Pergamon

Tetrahedron Vol. 51, No. 22, pp. 6209-6228, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00279-0

Total Syntheses of Myriocin and Z-Myriocin, Two Potent Immunosuppressants, from 2-Deoxy-D-Glucose[1]

Masayuki Yoshikawa,* Yoshihiro Yokokawa, Yasuhiro Okuno, Nobutoshi Murakami

Kyoto Pharmaceutical University, 5 Nakauchi-cho, Misasagi, Yamashina-ku, Kyoto 607, Japan

Abstract: Total syntheses of myriocin (thermozymocidin, ISP-1, **21**) and its analog, Z-myriocin (**22**), which showed potent immunosuppressive activity, were accomplished starting from 2-deoxy-D-glucose by employing a modified Darzen reaction as a key reaction. The stereoselectivity of the modified Darzen reaction for six-membered cyclic ketones was discussed on the basis of physicochemical evidence including the conformational analyses of the cyclic ketones based on molecular mechanics calculation.

INTRODUCTION

Myriocin and thermozymocidin were isolated as an antifungal principle from the fermentation broth of thermophilic fungi *Myriococcus albomyces* (ATCC 16425)[2] and *Mycelia sterilia* (ATCC 20349)[3], respectively. Afterwards, myriocin and thermozymocidin were found to be identical and the absolute stereostructure (**21**) was determined by physicochemical evidence including the X ray analysis[4] and by a synthesis of the enantiomer of anhydromyriocin.[5] First total synthesis of myriocin (**21**) was accomplished from D-fructose by using a Strecker reaction in forming the key synthetic intermediate.[6] However, it was reported that the Strecker reaction of D-fructose derivative proceeded with poor diastereoselectivity and the desired synthetic intermediate was obtained as a minor product. Recently, a potent immunosuppressant designated as ISP-1 was isolated from the culture broth of *Isaria sinclairii* (ATCC 24400) and was finally identified with myriocin (**21**).[7] *Isalia sinclairii* was known to be one of the fungi composing a famous Chinese natural medicine (Chinese and Japanese name " 冬虫夏草 ") which has been used as a tonic.[8] Myriocin (**21**) was found to show 10- to 100-fold more potent immunosuppressive activity than cyclosporin A in *in vitro* and *in vivo* bioassay. In view of these finding, myriocin (**21**) and related compounds are expected to be candidates for clinical application as a powerful immunosuppressant.[9] Furthermore, this fact has again stimulated synthetic study of myriocin (**21**) and its analogs, and its formal syntheses were reported recently.[10]

During the course of our chemical transformation studies on the effective utilization of natural carbohydrate as an optically pure starting material, we have found versatile methods for the syntheses of aminoglycosides antibiotics, carba-sugars, and carba-nucleosides.[11] As an extention of our synthetic studies for converting carbohydrate to carba-sugars, we have developed an efficient method for transforming D-glucuronolactone into carba-α and β-D-glucopyranoses and validamine using a stereoselective nitromethane addition to a 5-keto-D-glucuronolactone derivative.[12] Furthermore, from a 4-keto-D-arabinopyranosyl derivative, we have successfully synthesized carba-α and β-D-arabinofuranoses and two antiviral carba-nucleosides, (+)-cyclaradine and carba-β-D-arabinofuranosyluridine.[13]

In this paper, we describe a full account of the synthesis of the natural immunosuppressant myriocin (**21**) and its new analog named Z-myriocin (**22**), which was also found to exhibit potent

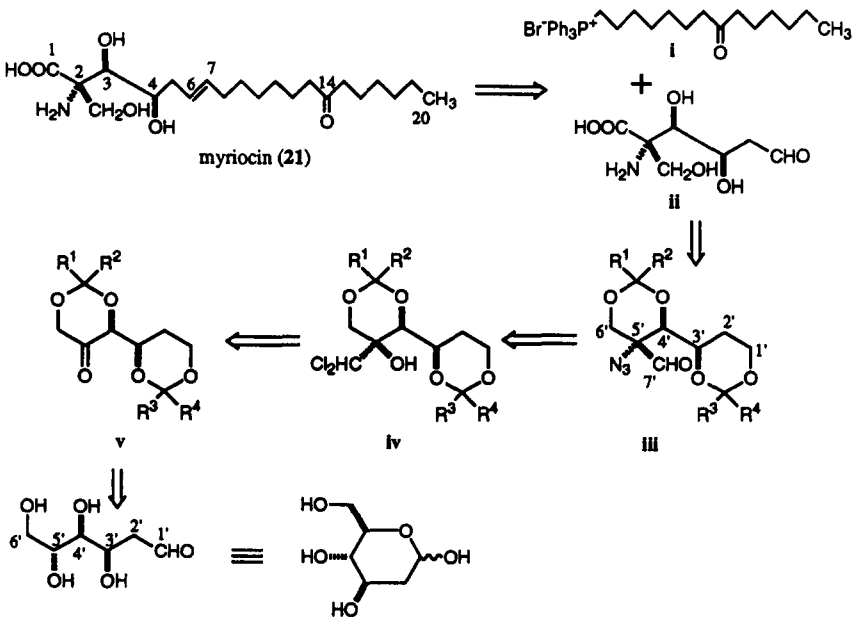


Chart 1

immunosuppressive activity,[14] from 2-deoxy-D-glucose. This synthetic pathway comprises a stereoselective construction of a chiral α, α-disubstituted amino acid derivative (**15**) from an isopropylidene six-membered cyclic ketone (**8**) by utilizing a modified Darzen reaction[15] as a key step. In addition, the stereoselectivity of the modified Darzen reaction was discussed on the basis of conformational analysis of the six-membered cyclic ketones (**2**, **5**) using theoretical calculations.

RESULTS AND DISCUSSION

Synthesis of Myriocin (21)

Our synthetic strategy from 2-deoxy-D-glucose (**1**) to myriocin (**21**) was shown in Chart 1. 2-Deoxy-D-glucose (**1**), whose asymmetric centers at C-3 and C-4 of **1** correlate to C-4 and C-3 of **21**, respectively, could be transformed to a cyclic ketone (**v**) by selective protection of 1, 3-diol and 4, 6-diol moieties followed by oxidation of 5-hydroxyl group. The six-membered cyclic ketone (**v**) is stereoselectively converted to the key 5-azido-aldehyde (**iii**) *via* a dichloromethane addition product (**iv**) by a modified Darzen reaction. The azido-aldehyde (**iii**) would be converted to the α, α-disubstituted amino acid derivative (**ii**), by oxidation of the 1-and 6-hydroxyl groups to the 1-aldehyde and 6-carboxyl groups and reduction of the 7-aldehyde and 5-azide groups to the hydroxylmethyl and amino groups, respectively. Finally,

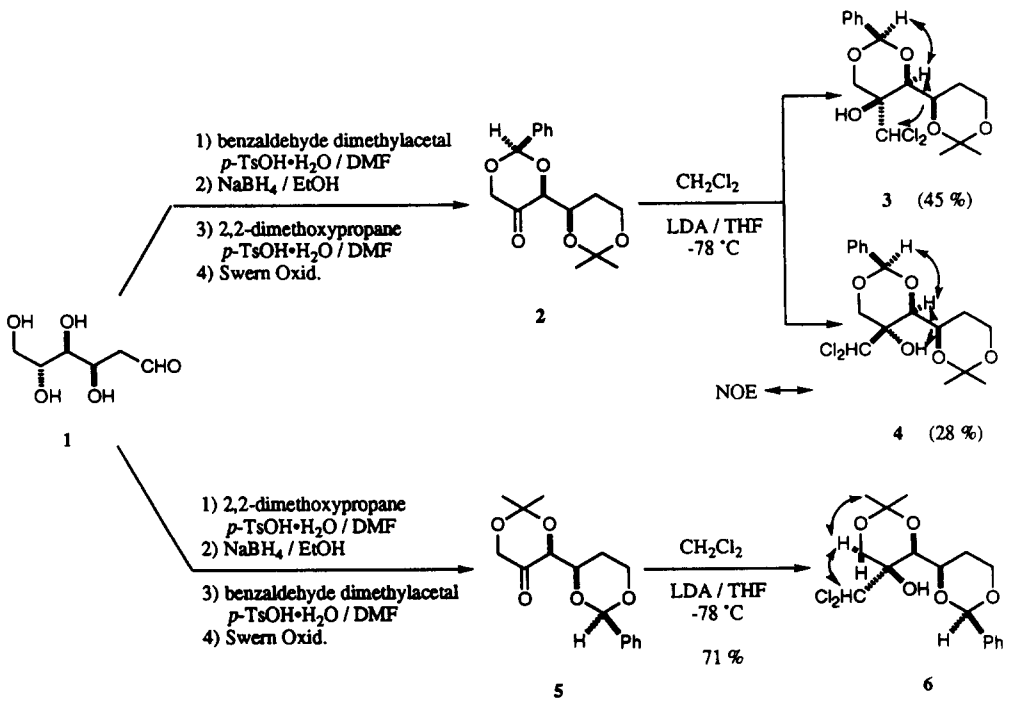


Chart 2

elongation of the carbon chain at the 1-aldehyde of **ii** could be performed by means of a Wittig reaction with **i**.

In order to examine the stereoselectivity of the Darzen reaction for the six-membered cyclic ketone (**v**), the starting material, 2-deoxy-D-glucose (**1**), was first converted to a 4, 6-benzylidene 5-keto derivative (**2**) through successive reactions; 1) benzylidene protection of the 4, 6-diol moiety with benzaldehyde dimethylacetal in *N, N*-dimethylformamide (DMF) in the presence of *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H2O), 2) reduction with sodium borohydride ($NaBH_4$) in ethanol, 3) isopropylidene protection of the 1, 3-diol moiety with 2, 2-dimethoxypropane in DMF in the presence of *p*-TsOH•H2O, and 4) Swern oxidation of the 5-hydroxyl group. Treatment of **2** with dichloromethyllithium, which was prepared by lithiation of dichloromethane (CH_2Cl_2) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C, furnished two addition products **3** (45 %) and **4** (28 %). The structures of **3** and **4** were characterized on the basis of spectral evidence, particularly the configurations at the 5-position of **3** and **4** were easy to determine by examination of their nuclear Overhauser and exchange spectroscopy (NOESY) experiments of proton nuclear magnetic resonance (^1H NMR) spectra as shown in Chart 2.

On the other hand, treatment of the 4, 6-isopropylidene 5-keto derivative (**5**), which was prepared from **1** through reaction sequences changed the order of those used for **2**, with dichloromethyllithium afforded selectively **6** in 71 % yield. The stereostructure of **6** was confirmed by its NOESY data as shown in Chart 2. In order to characterize the specific stereoselectivity of **5** in addition reaction with dichloromethyllithium,

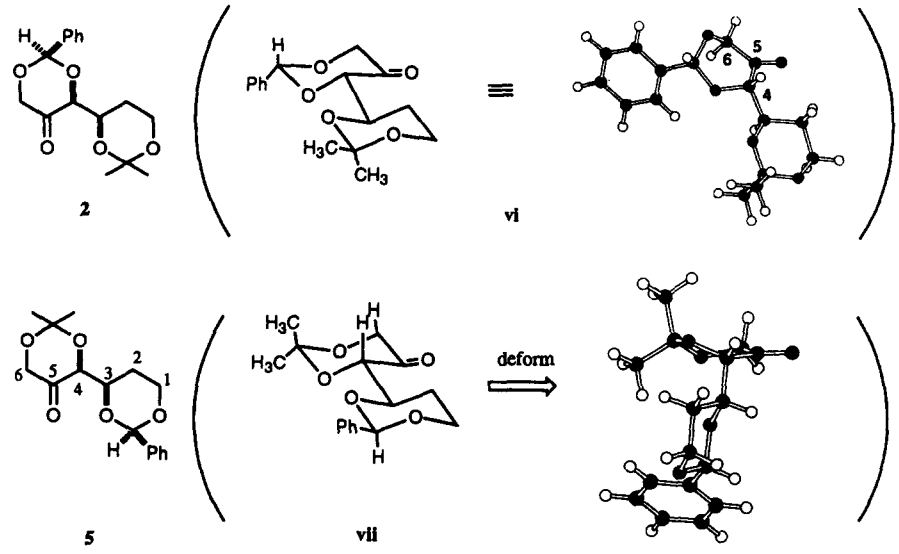
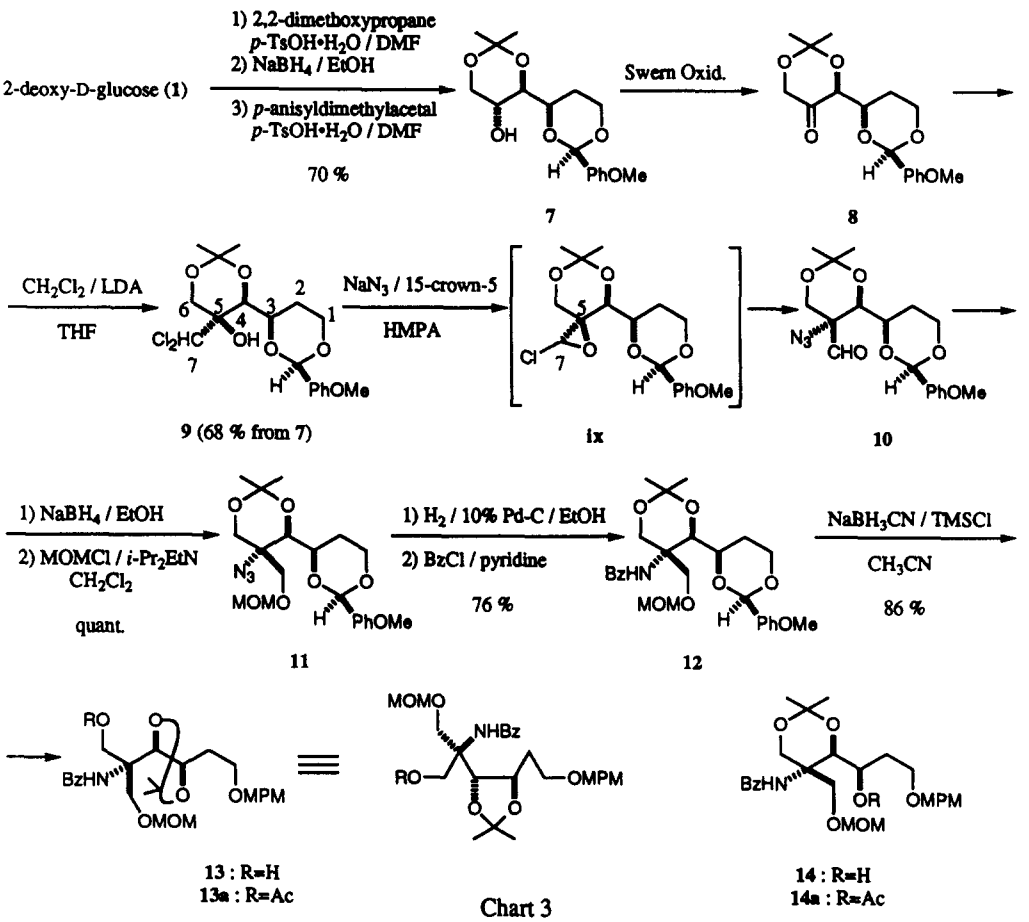


Fig. 1

the conformations of **2** and **5** were examined. The infrared (IR) spectrum of **2** showed absorption band due to carbonyl group at 1735 cm^{-1}, while, in the IR spectrum of **5**, that of carbonyl group was observed at 1750 cm^{-1}. In the circular dichroism (CD) spectra, **2** and **5** showed absorption max at 310 nm ($[\theta]_{max}$ -4000) and 309 nm ($[\theta]_{max}$ -14000), respectively. In the ^1H NMR spectra of **2** and **5**, the 3, 4 and 6-protons around the carbonyl group of **5** were observed at higher field than those of **2**. Based on these evidences, it has been deduced that the carbonyl group of **5** has much more strain than that of **2** and the conformation of six-membered cyclic ketone moiety in **5** exists as not a chair form but a deformed type by sterical repulsion between the isopropylidene axial methyl group and 4 and 6-axial protons in a chair form (**vii**). Finally, the conformations (**vi**, **viii**) of **2** and **5** were obtained by molecular mechanics calculation. As shown in Fig. 1, the one side of the carbonyl group in the deformed conformation (**viii**) of **5** was hindered by the bulky 1, 3-benzylidene group at 4α-position, so that the attack of dichloromethyllithium at the 5-carbonyl group would selectively occure from the less hindered side.

After above mentioned preliminary experiment, **1** was converted to a 4, 6-isopropylidene ketone (**8**) having a 1, 3-*p*-methoxybenzylidene group which could be selectively deprotected. Namely, the isopropylidene protection of the 4, 6-diol part in **1** followed by reduction with $NaBH_4$ gave a 2-deoxy-D-glucitol derivative which was subsequently treated with *p*-anisaldehyde in DMF in the presence of *p*-TsOH•H_2O to furnish **7** in 70 % yield. Swern oxidation of **7** gave an unstable ketone (**8**) which was subjected to a modified Darzen reaction. Namely, treatment of **8** with dichloromethyllithium at -78 °C in THF afforded an addition product (**9**) stereoselectively, which showed that the addition reaction took place from the less sterically hindered α-side of **8** in similar to the case of **5**. The stereostructure of C-5 position in **9** was corroborated by its spectral data including the NOESY experiment, in which the NOEs were observed



between the following pairs of protons: 7-H and 6α-H, 5-OH and 6β-H, 6α-H and 4α-H, 6α-H and α-axial methyl protons of isopropylidene group.

Treatment of **9** with sodium azide (NaN_3) in hexamethylphosphoramide (HMPA) in the presence of 15-crown-5 as a catalyst at 100 °C furnished **10** stereoselectively *via* the formation of the chloroepoxide (**ix**) at 5, 7-position and subsequent ring opening of the chloroepoxide with azide anion regiospecifically from the sterically less hindered α-side [in a similar manner as dichloromethane addition reaction to the ketone (**8**)] in 71 % yield. The IR spectrum of **10** showed absorption bands due to azide and formyl groups at 2124 and 1725 cm^{-1} respectively, while the formyl proton signal appeared at 10.1 ppm (1H, s) in its ^1H NMR spectrum. The 5*R*-configuration for **10** was deduced from the reaction mechanism[15] and also eventually substantitated by the following conversions (*vide infra*) to myriocin (**21**). Reduction of **10** with $NaBH_4$ in ethanol and subsequent treatment of the product with methoxymethyl chloride (MOMCl) in CH_2Cl_2 in the

presence of *N*, *N*-diisopropylethylamine yielded **11** quantitatively. Reduction of **11** with 10 % palladium on carbon in ethanol under hydrogen atmosphere and successive benzoylation with benzoyl chloride in pyridine afforded **12** in 76 % yield. In the fast atom bombardment mass (FAB MS) spectrum of **12**, the quassimolecular ion peak was observed at m/z 502 $(M+H)^+$, and the IR spectrum showed absorption band due to amide group at 1665 cm^{-1}. The ^1H NMR spectrum of **12** showed the signals attributable to three methylenes (1, 6, 7-H_2) bearing oxygen functions, one methylene (2-H_2) and two methine protons (3, 4-H) bearing oxygen function, together with an isopropylidene, a methoxymethoxyl, a *p*-methoxylbenzylidene, and a benzoyl groups. The stereostructure on C-5 in **12** was substantiated by NOESY experiments, in which the NOE enhancements were observed between 6β-H and 7-H_2.

In order to remove the 1, 3-*p*-methoxybenzylidene group of **12**, the reductive ring-opening reaction of *p*-methoxybenzylidene group was applied. For the regioselective ring-opening reaction of *p*-methoxybenzylidene group in methyl 2, 3-di-*O*-benzyl-4, 6-*O*-*p*-methoxybenzylidene-α-D-glucopyranoside with sodium cyanoborohydride ($NaBH_3CN$), it has been reported that the reductive condition in the presence of trimethylsilyl chloride (TMSCl) in acetonitrile (CH_3CN) was used for obtaining the 4-*O*-*p*-methoxybenzyl derivative, whereas the condition in the presence of trifluoroacetic acid (TFA) in DMF gave the 6-*O*-*p*-methoxybenzyl derivative.[16] In the case of **12**, by treatment with $NaBH_3CN$ (2 eq.) and TMSCl (2 eq.) in CH_3CN as well as with $NaBH_3CN$ (10 eq.) and TFA (20 eq.) in DMF, **14** was obtained in 70 % and 60 % yields, respectively. Furthermore, we have found that treatment of **12** with $NaBH_3CN$ (2 eq.) and TMSCl (4 eq.) in CH_3CN yielded **13** in 86 % yield, which was formed *via* regioselective reductive ring-opening of 1, 3-*O*-*p*-methoxybenzylidene group to 1-*O*-*p*-methoxybenzyl group and subsequent migration of the 4, 6-*O*-isopropylidene group to 3, 4-position. The structures of **13** and **14** were characterized by the ^1H NMR analysis of their acetyl derivatives **13a** and **14a** which were derived from **13** and **14** by ordinary acetylation, respectively. The ^1H NMR spectrum of **13a** showed signals due to methylene protons bearing an acetoxyl group at δ 4.69 (s,6-H_2), while a methine proton bearing an acetoxyl group [δ 5.39 (ddd, *J*=4.3, 6.6, 6.6 Hz, 3-H)] was observed in the ^1H NMR spectrum of **14a**.

Swern oxidation of **13** gave 6-aldehyde which was treated with sodium chlorite ($NaClO_2$) and sulfamic acid (NH_2SO_3H) in dioxane-H_2O followed by diazomethane methylation to furnish the chiral α, α-disubstituted amino acid derivative **15**. Deprotection of the *p*-methoxybenzyl group in **15** with 2, 3-dichloro-5, 6-dicyano-*p*-benzoquinone (DDQ)[17] in CH_2Cl_2 followed by Swern oxidation furnishe 1-aldehyde (**16**) which included all asymmetric carbons of myriocin (**21**). The absorption bands characteristic of the ester (1748 cm^{-1}), formyl (1728 cm^{-1}), and amide groups (1653 cm^{-1}) were observed in the IR spectrum of **16**, while the ^1H NMR spectrum showed signals due to two methoxyl groups (δ 3.31 (3H, s), δ 3.83 (3H, s)) and a formyl group (δ 9.81 (1H, dd, *J*=1.3, 2.6 Hz)). In the FAB MS spectrum of **16**, the quassimolecular ion peak was observed at m/z 410 $(M+H)^+$. Treatment of **16** with the phosphonium salt (**17**), which was prepared in the literature procedure,[5] in the presence of *n*-BuLi in *t*-BuOH-THF afforded the condensation product (**18**) as a geometric mixture of *E*- (**18a**) and *Z*- (**18b**) isomers in a *ca* 1: 3 ratio.[18] The photochemical isomerization of the geometric mixture (**18**) with high pressure mercury lamp (300W) in the presence of diphenyl disulfide by using a Pyrex vessel was occured with the deprotection of the 2, 2-dimethyl-1, 3-dioxane group to give a mixture of *E*-isomer (**19**) as a major product and its *Z*-isomer, which

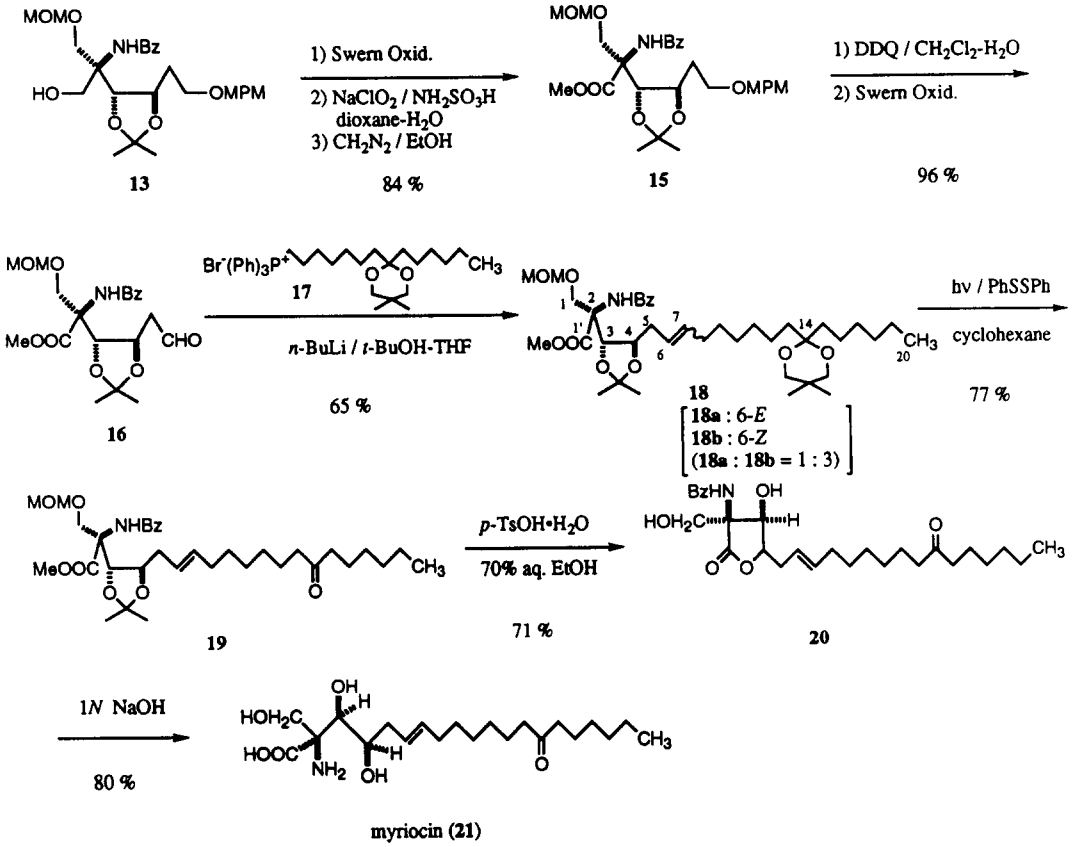


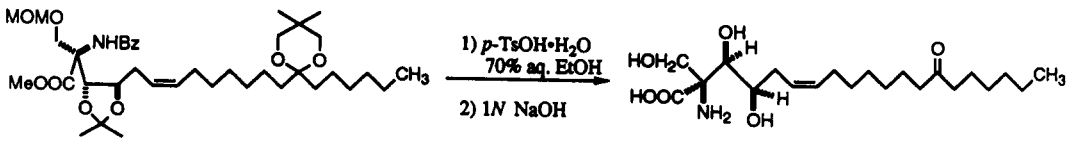
Chart 4

was separated by using high performance liquid chromatography (HPLC) to furnish **19** in 77 % yield. The IR spectrum of **19** showed absorption bands due to carbomethoxyl (1750 cm^{-1}), ketone (1717 cm^{-1}) and amide groups (1667 cm^{-1}), whereas its FAB MS spectrum showed the quassimolecular ion peak at m/z 626 $(M+Na)^+$. Furthermore, in the ^1H NMR study of **19**, the analysis of the coupling constant of the olefinic protons (6-H: δ 5.81 (dt, *J*=6.3, 15.2 Hz); 7-H: δ 5.69 (dt, *J*=5.6, 15.2 Hz)) clarified its structure. Treatment of **19** with *p*-TsOH•H_2O in 70 % aq. EtOH gave *N*-benzoylanhydromyriocin (**20**) *via* deprotection of the isopropylidene and methoxymethyl groups and subsequent lactonization between the 1' and 4-positions. In the FAB MS spectrum of **20**, the quassimolecular ion peak was observed at m/z 488 $(M+H)^+$. The IR spectrum of **20** showed absorption bands due to ketone (1711 cm^{-1}), amide (1647 cm^{-1}) and carbonyl groups (1779 cm^{-1}) of five-membered lactone, while its ^1H NMR spectrum showed the signal of 4-H [δ 4.67 (ddd, *J*=3.6, 6.9, 6.9 Hz)] which was shifted downfield due to lactonization. Finally, the deprotection

and lactone ring cleavage of **20** with 1*N* NaOH afforded myriocin (**21**) in 5.1 % overall yield from **1**. The synthetic **1** has been identified by comparison of its physical data such as TLC, mp., $[\alpha]_D$, IR and ^1H NMR (CD_3OD) with those of authentic sample. This conversion method for myriocin seems to be improved overall yield as compared with the previous method (0.48 % overall yield from D-fructose)[6].

Synthesis of Z-myriocin (22)

To develop a new immunosuppresant with low-toxicity and elucidate the structure-activity relationship,[14] we synthesized an analog of myriocin named *Z*-myriocin (**22**). The *Z*-olefin (**18b**) was separated by HPLC (CH_2Cl_2: *n*-hexane: AcOEt = 4:6:1) from the geometric mixture (**18**). In the FAB MS spectrum of **18b**, the quassimolecular ion peak was observed at m/z 712 $(M+Na)^+$, whereas its IR spectrum showed absorption bands due to carbomethoxyl group (1750 cm^{-1}) and amide group (1669 cm^{-1}). The ^1H NMR spectrum of **18b** showed the signals of the olefinic protons, whose coupling constant (J=10.9 Hz) indicated its *Z*-form structure. Treatment of **18b** with *p*-TsOH•H_2O in 70 % aq. EtOH and subsequent hydrolysis with 1*N* NaOH furnished *Z*-myriocin (**22**) in 4.0 % overall yield from **1**. We are currently working on the further application of this method to the synthesis of other congeners of myriocin (**21**).



18b 51 % Z-myriocin (**22**)

Chart 5

EXPERIMENTAL SECTION

General

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were measured with a Horiba high sensitive SEPA-300 digital polarimeter in a 0.5 dm length cell. Low- and high-resolution FAB mass spectra were taken on a JEOL JMS-SX 102 spectrometer. IR spectra were obtained by using Shimadzu FT-IR DR-8000 or JASCO IR-810 spectrometers. ^1H NMR spectra were recorded on JEOL EX-270 (270 MHz) or JEOL JMX GX-500 (500 MHz) spectrometers with $(CH_3)_4Si$ as the internal standard. ^{13}C NMR spectra were determined on JEOL EX-270 (67.5 MHz) or JEOL JNM GX-500 (125 MHz) spectrometers with $(CH_3)_4Si$ (0 ppm) as the internal standard. The following experimental conditions were used for chromatography: column chromatography, silica gel BW-200 (Fuji-Davidson Chemical); analytical and preparative thin-layer chromatography (TLC), precoated silica gel 60 F_{254} plates (Merck, 0.25 and 0.5 mm layer thickness). Computational results obtained using

software programs from Biosym Technologies of San Diego, CA, U.S.A. --- compounds were converted from the 2D sketch to 3D structure with Sketch[19], dynamics calculations were done with the Discover program[20] using the CVFF forcefield, the molecular structures were build under the NOE distance and dihedral restraints with NMRchitect[21] and graphical displays were printed out from the Insight II[22] molecular modeling system.

Conversion from 1 to 2

A solution of 2-deoxy-D-glucose (**1**, 3.7 g, 22.6 mmol) in DMF (16 ml) was treated with benzaldehyde dimethylacetal (3.73 ml, 27.1 mmol) in the presence of *p*-TsOH•H_2O (32 mg) as a catalyst, and the whole mixture was stirred at room temperature (25 °C) for 12 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 160 g, benzene-acetone (2:1)] to furnish the benzylidene derivative of **1** (2.37 g, 41 %). A solution of the benzylidene derivative (2.37 g, 9.4 mmol) in EtOH (20 ml) was treated with $NaBH_4$ (356 mg, 37 mmol) in an ice-cooling bath, and the whole mixture was stirred at room temperature (25 °C) for 10 min. Acetone was added to the reaction mixture to quench the reaction, and the whole was neutralized with Dowex HCR-W2 and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure yielded the reduction product (2.38 g, quant.). A solution of the product (480 mg, 1,89 mmol) in DMF (2.5 ml) was treated with 2,2-dimethoxypropane (0.70 ml, 5.67 mmol) in the presence of *p*-TsOH•H_2O (5 mg) and the whole mixture was stirred at room temperature (25 °C) for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product which was purified by column chromatography [SiO_2 20 g, $CHCl_3$-AcOEt (5:1)] to furnish the isopropylidene derivative (528 mg, 95 %). Dimethyl sulfoxide (DMSO) (0.72 ml, 10.1 mmol)was added dropwise to a solution of oxalyl chloride (0.59 ml, 6.76 mmol) in CH_2Cl_2 (12 ml) at -78 °C. After stirring at -78 °C for 15 min, a solution of the isopropylidene derivative (995 mg, 3.38 mmol) in CH_2Cl_2 (6 ml) was added to the reaction mixture. Stirring was continued at -78 °C for 30 min, then Et_3N (4.72 ml, 33.8 mmol)was added. After removal of the cooling bath, the reaction mixture was allowed to warm to room temperature, then poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude product which was purified by column chromatography [SiO_2 35 g, *n*-hexane-AcOEt (2:1)] to furnish **2** (802 mg, 81 %). **2**, a colorless oil, CD($CHCl_3$) $[\theta]_{max}$ (nm): -4000 (310). IR(film): 1738, 1458, 1383, 1109, 700 cm^{-1}, ($CHCl_3$): 1735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.38, 1.42 (3H each, both s, isopropylidene), 1.44 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 2.21 (1H, dddd, *J*=5.6, 12.2, 12.2, 12.2 Hz, 2-Hax), 3.91 (1H, ddd, *J*=1.8, 5.6, 12.2 Hz, 1-Heq), 4.12 (1H, ddd, *J*=3.0, 12.2, 12.2 Hz, 1-Hax), 4.35 (1H, ddd, *J*=1.5, 1.5, 3.2 Hz, 4-H), 4.39, 4.49 (1H each, both dd, *J*=1.5, 12.5 Hz, 6-H_2), 4.50 (1H, ddd, *J*=3.2, 3.2, 12.2 Hz, 3-H), 5.91 (1H, s, PhC<u>H</u>), 7.37 - 7.59 (5H, m, Ph).

Dichloromethane addition reaction of 2

n-Butyl lithium (1.6 M solution in *n*-hexane, 3.52 ml, 5.64 mmol) was added to a solution of diisopropylamine (0.79 ml, 5.64 mmol) in THF (9 ml) at -78 °C and the whole mixture was stirred for 30 min. Then, CH_2Cl_2 (1.80 ml, 2.82 mmol) was mixed with the reaction mixture and the whole was stirred at -78 °C for 15 min. A solution of **2** (500 mg, 0.16 mmol) in THF (6 ml) was added to the above solution and the whole was stirred at -78 °C for 15 min. Sat. aq. NH_4Cl was added to the reaction mixture to quench the reaction, and the whole mixture was warmed to room temperature and extracted with AcOEt. The AcOEt extract was washed with brine and dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give a product which was purified by column chromatography [SiO_2 35 g, *n*-hexane-AcOEt (4:1)] to furnish **3** (484 mg, 45 %) and **4** (300 mg, 28 %). **3**, a colorless oil, $[\alpha]_D^{28}$ -12.8° (*c*=2.5, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{17}H_{23}O_5{}^{35}Cl_2$ $(M+H)^+$: 377.0923. Found: 377.0933. IR(KBr): 3435, 1388, 1038 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.28 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 1.42, 1.52 (3H each, both s, isopropylidene), 2.38 (1H, dddd, *J*=5.3, 12.2, 12.2, 12.2 Hz, 2-Hax), 3.88 (1H, ddd, *J*=1.3, 5.3, 12.2 Hz, 1-Heq), 4.01 (1H, ddd, *J*=3.0, 12.2, 12.2 Hz, 1-Hax), 4.16, 4.24 (2H, ABq, *J*=11.2 Hz, 6-H_2), 4.21 (1H, d, *J*=2.3 Hz, 4-H), 4.54 (1H, ddd, *J*=2.3, 2.3, 12.2 Hz, 3-H), 5.54 (1H, s, PhC<u>H</u>), 5.81 (1H, s, $CHCl_2$), 7.35 - 7.58 (5H, m, Ph). FAB MS (m/z, %): 377 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl_2$, 2.1], 379 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl^{37}Cl$, 1.6], 381 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{37}Cl_2$, 0.3]. **4**, a colorless oil, $[\alpha]_D^{28}$ +0.5° (*c*=0.8, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{17}H_{23}O_5{}^{35}Cl_2$ $(M+H)^+$: 377.0923. Found: 377.0914. IR(KBr): 3430, 1401, 1025 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.42, 1.47 (3H, each, both s, isopropylidene), 1.58 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 2.11 (1H, dddd, *J*=5.6, 11.9, 11.9, 11.9 Hz, 2-Hax), 2.90 (br s, OH), 3.70, 4.64 (1H, each, both d, *J*=11.5 Hz, 6-H_2), 3.87 (1H, ddd, *J*=1.3, 5.6, 11.9 Hz, 1-Heq), 3.88 (1H, d, *J*=4.6 Hz, 4-H), 3.98 (1H, ddd, *J*=3.0, 11.9, 11.9 Hz, 1-Hax), 4.45 (1H, ddd, *J*=2.6, 4.6, 11.9 Hz, 3-H), 5.59 (1H, s, PhC<u>H</u>), 6.46 (1H, s, $CHCl_2$), 7.36 - 7.58 (5H, m, Ph). FAB MS (m/z, %): 377 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl_2$, 1.3], 379 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl^{37}Cl$, 0.9], 381 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{37}Cl_2$, 0.2].

Conversion from 1 to 5

A solution of 2-deoxy-D-glucose (**1**, 200 mg, 1.22 mmol) in DMF (1 ml) was treated with 2,2-dimethoxypropane (0.030 ml, 2.44 mmol) in the presence of *p*-TsOH•H_2O (1.5 mg), and the whole mixture was stirred at room temperature (25 °C) for 3 h. The reaction mixture was neutralized with Amberlite IRA-93ZU and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product which was purified by column chromatography [SiO_2 10 g, $CHCl_3$-MeOH (10:1)] to furnish the isopropylidene derivative (196 mg, 87 %) and recovered **1** (22 mg, 10 %). A solution of the isopropylidene derivative (4.70 g, 23 mmol) in EtOH (25 ml) was treated with $NaBH_4$ (326 mg, 35 mmol) in an ice-cooling bath, and then the whole mixture was stirred at room temperature (25 °C) for 10 min. Acetone was added to the reaction mixture to quench the reaction, and then the whole was neutralized with Dowex HCR-W2 and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure yielded the reduction product (4.71 g, quant.). A solution of the product (101 mg, 0.49 mmol) in DMF (1 ml) was treated with benzaldehyde dimethylacetal (1.47 ml, 0.98 mmol) in the presence

of *p*-TsOH•H_2O (20 mg) and the whole mixture was stirred at room temperature (25 °C) for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 6 g, *n*-hexane-AcOEt (2:1→ 1:1)] to furnish the benzylidene derivative (85 mg, 59 %). DMSO (0.022 ml, 0.31 mmol) was added dropwise to a solution of oxalyl chloride (0.018 ml, 0.24 mmol) in CH_2Cl_2 (0.5 ml) at -78 °C and the whole mixture was stirred at -78 °C for 15 min. A solution of the benzylidene derivative (30 mg, 0.10 mmol) in CH_2Cl_2 (1 ml) was mixed with the reaction mixture. Stirring was continued at -78 °C for 30 min, then Et_3N (0.14 ml, 1.02 mmol) was added. The reaction mixture was warmed to room temperature and poured into ice-water and then the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 3 g, *n*-hexane-AcOEt (3:1)] to furnish **5** (26 mg, 86 %). **5**, a colorless oil, CD($CHCl_3$) $[\theta]_{max}$ (nm): -14000 (309). IR(film): 1750, 1456, 1374, 1225, 1098 cm^{-1}, ($CHCl_3$): 1750 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, δ): 1.43 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 1.47, 1.50 (3H each, both s, isopropylidene), 2.26 (1H, dddd, *J*=5.3, 11.5, 11.5, 11.5 Hz, 2-Hax), 3.99 (1H, d, *J*=16.8 Hz, 6-Hax), 4.30 (1H, dd, *J*=1.3, 16.8 Hz,6-Heq), 4.02 (1H, ddd, *J*=2.6, 11.5, 11.5 Hz, 1-Hax), 4.24 (1H, d, *J*=3.6 Hz, 4-H), 4.29 (1H, ddd, *J*=1.3, 5.3, 11.5 Hz, 1-Heq), 4.42 (1H, ddd, *J*=2.3, 3.6, 11.5 Hz, 3-H), 5.52 (1H, s, PhC<u>H</u>), 7.31 - 7.60 (5H, m, Ph).

Dichloromethane addition reaction of 5

n-Butyl lithium (1.6 M solution in *n*-hexane, 8.09 ml, 12.9 mmol) was added to a solution of diisopropylamine (1.81 ml, 12.9 mmol) in THF (9 ml) at -78 °C and the whole mixture was stirred for 30 min. Then, CH_2Cl_2 (94.15 ml, 64.7 mmol) was mixed with the above solution and the resulting mixture was stirred at -78 °C for 15 min. A solution of **5** (1.89 g, 6.47 mmol) in THF (10 ml) was added to the reaction solution and the whole was stirred at -78 °C for 15 min. Sat. aq. NH_4Cl was added to the reaction mixture to quench the reaction, and the whole was warmed to room temperature and then extracted with AcOEt. The AcOEt extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent from the extract under reduced pressure gave a product which was purified by column chromatography [SiO_2 70 g, *n*-hexane-AcOEt (5:1)] to furnish **6** (1.75 g, 71 %). **6**, a colorless oil, $[\alpha]_D^{28}$ -22.0° (*c*=1.5, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{17}H_{23}O_5{}^{35}Cl_2$ $(M+H)^+$: 377.0923. Found: 377.0920. IR(KBr): 3453, 1366, 1078 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.35 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 1.44, 1.49 (3H each, both s, isopropylidene), 2.51 (1H, dddd, *J*=5.3, 12.2, 12.2, 12.2 Hz, 2-Hax), 3.78, 4.12 (2H, ABq, *J*=11.9 Hz, 6-H_2), 4.01 (1H, ddd, *J*=2.3, 12.2, 12.2 Hz, 1-Hax), 4.21 (1H, d, *J*=2.3 Hz, 4-H), 4.33 (1H, ddd, *J*=1.0, 5.3, 12.2 Hz, 1-Heq), 4.51 (1H, ddd, *J*=2.3, 2.3, 12.2 Hz, 3-H), 5.56 (1H, s, PhC<u>H</u>), 5.96 (1H, s, $CHCl_2$), 7.31 - 7.48 (5H, m, Ph). FAB MS (m/z, %): 377 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl_2$, 9.8], 379 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{35}Cl^{37}Cl$, 6.6], 381 [$(M+H)^+$, $C_{17}H_{23}O_5{}^{37}Cl_2$, 1.4].

Conversion from 1 to 7

A solution of 2-deoxy-D-glucose (**1**, 200 mg, 1.22 mmol) in DMF (1 ml) was treated with 2,2-dimethoxypropane (0.030 ml, 2.44 mmol) in the presence of *p*-TsOH•H_2O (1.5 ml) as a catalyst, and the whole mixture was stirred at room temperature (25 °C) for 3 h. The reaction mixture was neutralized with Amberlite IRA-93ZU and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a crude product which was purified by column chromatography [SiO_2 10 g, $CHCl_3$-MeOH (10:1)] to furnish the isopropylidene derivative (196 mg, 87 %). A solution of the isopropylidene derivative (4.70 g, 23 mmol) in EtOH (25 ml) was treated with $NaBH_4$ (326 mg, 35 mmol) in an ice-cooling bath, and then the whole mixture was stirred at room temperature (25 °C) for 10 min. Acetone was added to the reaction mixture to quench the reaction, and then the whole was neutralized with Dowex HCR-W2 and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure yielded the reduction product (4.71 g, quant.). A solution of the product (166 mg, 0.81 mmol) in DMF (2 ml) was treated with *p*-anisaldehyde dimethylacetal (0.21 ml, 1.22 mmol) in the presence of *p*-TsOH•H_2O (40 mg) and the whole mixture was stirred at room temperature (25 °C) for 1 h. The reaction mixture was poured into sat. aq. $NaHCO_3$ and the whole was extracted with AcOEt. The extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 12 g, *n*-hexane-AcOEt (2:1)] to furnish **7** (214 mg, 81 %). **7**, a colorless oil, $[\alpha]_D^{24}$ +12.2° (*c*=0.50, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{17}H_{25}O_6$ $(M+H)^+$: 325.1651. Found: 325.1628. IR (film): 3469, 1616, 1588, 1520, 830 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ):1.38, 1.48 (3H each, both s, isopropylidene), 1.58 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 2.12 (1H, dddd, *J*=4.0, 11.9, 11.9, 11.9 Hz, 2-Hax), 3.60 (1H, ddd, *J*=2.3, 4.6, 11.9 Hz, 3-H), 3.79 (3H, s, MPh), 3.84-4.04 (4H, m, 4, 5-H, 6-H_2), 4.23 (1H, ddd, *J*=4.3, 11.9, 11.9 Hz, 1-Hax), 4.53 (1H, ddd, *J*=2.3, 4.0, 11.9 Hz, 1-Heq), 5.46 (1H, s, MPhCH), 6.87(2H, d, *J*=8.6 Hz, MPh, 3', 5'-H), 7.37 (2H, d, *J*=8.6 Hz, MPh, 2', 6'-H). FAB MS (m/z, %): 325 [$(M+H)^+$, 57], 137 (100). Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.93; H, 7.46. Found: C, 63.01; H, 7.44.

Swern oxidation of 7

DMSO (0.12 ml, 1.65 mmol) was added dropwise to a solution of oxalyl chloride (0.096 ml, 1.1 mmol) in CH_2Cl_2 (2 ml) at -78 °C and the whole was stirred at -78 °C for 15 min. A solution of **7** (178 mg, 0.55 mmol) in CH_2Cl_2 (3 ml) was added to the reaction mixture. Stirring was continued at -78 °C for 30 min, then Et_3N (0.77 ml, 5.5 mmol) was added. The reaction mixture was warmed to room temperature and poured into ice-water. The whole mixture was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude ketone **8**. Due to its unstability, the product was used in next reaction without purification. A part of the crude product of **8** was purified by preparative TLC [*n*-hexane-AcOEt (1:1)] for obtaining its physical data. **8**, a colorless oil, IR ($CHCl_3$): 3447, 1750, 1617, 1588, 1520, 1252, 1101 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.46, 1.49 (3H each, both s, isopropylidene), 1.52 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 2.24 (1H, dddd, *J*=5.2, 12.2, 12.2, 12.2 Hz, 2-Hax), 3.79 (3H, s, MPh), 3.97 (1H, d, *J*=16.5 Hz, 6-Hax), 3.98 (1H, ddd, *J*=2.3, 12.2, 12.2 Hz, 1-Hax), 4.23 (1H, dd, *J*=1.3, 3.6 Hz, 4-H), 4.28 (1H, dd, *J*=1.3, 16.5 Hz, 6-Heq), 4.29 (1H, ddd, *J*=1.3, 5.2, 12.2 Hz, 1-Heq), 4.39 (1H, ddd, *J*=2.3, 3.6, 12.2

Hz, 3-H), 5.47 (1H, s, MPhCH), 6.87 (2H, d, *J*=8.9 Hz, MPh, 3', 5'-H), 7.37 (2H, d, *J*=8.9 Hz, MPh, 2', 6'-H).

Dichloromethane addition reaction of 8

n-Butyl lithium (1.6 M solution in *n*-hexane, 0.19 ml, 0.32 mmol) was added to a solution of diisopropylamine (0.044 ml, 0.32 mmol) in THF (0.7 ml) at -78 °C and the mixture was stirred for 30 min. CH_2Cl_2 (0.10 ml, 1.6 mmol) was added to the reaction mixture and the whole was stirred at -78 °C for 15 min. A solution of the crude ketone **8** (50 mg, 0.16 mmol) in THF (0.8 ml) was mixed with the reaction solution and the whole was stirred at -78 °C for 15 min. Sat. aq. NH_4Cl was added to the reaction mixture to quench the reaction, and the whole mixture was warmed to room temperature and then extracted with AcOEt. The AcOEt extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 2 g, *n*-hexane-AcOEt (5:1)] to furnish **9** (44 mg, 68 % from **7**). **9**, a white powder, $[\alpha]_D^{24}$ -26.0° (*c*=0.20, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{18}H_{25}O_6{}^{35}Cl_2$ $(M+H)^+$: 407.1028. Found: 407.1006. IR ($CHCl_3$): 3447, 1617, 1588, 1520, 1252, 1101 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.33 (1H, br d, *J*=*ca.* 13 Hz, 2-Heq), 1.44, 1.49 (3H each, both s, isopropylidene), 2.48 (1H, dddd, *J*=4.0, 12.5, 12.5, 12.5 Hz, 2-Hax), 3.77, 4.11 (2H, ABq, *J*=11.9 Hz, 6-H_2), 3.80 (3H, s, MPh), 3.99 (1H, ddd, *J*=2.6, 12.5, 12.5 Hz, 1-Hax), 4.20 (1H, d, *J*=2.3 Hz, 4-H), 4.30 (1H, ddd, *J*=1.3, 4.0, 12.5 Hz, 1-Heq), 4.49 (1H, ddd, *J*=2.3, 2.3, 12.5 Hz, 3-H), 5.51 (1H, s, MPhCH), 5.73 (1H, s, $CHCl_2$), 6.88 (2H, d, *J*=8.9 Hz, MPh, 3', 5'-H), 7.38 (2H, d, *J*=8.9 Hz, MPh, 2', 6'-H). FAB MS (m/z, %): 407 [$(M+H)^+$, $C_{18}H_{25}O_6{}^{35}Cl_2$, 100], 409 [$(M+H)^+$, $C_{18}H_{25}O_6{}^{35}Cl^{37}Cl$, 54], 411 [$(M+H)^+$, $C_{18}H_{25}O_6{}^{37}Cl_2$, 10].

Conversion from 9 to 10

A solution of **9** (106 mg, 0.26 mmol) in HMPA (1.5 ml) was treated with sodium azide (85 mg, 1.3 mmol) and 15-crown-5 (0.026 ml, 0.13 mmol) and the whole mixture was stirred at 100 °C for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was washed with H_2O, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 3 g, *n*-hexane-AcOEt (5:1)] to yield **10** (81 mg, 71 %). **10**, a colorless oil, $[\alpha]_D^{24}$ -43.2° (*c*=0.50, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{18}H_{24}N_3O_6$ $(M+H)^+$: 378.1665. Found: 378.1651. IR(film): 2124, 1725, 1617, 1588, 1520, 1252 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.30 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 1.50, 1.52 (3H each, both s, isopropylidene), 2.32 (1H, dddd, *J*=4.0, 12.0, 12.0, 12.0 Hz, 2-Hax), 3.80 (3H, s, MPh), 3.90 (1H, d, *J*=2.3 Hz, 4-H), 3.92, 4.00 (2H, ABq, *J*=11.2 Hz, 6-H_2), 3.96 (1H, ddd, *J*=2.6, 12.0, 12.0 Hz, 1-Hax), 4.19 (1H, ddd, *J*=2.3, 2.3, 12.0 Hz, 3-H), 4.32 (1H, ddd, *J*=1.0, 4.0, 12.0 Hz, 1-Heq), 5.43 (1H, s, MPhCH), 6.89 (2H, d, *J*=8.6 Hz, MPh, 3', 5'-H), 7.30 (2H, d, *J*=8.6 Hz, MPh, 2', 6'-H), 10.1 (1H, s, CHO). FAB MS (m/z, %): 378 [$(M+H)^+$, 100].

Reduction of 10 followed by methoxymethylation

A solution of **10** (22 mg, 0.050 mmol) in EtOH (1 ml) was treated with $NaBH_4$ (1.9 mg, 0.050 mmol) in an ice-cooling bath and the whole mixture was stirred at room temperature (25 °C) for 10 min. Acetone was added to the reaction mixture to quench the reaction and the mixture was poured into ice-water, then the whole was extracted with AcOEt. The AcOEt extract was washed with brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (22 mg, quant.). A solution of the product (22 mg, 0.050 mmol) in CH_2Cl_2 (1 ml) was treated with chloromethyl methyl ether (0.024 ml, 0.30 mmol) and diisopropylethylamine (0.070 ml, 0.40 mmol), and the resulting mixture was heated under reflux for 2.5 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described for the preparation of **8** gave **11** (24 mg, quant.). **11**, a colorless oil, $[\alpha]_D^{24}$ -59.5° (*c*=0.40, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{20}H_{30}N_3O_7$ $(M+H)^+$: 424.2084. Found: 424.2085. IR(film): 2107, 1617, 1588, 1518, 1252 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.35 (1H, br d, *J*=*ca.* 12 Hz, 2-Heq), 1.44 (6H, s, isopropylidene), 2.20 (1H, dddd, *J*=5.0, 11.6, 11.6, 11.6 Hz, 2-Hax), 3.39 (3H, s, CH_2OMOM), 3.60 (1H, d, *J*=3.0 Hz, 4-H), 3.71, 4.24 (2H, ABq, *J*=11.5 Hz, 6-H_2), 3.80 (3H, s, MPh), 3.98 (1H, ddd, *J*=2.6, 11.6, 11.6 Hz, 1-Hax), 4.02, 4.18 (2H, ABq, *J*=11.2 Hz, CH_2OMOM), 4.11 (1H, ddd, *J*=3.0, 3.0, 11.6 Hz, 3-H), 4.28 (1H, ddd, *J*=1.0, 5.0, 11.6 Hz, 1-Heq), 4.66 (2H, s, CH_2OMOM), 5.49 (1H, s, MPhCH), 6.88 (2H, d, *J*=8.9 Hz, MPh, 3', 5'-H), 7.40 (2H, d, *J*=8.9 Hz, MPh, 2', 6'-H). FAB MS (m/z, %): 424 $[(M+H)^+$, 100].

Hydrogenation of 11 followed by benzoylation

A solution of **11** (8 mg, 0.017 mmol) in EtOH (1 ml) was hydrogenated in the presence of 10% Pd-C (4 mg) at room temperature (25°C) for 4 h. The catalyst was filtered off, and the solvent of the filtrate was evaporated under reduced pressure to give a product (7 mg, quant.). A solution of the product (6 mg, 0.013 mmol) in pyridine (0.4 ml) was treated with benzoyl chloride (0.1 ml, 0.86 mmol) and the whole mixture was stirred at room temperature (25 °C) for 30 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **8** gave a product which was purified by column chromatography [SiO_2 1 g, *n*-hexane-AcOEt (5:2)] to furnish **12** (5 mg, 76 %). **12**, a white powder, $[\alpha]_D^{24}$ -121° (*c*=0.39, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{27}H_{36}NO_8$ $(M+H)^+$: 502.2441. Found: 502.2435. IR(film): 1665, 1617, 1582, 1518, 1250 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.38 (1H, br d, *J*=*ca.* 12 Hz, 2-Hax), 1.47, 1.64 (3H each, both s, isopropylidene), 2.25 (1H, dddd, *J*=4.3, 12.2, 12.2, 12.2 Hz, 2-Hax), 3.34 (3H, s, CH_2OMOM), 3.81 (3H, s, MPh), 3.91 (1H, ddd, *J*=2.6, 12.2, 12.2 Hz, 1-Hax), 3.92, 4.48 (2H, ABq, *J*=11.2 Hz, CH_2OMOM), 4.07, 4.61 (2H, ABq, *J*=11.2 Hz, 6-H_2), 4.17 (1H, ddd, *J*=2.6, 2.6, 12.2 Hz, 3-H), 4.23 (1H, ddd, *J*=1.2, 4.3, 12.2 Hz, 1-Heq), 4.65, 4.67 (2H, ABq, *J*=11.2 Hz, CH_2OMOM), 5.35 (1H, d, *J*=2.6 Hz, 4-H), 5.45 (1H, s, MPhCH), 6.88 (2H, d, *J*=8.9 Hz, MPh, 3', 5'-H), 6.98 (1H, br s, NHBz), 7.41 (2H, d, *J*=8.9 Hz, MPh, 2', 6'-H), 7.43 - 7.78 (5H, m, NHBz). FAB MS (m/z, %): 502 $[(M+H)^+$, 32], 105 (100).

Conversion from 12 to 13

A solution of **12** (243 mg, 0.48 mmol) in CH_3CN (48 ml) was treated with $NaBH_3CN$ (60 mg, 0.96 mmol) and TMSCl (0.24 ml, 1.92 mmol) in an ice-cooling bath, and stirred at room temperature (25 °C) for

3 h. The reaction mixture was poured into ice-cooling sat. aq. $NaHCO_3$ and the whole was extracted with AcOEt. The AcOEt extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 8 g, *n*-hexane-AcOEt (1:1)] to furnish **13** (210 mg, 86 %). **13**, a colorless oil, $[\alpha]_D^{24}$ +36.2° (*c*=0.50, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{27}H_{38}NO_8$ $(M+H)^+$: 504.2597. Found: 504.2592. IR(film): 3407, 1653, 1615, 1580, 1516 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.40, 1.47 (3H each, both s, isopropylidene), 1.81 - 1.96 (2H, m, 2-H_2), 3.37 (3H, s, CH_2OMOM), 3.56, 4.05 (2H, ABq, *J*=9.2 Hz, CH_2OMOM), 3.58 - 3.63 (2H, m, 1-H_2), 3.78 (3H, s, MPM), 3.85, 3.90 (2H, ABq, *J*=12.2 Hz, 6-H_2), 4.22 (1H, ddd, *J*=2.6, 7.6, 7.6 Hz, 3-H), 4.31 (1H, d, *J*=7.6 Hz, 4-H), 4.41 (2H, s, MPM), 4.64, 4.69 (2H, ABq, *J*=15.5 Hz, CH_2OMOM), 6.83 (2H, d, *J*=8.9 Hz, MPM, 3', 5'-H), 6.91 (1H, br s, NHBz), 7.22 (2H, d, *J*=8.9 Hz, MPM, 2', 6'-H), 7.40 - 7.76(5H, m, NHBz). FAB MS (m/z, %): 504 [$(M+H)^+$, 36], 121 (100). Anal. Calcd for $C_{27}H_{37}NO_8$: C, 64.38; H, 7.41; N, 2.78. Found: C, 64.00; H, 7.57; N, 2.84.

Acetylation of 13

A solution of **13** (1.5 mg, 0.003 mmol) in pyridine (0.1 ml) was treated with acetic anhydride (Ac_2O) (0.05 ml) and stirred at room temperature (25 °C) for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave **13a** (2 mg, quant.). **13a**, a colorless oil, ^1H NMR (270 MHz, $CDCl_3$, δ): 1.38, 1.43 (3H each, both s, isopropylidene), 1.87 - 2.05 (2H, m, 2-H_2), 1.98 (3H, s, Ac), 3.34 (3H, s, CH_2OMOM), 3.57 - 3.62 (2H, m, 1-H_2), 3.84, 4.07 (2H, ABq, *J*=9.9 Hz, CH_2OMOM), 4.39 (2H, s, MPM), 4.41 (1H, d, *J*=6.9 Hz, 4-H), 4.43 (1H, ddd, *J*=2.6, 6.9, 6.9 Hz, 3-H), 4.63 (2H, s, CH_2OMOM), 4.69 (2H, s, 6-H_2), 6.81 (2H, d, *J*=8.6 Hz, MPM, 3',5'-H), 7.18 (2H, d, *J*=8.6 Hz, MPM, 2',6'-H), 7.38 - 7.76 (5H, m, NHBz).

Conversion from 12 to 14

The conversion of **12** (37 mg, 0.072 mmol) was performed by a method similar to that described for the synthesis of **13** using $NaBH_3CN$ (9 mg, 0.14 mmol) and TMSCl (0.018 ml, 0.14 mmol). The crude product was purified by column chromatography [SiO_2 2 g, *n*-hexane-AcOEt (3:2)] to furnish **14** (26 mg, 70 %). **14**, a colorless oil, ^1H NMR (270 MHz, $CDCl_3$, δ): 1.45, 1.64 (3H each, both s, isopropylidene), 1.80 - 1.96 (2H, m, 2-H_2), 3.35 (3H, s, CH_2OMOM), 3.52 - 3.66(2H, m, 1-H_2), 3.77 (3H, s, MPM), 3.87, 4.66 (2H, ABq, *J*=11.2 Hz, 6-H_2), 4.04 (1H, m, 3-H), 4.05, 4.33 (2H, ABq, *J*=10.6 Hz, CH_2OMOM), 4.35 (2H, s, MPM), 4.70 (2H, s, CH_2OMOM), 5.17 (1H, d, *J*=2.0 Hz, 4-H), 6.97 (1H, br s, NHBz), 6.77 (2H, d, *J*=8.6 Hz, MPM, 3', 5'-H), 7.13 (2H, d, *J*=8.6 Hz, MPM, 2', 6'-H), 7.39 - 7.76 (5H, m, NHBz).

Acetylation of 14

A solution of **14** (3 mg, 0.006 mmol) in pyridine (0.2 ml) was treated with Ac_2O (0.1 ml) in the presence of 4-dimethylaminopyridine (1 mg) and the whole mixture was stirred at room temperature (25 °C) for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over

$MgSO_4$. Removal of the solvent under reduced pressure gave **14a** (3 mg, quant.). **14a**, a colorless oil, ^1H NMR (270 MHz, $CDCl_3$, δ): 1.44, 1.59 (3H each, both s, isopropylidene), 1.96 - 2.05 (2H, m, 2-H_2), 2.04 (3H, s, Ac), 3.34 (3H, s, CH_2OMOM), 3.40 - 3.49 (2H, m, 1-H_2), 3.70, 4.29 (2H, ABq, J=10.6 Hz, CH_2OMOM), 3.83, 4.65 (2H, ABq, J=11.2 Hz, 6-H_2), 3.77 (3H, s, MPM), 4.34 (2H, s, MPM), 4.65 (2H, s, CH_2OMOM), 5.31 (1H, d, J=4.6 Hz, 4-H), 5.39 (1H, ddd, J=4.3, 6.6, 6.6 Hz, 3-H), 6.78 (2H, d, J=8.9 Hz, MPM, 3',5'-H), 6.89 (1H, br s, NHBz), 7.16 (2H, d, J=8.9 Hz, MPM, 2',6'-H), 7.38 - 7.75 (5H, m, NHBz).

Conversion from 13 to 15

DMSO (0.088 ml, 1.22 mmol) was added dropwise to a stirred solution of oxalyl chloride (0.072 ml, 0.81 mmol) in CH_2Cl_2 (8 ml) at -78 °C and the whole mixture was stirred at -78 °C for 15 min. A solution of **13** (138 mg, 0.27 mmol) in CH_2Cl_2 (8 ml) was mixed with the reaction solution. Stirring was continued at -78 °C for 30 min, then Et_3N (0.57 ml, 4.05 mmol) was added to the reaction mixture. After stirring at -78 °C for 15 min, the reaction mixture was warmed to room temperature (25 °C) and poured into ice-water and the whole was extracted with AcOEt. The AcOEt extract was successively washed with 5% aq. HCl, sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 4g, *n*-hexane-AcOEt (3:1)] to furnish the aldehyde (116 mg, 84%). A solution of the aldehyde (282 mg, 0.56 mmol) in dioxane-H_2O (3:1, 28 ml) was treated with sodium chlorite (203 mg, 2.24 mmol) and sulfamic acid (109 mg, 1.12 mmol) in an ice-cooling bath and stirred at room temperature (25 °C) for 30 min. The reaction mixture was poured into brine and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (291 mg, quant.). An etheral solution of diazomethane (5 ml) was added to a stirred solution of the product (291 mg, 0.56 mmol) in MeOH (3 ml) and the whole was stood at room temperature (25 °C) for 5 min. The solvent of the reaction mixture was evaporated under reduced pressure to yield **15** (298 mg, quant.). **15**, a colorless oil, $[\alpha]_D^{24}$ +32.3° (c=0.30, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{28}H_{38}NO_9$ $(M+H)^+$: 532.2547. Found: 532.2531. IR(film): 1750, 1667, 1613, 1582, 1514, 1248, 1040 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.34, 1.36 (3H each, both s, isopropylidene), 1.94 - 2.05 (2H, m, 2-H_2), 3.27 (3H, s, CH_2OMOM), 3.61 - 3.68 (2H, m, 1-H_2), 3.78 (3H, s, MPM), 3.82 (3H, s, $COOCH_3$), 4.15, 4.40 (2H, ABq, J=10.2 Hz, CH_2OMOM), 4.39 - 4.48 (2H, m, 3, 4-H), 4.45 (2H, s, MPM), 4.56, 4.59 (2H, ABq, J=9.9 Hz, CH_2OMOM), 6.82 (2H, d, J=8.6 Hz, MPM, 3', 5'-H), 7.25 (2H, d, J=8.6 Hz, MPM, 2', 6'-H), 7.37 - 7.81 (5H, m, NHBz). FAB MS (m/z, %): 532 [$(M+H)^+$, 12], 121 (100).

Conversion from 15 to 16

A solution of **15** (80 mg, 0.15 mmol) in CH_2Cl_2-H_2O (20:1, 4 ml) was treated with 2,3-dichloro-5, 6-dicyano-*p*-benzoquinone (DDQ, 68 mg, 0.30 mmol) and stirred at room temperature (25 °C) for 1.5 h. The reaction mixture was poured into sat. aq. $NaHCO_3$, and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was successively washed with sat. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 5 g, *n*-hexane-AcOEt (1:2)] to furnish the alcohol (61 mg, quant.). DMSO (0.030 ml, 0.42 mmol) was added

dropwise to a stirred solution of oxalyl chloride (0.025 ml, 0.28 mmol) in CH_2Cl_2 (1.5 ml) at -78 °C and the whole mixture was stirred at -78 °C for 15 min. A solution of the product (58 mg, 0.14 mmol) in CH_2Cl_2 (1.3 ml) was added to the reaction solution and stirred at -78 °C for 30 min. Then, Et_3N (0.20 ml, 1.40 mmol) was added to the reaction mixture and the whole mixture was stirred at -78 °C for 30 min. The reaction mixture was warmed to room temperature and stirred for 15 min. The reaction mixture was poured into ice-water and the whole was extracted with AcOEt. Work-up of the AcOEt extract as described above for the preparation of **8** gave a product which was purified by column chromatography [SiO_2 2 g, *n*-hexane-AcOEt (2:3)] to furnish **16** (56 mg, 96 %). **16**, a colorless oil, $[\alpha]_D^{24}$ +7.3° (*c*=0.30, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{20}H_{28}NO_8$ $(M+H)^+$: 410.1815. Found: 410.1824. IR(film): 1748, 1728, 1653, 1603, 1582, 1244 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 1.36, 1.39 (3H each, both s, isopropylidene), 2.76 (1H, ddd, *J*=2.6, 8.3, 16.8 Hz, 2-H), 2.91 (1H, ddd, *J*=1.3, 3.3, 16.8 Hz, 2-H), 3.31 (3H, s, $CH_2OMO\underline{M}$), 3.83 (3H, s, $COOC\underline{H}_3$), 4.03, 4.29 (2H, ABq, *J*=9.6 Hz, $C\underline{H}_2OMOM$), 4.61 (1H, d, *J*=8.3 Hz, 4-H), 4.62 (2H, s, $CH_2O\underline{M}OM$), 4.75 (1H, ddd, *J*=3.3, 8.3, 8.3 Hz, 3-H), 7.06 (1H, br s, $N\underline{H}Bz$), 7.42 - 7.83 (5H, m, $NH\underline{Bz}$), 9.81 (1H, dd, *J*=1.3, 2.6 Hz, CHO). FAB MS (m/z, %): 410 [$(M+H)^+$, 9], 154 (100).

Wittig reaction of 16

n-Butyl lithium (1.6 M solution in *n*-hexane, 0.26 ml, 0.42 mmol) was added to a stirred solution of phosphonium salt[5] (**17**, 267 mg, 0.42 mmol) in THF (0.45 ml). After stirring at room temperature (25 °C) for 10 min, the reaction mixture was cooled to -78 °C. A solution of **16** (57 mg, 0.14 mmol) in THF (0.5 ml) was added to the reaction solution and the whole mixture was stirred at -78 °C for 10 min. *t*-BuOH (0.055 ml, 0.63 mmol) was added to the reaction mixture and the whole was warmed to room temperature, then stirred for 20 min. The reaction mixture was poured into sat. aq. NH_4Cl and the whole was extracted with AcOEt. The AcOEt extract was washed with brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by column chromatography [SiO_2 7 g, *n*-hexane-AcOEt (4:1 → 2:1)] to yield **18** [a mixture of **18a** and **18b** (1:3), 60 mg, 65 %]. The geometric mixture **18** was purified by HPLC [column: Deverosil 100-5, CH_2Cl_2-*n*-hexane-AcOEt (4:6:1)] to furnish **18a** (14.1mg) and **18b** (42.3mg). **18a**, a colorless oil, $[\alpha]_D^{28}$ +23.0° (*c*=0.1, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{39}H_{63}NO_6Na$ $(M+Na)^+$: 712.4401. Found: 712.4372. IR(film): 1748, 1669, 1603, 1582, 1242, 1046, 920 cm^{-1}. ^1H NMR (270 MHz, C_6D_6, δ): 0.85, 0.86 (3H each, both s, $C(CH_3)_2$ in dioxane ring), 0.94 (3H, t, *J*=6.3 Hz, 20-H_3), 1.36, 1.39 (3H each, both s, isopropylidene), 1.20 - 1.96 (20H, CH_2 x10), 2.04 - 2.16 (2H, m, 8-H_2), 2.50, 2.68 (1H each, both m, 5-H_2), 3.14 (3H, s, $CH_2OMO\underline{M}$), 3.44 (4H, s, CH_2 x2 in dioxane ring), 3.51 (3H, s, $COOC\underline{H}_3$), 4.36, 4.85 (2H, ABq, *J*=9.6 Hz, $C\underline{H}_2OMOM$), 4.50, 4.52 (2H, ABq, *J*=12.5 Hz, $CH_2O\underline{M}OM$), 4.67 (1H, ddd, *J*=3.6, 7.3, 7.3 Hz, 4-H), 4.98 (1H, d, *J*=7.6 Hz, 3-H), 5.68 (1H, dt, *J*=7.3, 15.2 Hz, 7-H), 5.79 (1H, dt, *J*=7.3, 15.2 Hz, 6-H), 7.46 (1H, br s, $N\underline{H}Bz$), 6.97 - 7.22 (3H, m, $NH\underline{Bz}$), 7.90 - 7.96 (2H, m, $NH\underline{Bz}$). FAB MS (m/z, %): 712 [$(M+Na)^+$, 7], 105 (100). **18b**, a colorless oil, $[\alpha]_D^{24}$ +22.0° (*c*=1.7, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{39}H_{63}NO_9Na$ $(M+Na)^+$: 712.4401. Found: 712.4385. IR(film): 1750, 1669, 1603, 1582, 1242, 1043, 920 cm^{-1}. ^1H NMR (270 MHz, C_6D_6, δ): 0.86, 0.87 (3H each, both s, $C(CH_3)_2$ in dioxane ring), 0.93 (3H, t, *J*=6.6 Hz, 20-H_3), 1.39, 1.42

(3H each, both s, isopropylidene), 1.35 - 1.92 (20H, CH_2 x10), 2.16 - 2.22 (2H, m, 8-H_2), 2.54, 2.77 (1H each, both m, 5-H_2), 3.15 (3H, s, CH_2OMOM), 3.45 (4H, s, CH_2 x2 in dioxane ring), 3.52 (3H, s, $COOCH_3$), 4.37, 4.84 (2H, ABq, *J*=9.6 Hz, CH_2OMOM), 4.50, 4.53 (2H, ABq, *J*=12.5 Hz, CH_2OMOM), 4.67 (1H, ddd, *J*=3.6, 7.9, 7.9 Hz, 4-H), 4.97 (1H, d, *J*=7.9 Hz, 3-H), 5.64 (1H, dt, *J*=7.3, 10.9 Hz, 7-H), 5.83 (1H, dt, *J*=6.9, 10.9 Hz, 6-H), 7.43 (1H, br s, NHBz), 6.98 - 7.20 (3H, m, NHBz), 7.90 - 7.93 (2H, m, NHBz). FAB MS (m/z, %): 712 [$(M+Na)^+$, 8], 105 (100).

Photoisomerization of 18

A cyclohexane solution (3 ml) of the geometric mixture **18** (15 mg, 0.022 mmol) and diphenyldisulfide (9.5 mg, 0.044 mmol) was irradiated by 300W high pressure mercury lamp at room temperature (25 °C) for 15 h with cut off at 280 nm by using a Pyrex vessel. The reaction mixture was poured into sat. aq. $NaHCO_3$ and the whole was extracted with AcOEt. The AcOEt was washed with brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product which was purified by HPLC [column: Develosil 100-5, CH_2Cl_2-*n*-hexane-AcOEt (5:5:1)] to furnish **19** (10 mg, 77 %). **19**, a colorless oil, $[\alpha]_D^{24}$ +38.9° (*c*=0.17, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{34}H_{53}NO_8Na$ $(M+Na)^+$: 626.3669. Found: 626.3652. IR(film): 1750, 1717, 1669, 1244, 1046 cm^{-1}. ^1H NMR (270 MHz, C_6D_6, δ): 0.92 (3H, t, *J*=6.9 Hz, 20-H_3), 1.24 - 1.69 (16H, CH_2 x8), 1.36, 1.39 (3H each, both s, isopropylidene), 1.82 - 2.01 (2H, m, 8-H_2), 2.06 (4H, t-like, 13, 15-H_2), 2.51, 2.72 (1H each, both m, 5-H_2), 3.14 (3H, s, CH_2OMOM), 3.51 (3H, s, $COOCH_3$), 4.35, 4.85 (2H, ABq, *J*=9.6 Hz, CH_2OMOM), 4.50, 4.53 (2H, ABq, *J*=13.9 Hz, CH_2OMOM), 4.68 (1H, ddd, *J*=4.0, 7.6, 7.6 Hz, 4-H), 4.99 (1H, d, *J*=7.6 Hz, 3-H), 5.69 (1H, dt, *J*=5.6, 15.2 Hz, 7-H), 5.81 (1H, dt, *J*=6.3, 15.2 Hz, 6-H), 6.93 - 7.11 (3H, m, NHBz), 7.90 - 7.94 (2H, m, NHBz). FAB MS (m/z, %): 626 [$(M+Na)^+$, 20], 546 (100).

Conversion from 19 to 20

A solution of **19** (7 mg, 0.012 mmol) in 70 % aq. EtOH (1 ml) was treated with *p*-TsOH•H_2O (25 mg) and the whole mixture was heated under reflux for 3 h. The reaction mixture was neutralized with Amberlite IRA-93ZU and the resin was filtered off. Removal of the solvent from the filtrate under reduced pressure gave a product which was purified by column chromatography [SiO_2 1 g, benzene-AcOEt (3:1)] to furnish **20** (4 mg, 71 %). **20**, a colorless oil, $[\alpha]_D^{24}$ +18.0° (*c*=0.20, $CHCl_3$). High resolution FAB MS (m/z); Calcd for $C_{28}H_{42}NO_6$ $(M+H)^+$: 488.3012. Found: 488.3040. IR(film): 3410, 1779, 1711, 1647, 1603, 1580, 1528 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$, δ): 0.87 (3H, t, *J*=6.9 Hz, 20-H_3), 1.18 - 1.62 (16H, CH_2 x8), 1.98 - 2.06 (2H, m, 8-H_2), 2.37, 2.39 (2H each, both t, *J*=7.3 Hz, 13, 15-H_2), 2.61 (2H, dd, *J*=6.9, 6.9 Hz, 5-H_2), 3.94, 4.03 (2H, ABq, *J*=11.9 Hz, 1-H_2), 4.67 (1H, ddd, *J*=3.6, 6.9, 6.9 Hz, 4-H), 4.83 (1H, d, *J*=3.6 Hz, 3-H), 5.45 (1H, dt, *J*=6.9, 15.5 Hz, 6-H), 5.63 (1H, dt, *J*=6.6, 15.5 Hz, 7-H), 7.01 (1H, br s, NHBz), 7.43 - 7.85 (5H, m, NHBz). FAB MS (m/z, %): 488 [$(M+H)^+$, 100].

Myriocin (21)

A solution of **20** (5 mg, 0.010 mmol) in 1*N* NaOH (1 ml) was heated under reflux for 2 h. The reaction mixture was neutralized with Amberlite IRC-76 and the resin was filtered off. Removal of the solvent from

the filtrate under reduced pressure gave a product which was purified by column chromatography [SiO_2 1 g, $CHCl_3$-MeOH-H_2O (10:3:1, lower phase)] to furnish myriocin (**21**, 3.3 mg, 80 %), which was confirmed to be identical with an authentic sample by TLC, mixed mp (180 - 182 °C), $[\alpha]_D^{24}$ +4.6° (*c*=0.35, MeOH), IR (KBr), ^1H NMR (CD_3OD), and FAB-MS.

Conversion from 18b to Z-myriocin (22)

A solution of **18b** (25 mg, 0.036 mmol) in 70 % aq. EtOH (2 ml) was treated with *p*-TsOH•H_2O (50 mg) and the whole mixture was heated under reflux for 2 h. The reaction mixture was neutralized with Amberlite IRA-93ZU and the resin was filtered off. Removal of the solvent from the filtrate under reduced pressure gave a product which was purified by column chromatography [SiO_2 2 g, benzene-AcOEt (3:1)] to yield the lactone (12 mg, 67 %). A solution of the product (11 mg, 0.022 mmol) in 1*N* NaOH (1 ml) was heated under reflux for 2 h. The reaction mixture was neutralized with Amberlite IRC-76 and the resin was removed by the filtration. Removal of the solvent from the filtrate under reduced pressure gave a product which was purified by column chromatography [SiO_2 2 g, $CHCl_3$-MeOH-H_2O(10:3:1, lower phase)] to furnish Z-myriocin (**22**, 7 mg, 77%). **22,** a colorless fine crystal, Mp 180 - 182 °C. $[\alpha]_D^{24}$ +12.2° (*c*=0.09, MeOH). High resolution FAB MS (m/z); Calcd for $C_{21}H_{40}NO_6$ $(M+H)^+$: 402.2855. Found: 402.2874. IR(KBr): 3387, 1715, 1663, 1046, 727 cm^{-1}. ^1H NMR (270 MHz, CD_3OD, δ): 0.90(3H, t, *J*=6.6 Hz, 20-H_3), 1.21 - 1.57 (16H, CH_2 x8), 2.01 - 2.14 (2H, m, 8-H_2), 2.33 (2H, dd, *J*=7.3, 7.3 Hz, 5-H_2), 2.44 (4H, t-like, 13, 15-H_2), 3.78 (1H, s, 3-H), 3.85 (1H, t, *J*=7.3 Hz, 4-H), 3.85, 3.99 (2H, ABq, *J*=10.9 Hz, 1-H_2), 5.36 (1H, dt, *J*=7.3 10.9 Hz, 6-H), 5.48 (1H, dt, *J*=7.3 10.9 Hz, 7-H). FAB MS (m/z, %): 402 [$(M+H)^+$, 100].

Acknowledgment

The authors are grateful for the computational modeling to Dr. Ryoichi Kataoka, Ryoka Systems, Inc. (Urayasu, Chiba 279, Japan).

REFERENCES

1. This work was partly reported in our preliminary communication: Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 994 - 996.
2. Kluepfel, D.; Bagli, J. F.; Baker, H.; Charest, M.; Kudelski, A.; Sehgal, S. N.; Vezina, C. *J. Antibiot.* **1972**, *25*, 109 - 115.
3. a) Craveri, R.; Manachini, P. L.; Aragozzini, F. *Experientia* **1972**, *28*, 867 - 868; b) Aragozzini, F.; Manachini, P. L.; Craveri, R.; Rindone, B.; Scolastico, C. *Tetrahedron* **1972**, *28*, 5493 - 5498.
4. a) Bagli, J. F.; Kluepfel, D. *J. Org. Chem.* **1973**, *38*, 1253 - 1260; b) Destro, R.; Colombo, A. *J. Chem. Soc., Perkin Trans 2* **1979**, 896 - 899.
5. Payette, D. R.; Just, G. *Can. J. Chem.* **1981**, *59*, 269 - 282.
6. Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613 - 1619;

7. a) Fujita, T.; Toyama, R.; Sasaki, S.; Okumoto, T.; Chiba, K. *Japan Patent (Japan Kokai)* **1989**, Heisei 1-104087; b) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 208 - 215.
8. *Dictionary of Chinese Crude Drug*, ed. by Chiang Su New Medical College; Shanghai Scientific Technologic Publisher, Shanghai, 1985; pp. 767 - 768.
9. a) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hoshino, Y.; Okumoto, T. *J. Antibiot.* **1994**, *47*, 216 - 225; b) Sasaki, S.; Hashimoto, R.; Kiuchi, M.; Inoue, K.; Ikumoto, T.; Hirose, R.; Chiba, K.; Hoshino, Y.; Okumoto, T.; Fujita, T. *J. Antibiot.* **1994**, *47*, 420 - 433.
10. a) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653 - 1656; b) Deloisy, S.; Thang, T. T.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.* **1994**, *35*, 4783 - 4786.
11. a) Kitagawa, I.; Yoshikawa, M. *Kagaku Zokan No. 108*, ed. by Nozaki, H.; Oshima, K.; Kagakudojin, Kyoto, 1986; pp. 1 - 10; b) Kitagawa, I.; Yoshikawa, M. *Kagaku Zokan No. 118*, ed. by Kanaoka, Y.; Goto, T.; Shiba, T.; Nakajima, T.; Mukaiyama, T.; Kagakudojin, Kyoto, 1990; pp. 161 - 177; c) Yoshikawa, M.; Okaichi, Y.; Cha, B. C.; Kitagawa, I. *Tetrahedron* **1990**, *46*, 7459 - 7470.
12. a) Yoshikawa, M.; Murakami, N.; Inoue, Y.; Hatakeyama, S.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 636 - 638 ; b) Yoshikawa, M.; Yokokawa, Y., Yamaguchi, S.; Murakami, N.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9961-9974.
13. a) Yoshikawa, M.; Murakami, N.; Inoue, Y.; Kuroda, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1993**, *41*, 1197 - 1199 ; b) Yoshikawa, M.; Murakami, N.; Yokokawa, Y.; Inoue, Y.; Kuroda, Y.; Kitagawa, I. *Tetrahedron* **1994**, *50*, 9619-9628.
14. Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Yagi, N.; Murakami, N. *Chem. Pharm. Bull.*, **1994**, *42*, 2662-2664.
15. Sato, K.; Suzuki, K.; Ueda, M.; Katayama, M.; Kajihara, Y. *Chem. Lett.* **1991**, 1469 - 1472.
16. a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885 - 888 ; b) Horita, K.; Yoshioka, T., Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42* 3021-3028.
17. Johansson, R.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371 - 2374.
18. The ratio of the *E* and *Z*- isomers in the mixture was measured by HPLC analysis.
19. Sketch User Guide, version 2. 3. San Diego: Biosym Technologies, 1993.
20. Discover User Guide, version 2. 95. San Diego: Biosym Technologies, 1993.
21. NMRchitect User Guide, version 2. 3. San Diego: Biosym Technologies, 1993.
22. Insight II User Guide, version 2. 3. San Diego: Biosym Technologies, 1993.

(*Received in Japan* 12 *January* 1995; *accepted* 5 *April* 1995)