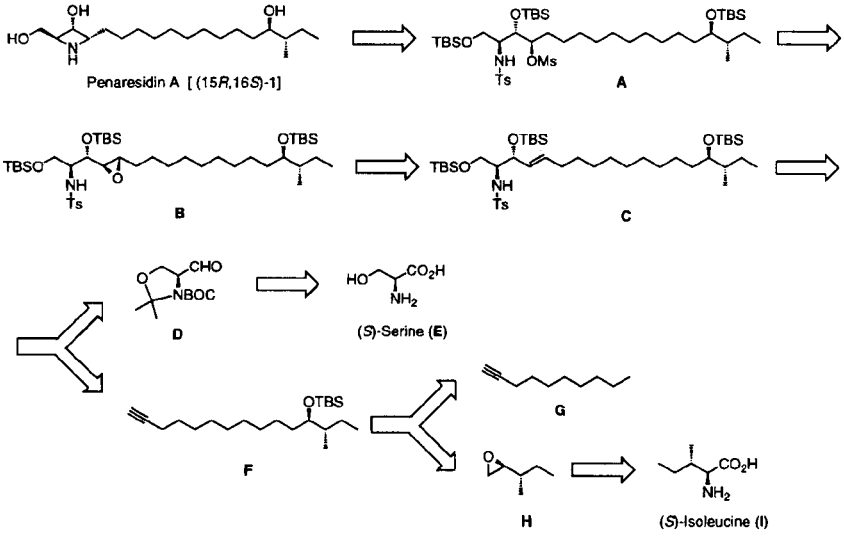


Figure 23

Synthesis-2

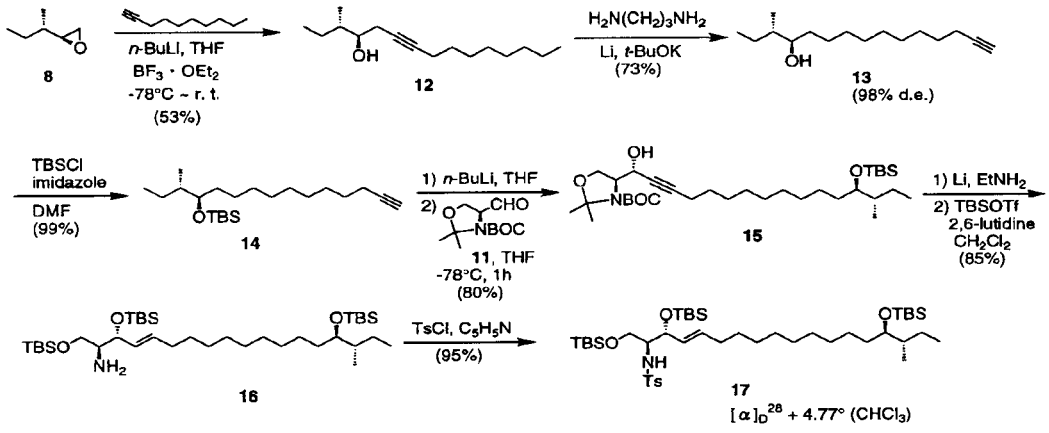
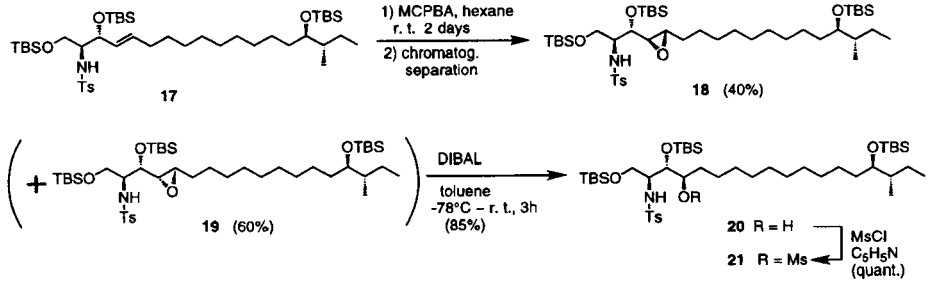


Figure 25

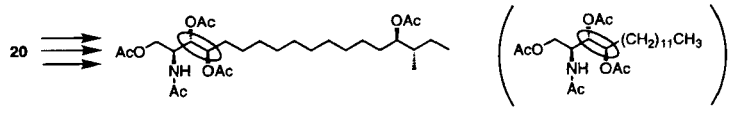
unfortunately the minor product. The stereochemistry of **18** was confirmed by its conversion (via **20**) to a phytosphingosine derivative as shown below in the Figure, whose ^{1}H-NMR spectrum was similar to that of Komori's phytosphingosine derivative. We examined various solvents other than hexane for the epoxidation reaction. We were, however, unable to improve the yield of **18**. Fortunately, **18** and **19** were separable by chromatography. Reduction of **18** with DIBAL gave **20**, which was mesylated to give the mesylate **21**.

As shown in Figure 27, when the mesylate **21** was treated with sodium hydride in THF, smooth cyclization took place to give the azetidine **22**. Reduction of **22** with sodium naphthalenide removed the tosyl group to furnish **23**. The TBS protective groups of **23** were then removed to give one of the stereoisomers of penaresidin A, (15*R*,16*S*)-**1**. For the purpose of comparison with the natural product, (15*R*,16*S*)-**1** was acetylated to give the

Synthesis-3



Determination of the stereochemistry of phytosphingosine moiety.



compared with Komori's phytosphingosine tetraacetate[1] by ^{1}H-NMR

1) S. Sugiyama, M. Honda and T. Komori, *Liebigs Ann. Chem.*, **1990**, 1068-1078

Figure 26

tetraacetyl derivative (15*R*,16*S*)-**24**. It showed a positive optical rotation. The mixture of the tetraacetyl derivatives of natural penaresidins A and B was dextrorotatory. If the azetidine portion of the molecule contributes to the sign and magnitude of the optical rotation much more than the terminal two stereogenic centers, the azetidine portion of penaresidin A must possess the same absolute configuration as that of (15*R*,16*S*)-**24**.

Because we synthesized (15*R*,16*S*)-**1**, one of the 15,16-*anti*-stereoisomers, we turned our attention to the synthesis of one of the 15,16-*syn*-isomers of **1**. Figure 28 summarizes the synthesis of (15*S*,16*S*)-penaresidin A (**1**) and its tetraacetyl derivative **24**. In order to invert the absolute configuration at C-4 of **13**, it was submitted to the Mitsunobu inversion to give **25**, which was converted to (15*S*,16*S*)-penaresidin A (**1**) and then to its tetraacetyl derivative **24**. The derivative **24** was also dextrorotatory.

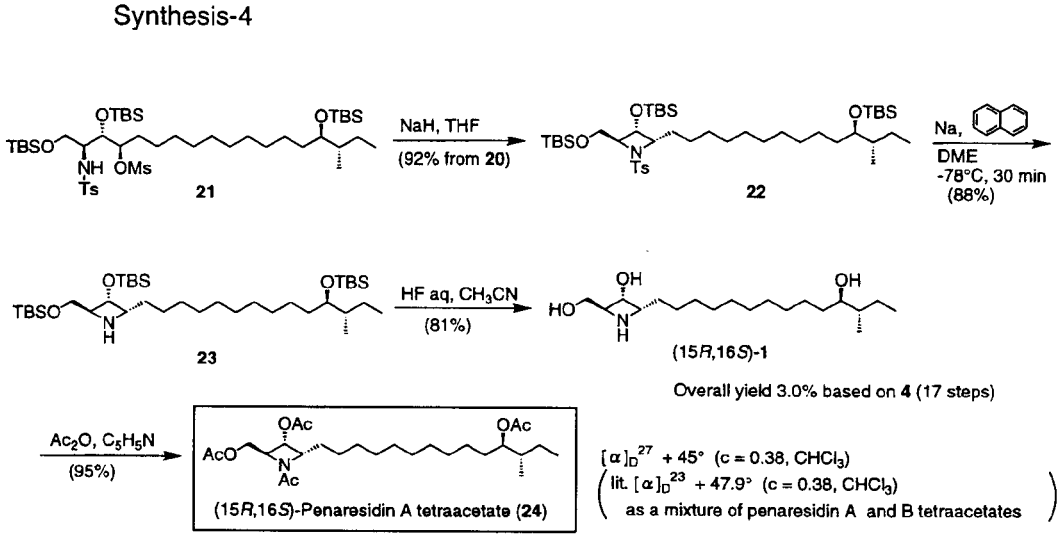


Figure 27

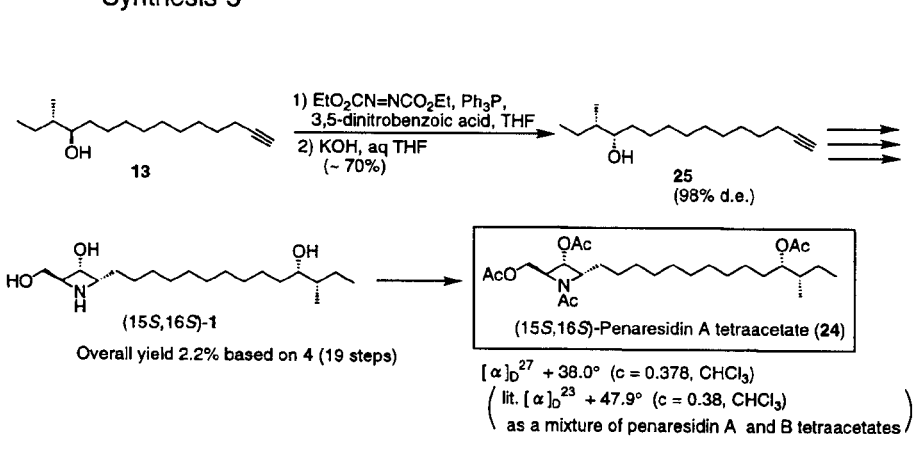


Figure 28

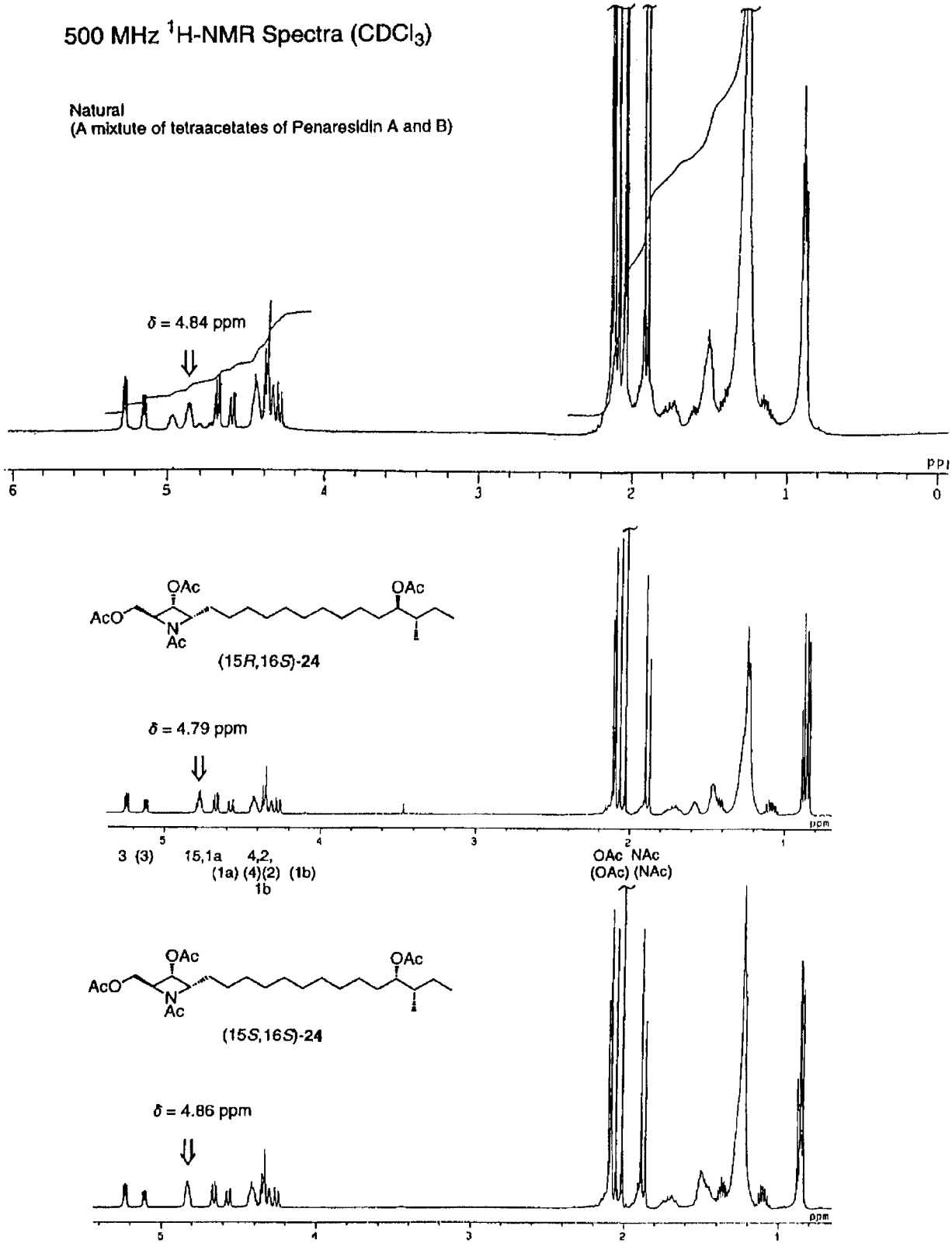

500 MHz ^{1}H-NMR Spectra ($CDCl_3$)
Natural
(A mixtute of tetraacetates of Penaresidin A and B)
δ = 4.84 ppm
ppm
6
5
4
3
2
1
0
OAc
OAc
AcO
N
Ac
(15R,16S)-24
δ = 4.79 ppm
ppm
3 (3)
15,1a
4,2,
(1a) (4)(2) (1b)
1b
OAc NAc
(OAc) (NAc)
OAc
OAc
AcO
N
Ac
(15S,16S)-24
δ = 4.86 ppm
ppm

Figure 29

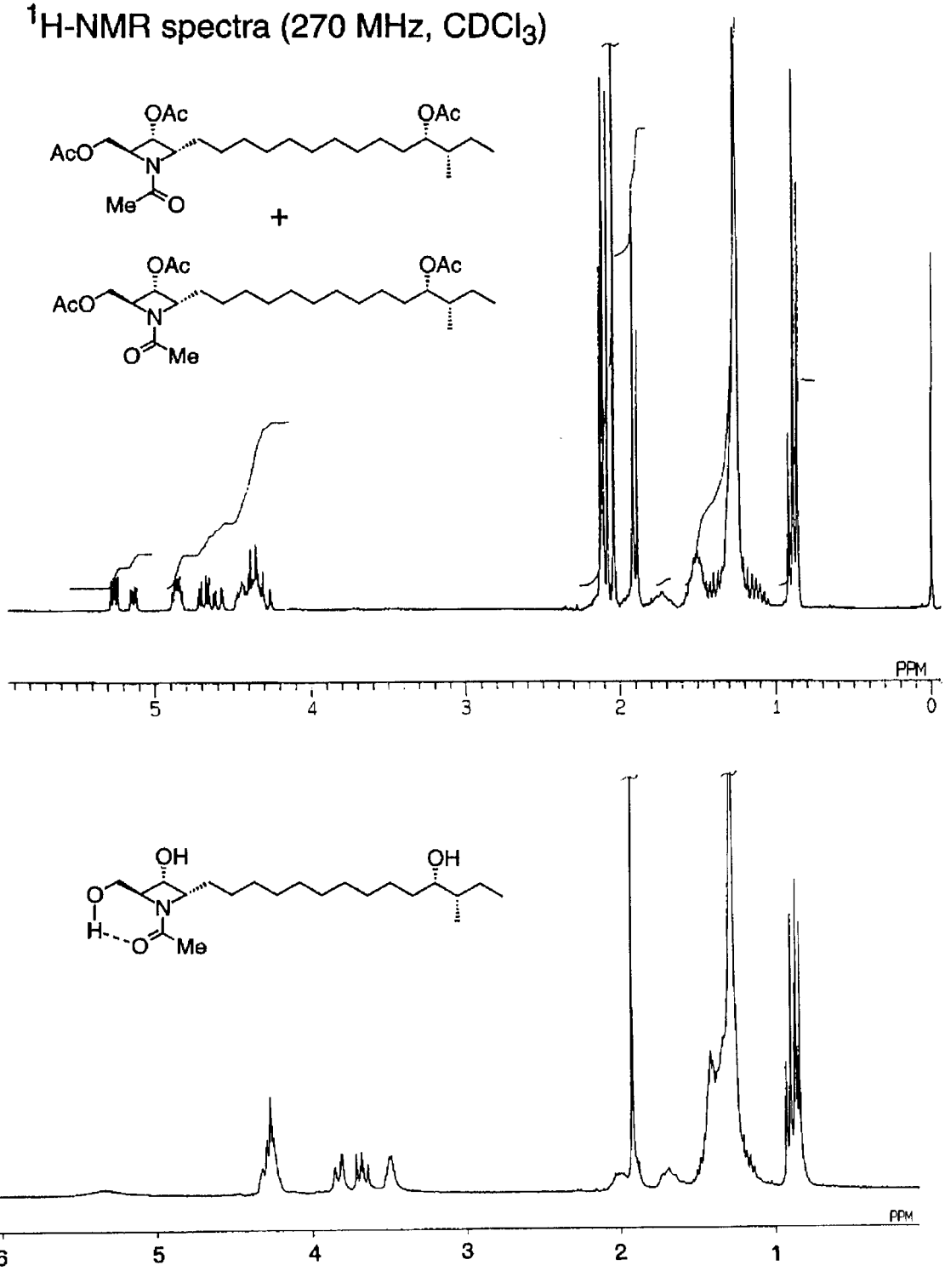

^{1}H-NMR spectra (270 MHz, $CDCl_3$)
OAc
OAc
AcO
N
Me
O
+
OAc
OAc
AcO
N
O
Me
PPM
5
4
3
2
1
0
OH
OH
O
H
N
O
Me
PPM
6
5
4
3
2
1

Figure 30

As shown in Figure 29, we compared the ^{1}H-NMR spectra of our (15*R*,16*S*)- and (15*S*,16*S*)-**24** with that of the mixture of the tetraacetyl derivatives of penaresidins A and B. The signal due to the proton at C-15 appeared at $\delta = 4.79$ in the case of (15*R*,16*S*)-**24**, while in the case of (15*S*,16*S*)-**24**, it appeared at $\delta = 4.86$. The tetraacetyl derivatives of the natural products showed a signal at $\delta = 4.84$. We therefore reasoned that the natural penaresidin A must possess either (15*S*,16*S*)- or (15*R*,16*R*)-*syn*-stereochemistry.

Incidentally, the signals due to the acetyl groups around the azetidine ring of **24** showed pairs of two singlets. This is due to the hindered rotation of the N-C bond of the *N*-acetyl group. Figure 30 further illustrates the effect of the hindered rotation of the N-C bond. In the upper part of the Figure, we can see the signals due to -NC(=O)**Me** as a pair of two singlets. In the case of a molecule in which the conformation of the *N*-acetyl group is fixed due to the hydrogen bonding, we see the NC(=O)**Me** signal as a 3H-singlet. This phenomenon of the hindered rotation of the amide N-C bond was previously reported by Paulsen and Todt in the case of a carbohydrate as shown in Figure 31.

The synthesis of (15*R*,16*R*)-penaresidin A (**1**) is summarized in Figure 32. The Sharpless asymmetric epoxidation of (*Z*)-2-penten-1-ol (**26**) gave the epoxy alcohol **27** of 89% e.e., which was purified *via* its crystalline 3,5-dinitrobenzoate to give **27** of over 98% e.e. Treatment of the epoxide **27** with trimethylaluminum and *n*-butyllithium yielded the diol **28**. This was converted to (15*R*,16*R*)-penaresidin A (**1**). Its tetraacetyl derivative **24** was again dextrorotatory.

Hindered Rotation of the Acetyl Group in Monosaccharides Containing an Acetamide Group in the Ring

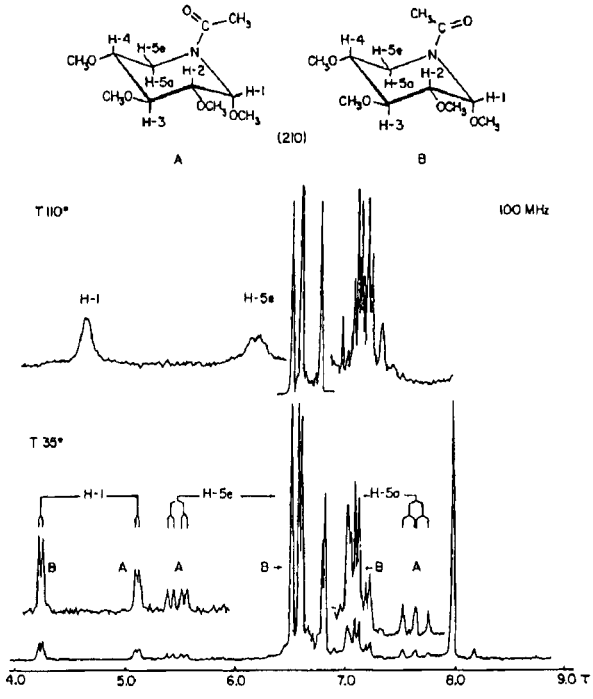


Fig . 3-Nuclear Magnetic Resonance Spectrrum of Methyl 5-Acetamido-5-deoxy-2,3,4-tri-*O*-methyl-a-Dxylopyranoside (210). [Taken at 100 MHz in tetrachloroethane; at 35°; lower curve; at 110°, upper curve; tetramethylsilane as internal standard.]

H. Paulsen and T. Todt in *Advances in Carboydrate Chemistry*, Vol. 23, M. L. Wolfrom and R. S. Tipson, Eds., Academic Press, New York and London, **1968**, 193-201.

Figure 31

Synthesis-6

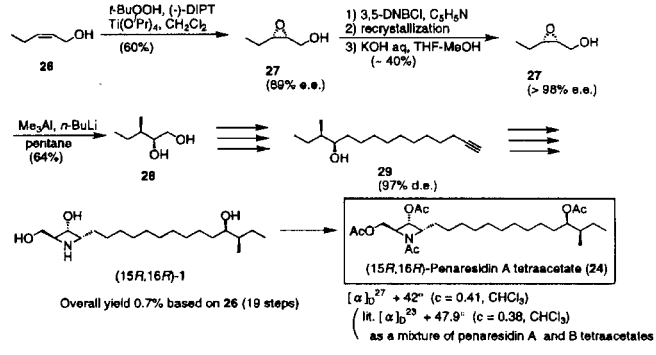


Figure 32

We compared the ^{1}H-NMR spectrum of (15*S*,16*S*)-**24** with that of (15*R*,16*R*)-**24** as shown in Figure 33. They were virtually identical. The azetidine portion of **24** is too far separated from the two stereogenic centers at C-15 and C-16 to cause any NMR difference between the diastereomers. Because the natural products were obtained as a mixture, we were unable to compare precisely the chiroptical properties of the natural and synthetic penaresidin A. At this moment we conclude that penaresidin A must possesses either (2*S*,3*R*,4*S*,15*R*,16*R*)- or (2*S*,3*R*,4*S*,15*S*,16*S*)-absolute configuration. For the complete solution of this stereochemical problem, we have to await the reisolation of penaresidin A in pure state.

Penazetidine A.

Another interesting azetidine alkaloid of marine origin was isolated by Crews and his coworkers in 1994. Penazetidine A (Figure 34) is an inhibitor of protein kinase C produced by the Indo-Pacific sponge *Penares sollasi*. Although the relative stereochemistry of the azetidine portion of this alkaloid was deduced by Crews, its absolute stereochemistry as well as the side-chain stereo-

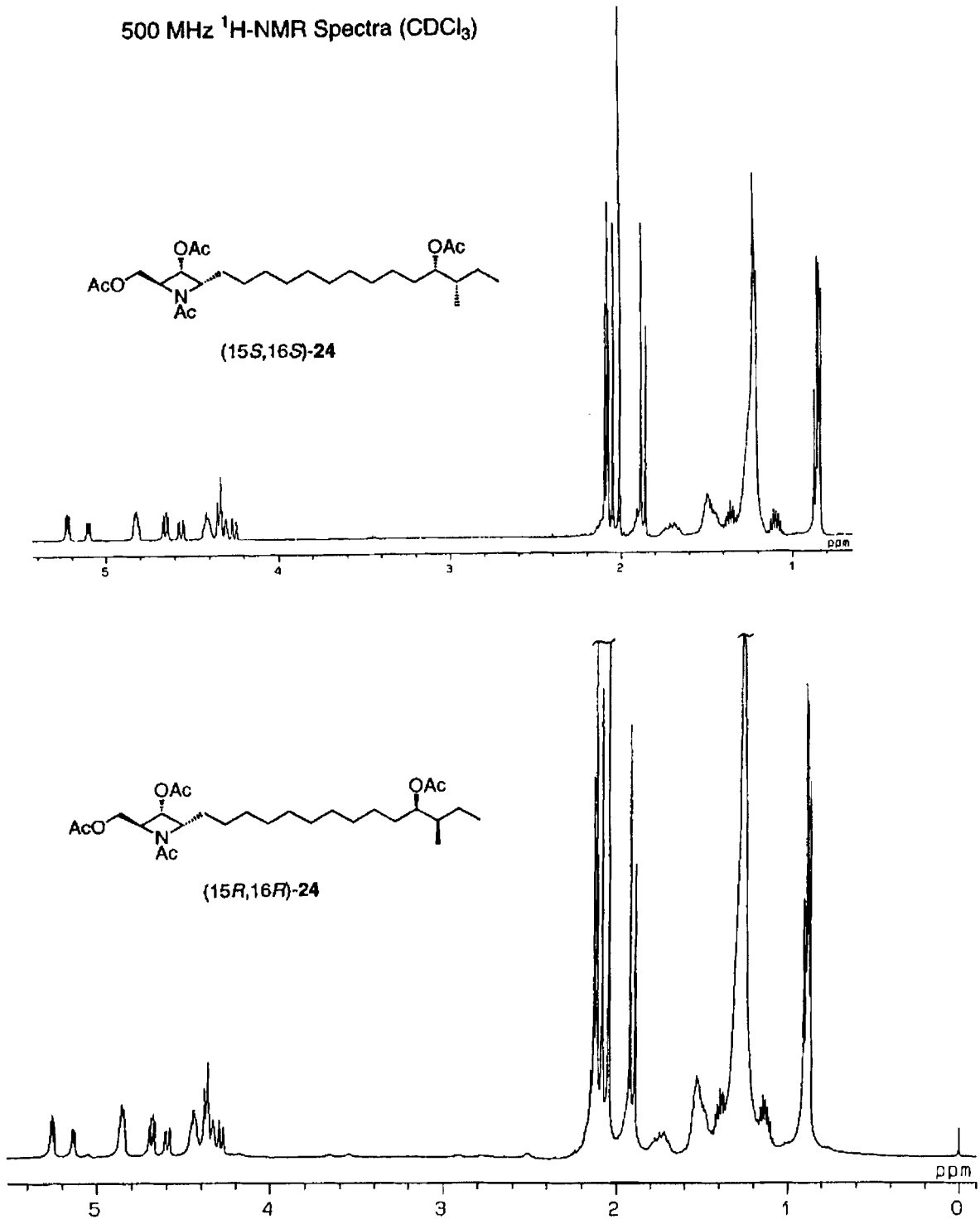
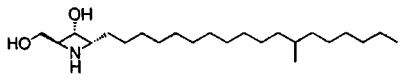

500 MHz ^{1}H-NMR Spectra ($CDCl_3$)
OAc
OAc
AcO
N
Ac
(15S,16S)-24
ppm
5
4
3
2
1
OAc
OAc
AcO
N
Ac
(15R,16R)-24
ppm
5
4
3
2
1
0

Figure 33

Penazetidine A



Penazetidine A (**1**) $[\alpha]_D$ = -16.9° (MeOH)

Isolation and structure elucidation :
K. A. Alvi, M. Jaspars and P. Crews, *Bioorg. Med. Chem. Lett.*, **1994**, *4*, 2447-2450.
Inhibitor of protein kinase C isolated from an Indo-Pacific sponge *Penares sollasi.*

Relative stereochemistry of the azetidine portion : Crews (1994)

Absolute stereochemistry : unknown

Figure 34

chemistry are unknown. In continuation of our work on penaresidin A, we started our endeavor to synthesize penazetidine A. Figure 35 shows the retrosynthetic analysis of penazetidine A. We adopted the same strategy as employed for the synthesis of penaresidin A. The possible intermediates are therefore **A**, **B**, **C**, **D** and **F**. The side-chain portion **F** is to be prepared from citronellol (**G**).

Synthesis of the side-chain portion **8** was executed as shown in Figure 36. (*S*)-Citronellol (**2**) was tosylated, and the resulting tosylate was treated with *n*-butylmagnesium chloride in the presence of dilithium tetrachlorocuprate to give the alkene **3**. Treatment of **3** with MCPBA followed by periodic acid gave the aldehyde **4**. Chain-elongation of **4** with 1-nonyne furnished **5**, which was submitted to the acetylene zipper reaction to give **6**. Deoxygenation of **6** was achieved *via* the mesylate **7**. Reduction of **7** with lithium triethylborohydride successfully gave (*R*)-13-methyl-1-nonadecyne (**8**). Addition of the anion of **8** to the Garner aldehyde yielded **9**. Conversion of **9** to the protected penazetidine A **14** is shown in Figure 37. Reduction of **9** with lithium in ethylamine was followed by silylation of the product to give **10**. The corresponding *p*-tolusnesulfonamide **11** was epoxidized with MCPBA. The product was purified by chromatography to give the epoxide **12** in 43% yield. Reductive cleavage of the epoxy ring of **12** with DIBAL was followed by mesylation of the resulting alcohol to give **13**. Treatment of **13** with sodium hydride effected the azetidine ring formation to furnish **14**. Removal of the tosyl group of **14** was achieved with sodium and naphthalene, and the product was treated with hydrofluoric acid in acetonitrile to give levorotatory (16*R*)-penazetidine A (**1**, Figure 38), $[a]_D^{26}$ = -8.3±0.1° (c = 0.4, MeOH). Crews reported the specific rotation of the natural product to be $[a]_D$ = -16.9° (c = 0.04, MeOH). The corresponding triacetyl derivative **15** was dextrorotatory. Similarly, by starting from (*R*)-citronellol and the Garner aldehyde, (16*S*)-penazetidine A (**1**), $[a]_D^{26}$ = -7.9±0.2° (c = 0.4, MeOH), was synthesized. The corresponding triacetyl derivative (16*S*)-**15** was again dextrorotatory.

Retrosynthetic Analysis of Penazetidine A

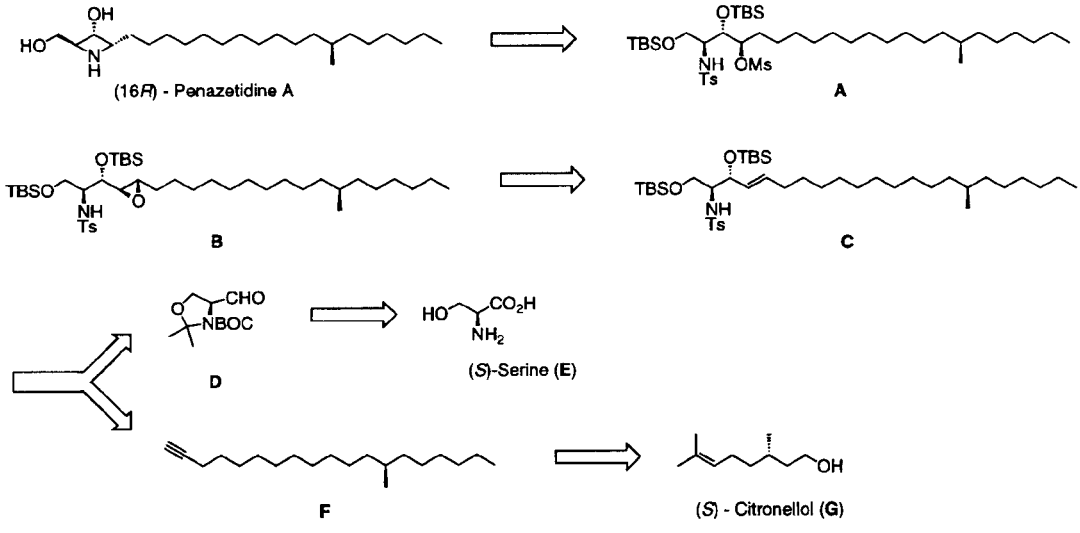


Figure 35

Synthesis - 1

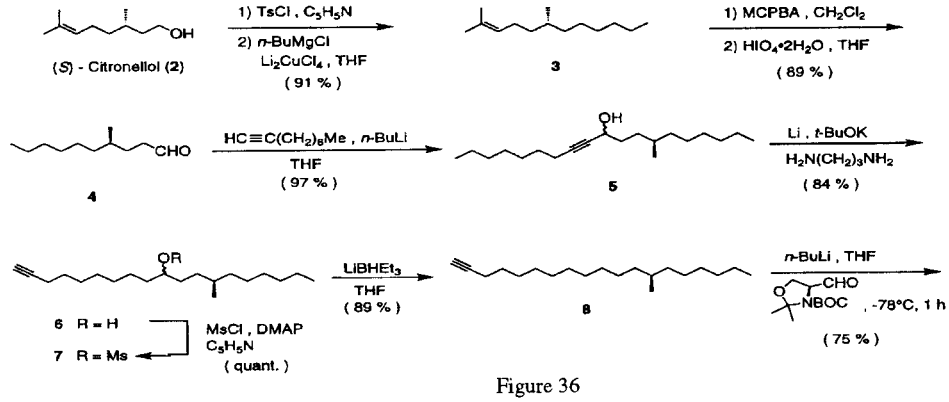


Figure 36

Synthesis - 2

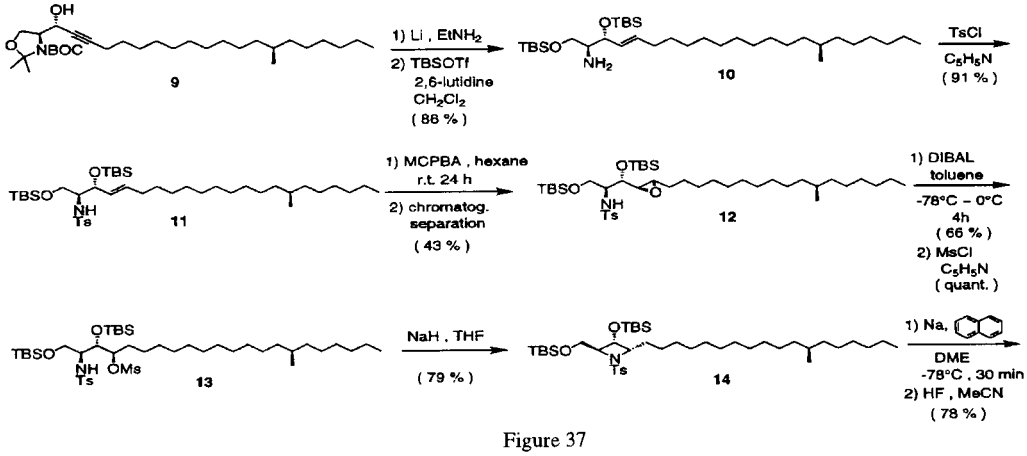
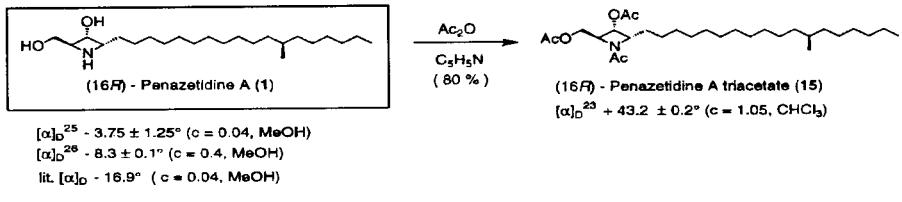


Figure 37

Synthesis - 3



Similarly :

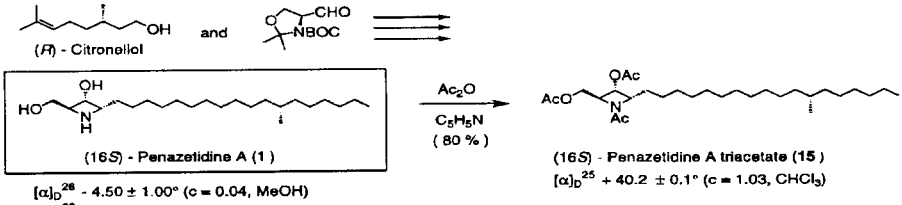


Figure 38

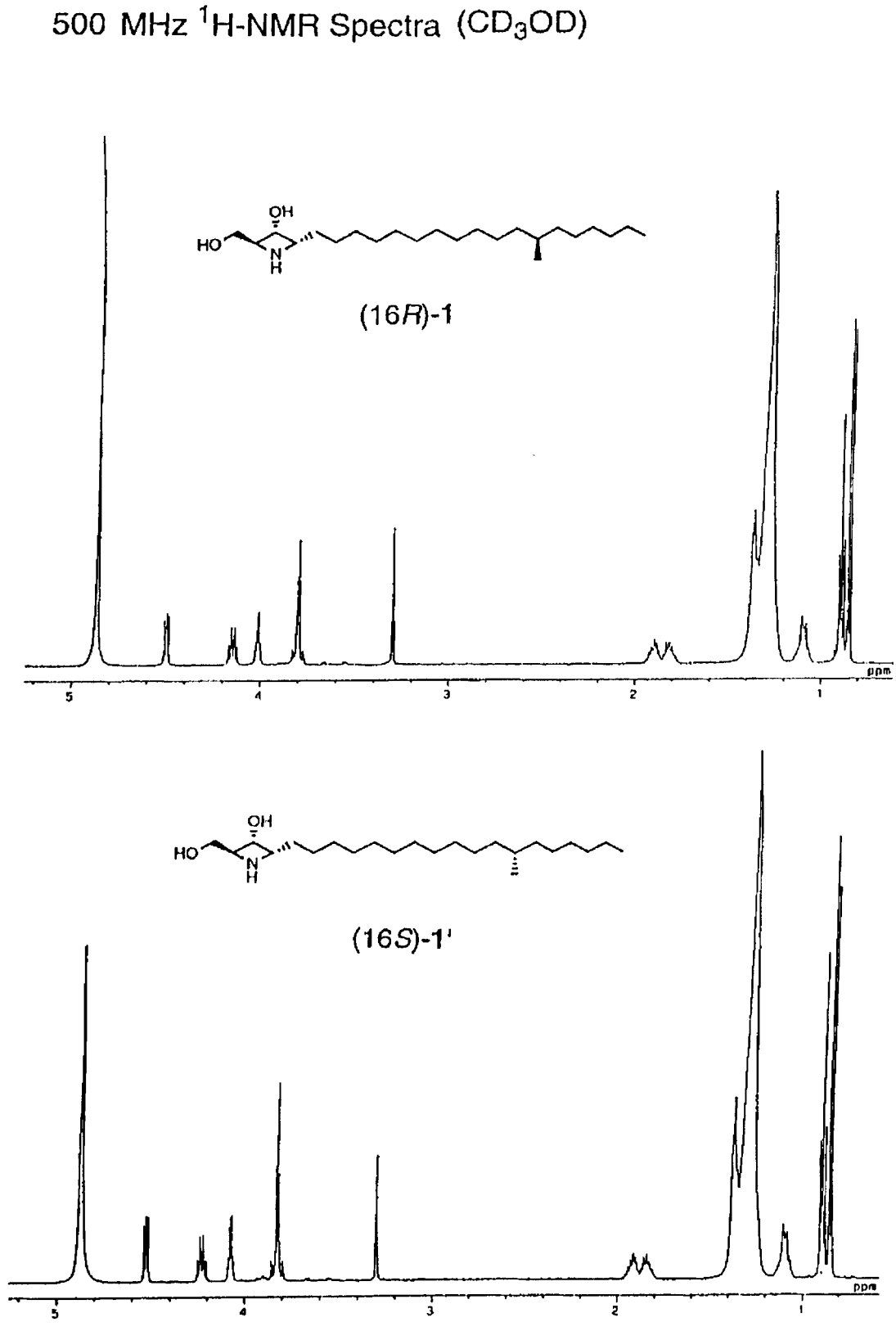

500 MHz ^{1}H-NMR Spectra (CD_3OD)
OH
HO
N
H
(16*R*)-1
ppm
5
4
3
2
1
OH
HO
N
H
(16*S*)-1'
ppm
5
4
3
2
1

Figure 39

Figure 39 shows the ^{1}H-NMR spectra of the samples of penazetidine A. The synthetic two stereoisomers, (16*R*)- and (16*S*)-penazetidine A, exhibited indistinguishable ^{1}H-NMR spectra, and their data were in good accord with the published data of the natural penazetidine A. Because there is no definite method for identification without an authentic sample, we conclude at the moment that penazetidine A is either (2*S*, 3*R*, 4*S*, 16*R*)- or (2*S*, 3*R*, 4*S*, 16*S*)-**1**.

Conclusion.

I reviewed my works on heterocyclic insect pheromones, and emphasized the importance of chirality in pheromone perception. Then the synthesis of (-)-koninginin A (Figure 40) was reported in detail. In this case, the present synthesis established the absolute configuration of the target molecule unambiguously. Finally, the synthesis of azetidine alkaloids such as penaresidin A and penazetidine A was described. In these cases, the synthesis provided the pure stereoisomers of penaresidin A and penazetidine A, perhaps including the natural products themselves. The absolute configuration of the natural products, however, remains to be determined rigorously by direct comparison of the synthetic and natural samples.

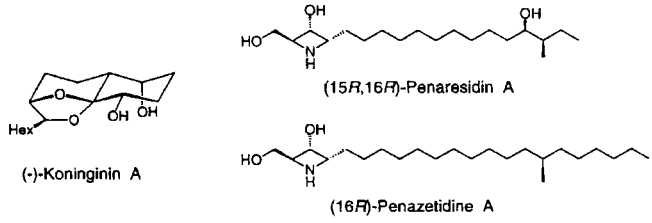


Figure 40

Acknowledgment.

The experimental works on koninginin A was carried out by Mr. K. Abe. Dr. H. Takikawa, Mr. T. Maeda and Mr. A. Yajima synthesized the azetidine alkaloids. I thank all of them for their enthusiasm and experimental skill. Professors E. L. Ghisalberti and J. Kobayashi kindly gave us advice and/or copies of the spectra of the natural product, whom we express our sincere thanks.