TOTAL SYNTHESIS OF A NOVEL IMMUNOSUPPRESSANT, MYRIOCIN (THERMOZYMOCIDIN, ISP-I), AND Z-MYRIOCIN

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Myriocin (thermozymocidin, ISP-I), which was known to exhibit several interesting biological properties such as potent immunosuppressive and antifungal activities, and a new analog Z-myriocin were synthesized from 2-deoxy-D-glucose. This synthetic pathway comprises a stereoselective formation of the chiral α, α-disubstituted amino acid structure in myriocin and Z-myriocin from the isopropylidene six-menbered ketone by using a modified Darzen reaction as its key step.

KEYWORDS myriocin ; thermozymocidin ; ISP-I ; immunosuppressant ; chiral α, α-disubstituted amino acid ; 2-deoxy-D-glucose

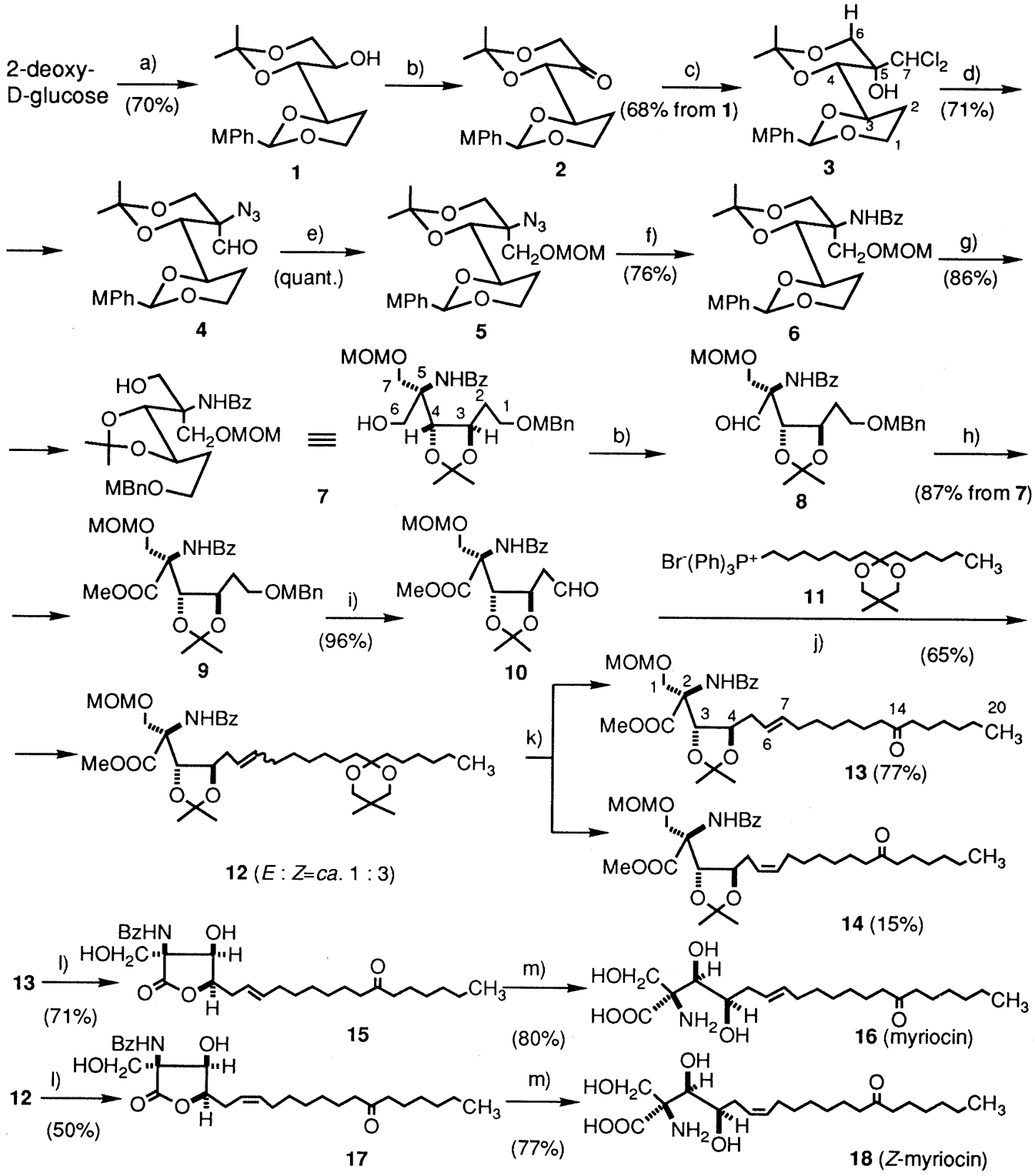
Myriocin (thermozymocidin, **16**) was isolated from the fermentation broth of the thermophilic fungus *Myriococcum albomyces* as an antifungal principle [1] and the absolute stereostructure was determined by physicochemical evidence including X ray analysis and synthetic studies.[2] Afterwards, a total synthesis of myriocin from D-fructose was also reported.[3] Recently, a potent immunosuppressant designated as ISP-I was isolated from the culture broth of *Isaria sinclairri*, and ISP-I was found to be identical with myriocin (**16**).[4] This fact has again stimulated synthetic study of myriocin (**16**)[5] and its analogs.

In the course of our studies on the effective utilization of natural carbohydrate as an optically pure starting material, we have so far found versatile methods for the syntheses of aminoglycoside antibiotics, carba-sugar, and carba-nucleoside.[6] As an extension of our studies on synthesizing bioactive compounds from carbohydrate, we have developed an efficient method for transforming the keto derivatives derived from carbohydrate to the chiral α, α-disubstituted amino acid by using a modified Darzen reaction [7] and, by utilizing this method, have successfully synthesized myriocin (**16**) and its analogs.[8] This paper deals with syntheses of myriocin (**16**) and its new analog named Z-myriocin (**18**) from 2-deoxy-D-glucose.

1,3-*O*-*p*-Methoxybenzylidene-4, 6-*O*-isopropylidene-D-glucitol (**1**) [9] was prepared from commercial 2-deoxy-D-glucose in the sequence of protection of 4, 6-diol part as a isopropylidene ketal, $NaBH_4$ reduction, and then protection of 1, 3-diol part as a *p*-methoxybenzylidene ketal. Swern oxidation of **1** furnished an unstable ketone (**2**) which was subjected to a modified Darzen reaction. Namely, treatment of **2** with dichloromethane and LDA in THF at -78°C afforded an addition product **3**[10] stereoselectively. On the other hand, another 5-keto derivative derived from 1, 3-*O*-isopropylidene-4, 6-*O*-benzylidene-D-glucitol was found to give a C-5 epimeric mixture of the addition products in the preliminary experiment of the addition reaction. The stereostructure of C-5 position in **3** was characterized by examination of its spectral data including the NOE observation in the following pairs of protons (7-H & 6β-H ; 5-OH & 6α-H ; 6β-H & 4β-H).

By treatment of **3** with NaN_3 and 15-crown-5 in HMPA at 100°C, **4** was stereoselectively obtained *via* the formation of the chloroepoxide at 5, 7-position and subsequent ring opening of the chloroepoxide with azido anion from the less hindered β-side [in a similar manner as dichloromethane addition reaction to the ketone (**2**)]. The 5-(*R*)-configuration in **4** was deduced from the reaction mechanism and, finally, substantiated by the following conversions (*vide infra*) to myriocin (**16**).

Reduction of **4** with $NaBH_4$ followed by introduction of a methoxymethyl group furnished **5**, which was subjected to reduction of the azido group and subsequent benzoylation to give **6**. By treatment of **6** with $NaBH_3CN$ and trimethylsilyl chloride (TMSCl) in CH_3CN, **7** was obtained *via* regioselective reductive ring-opening of 1, 3-*O*-*p*-methoxybenzylidene acetal group to 1-*O*-*p*-methoxybenzyl group and subsequent migration of 4, 6-*O*-isopropylidene group to the 3, 4-position. It was reported that the reductive condition in the presence of TMSCl in CH_3CN was used for obtaining the 3-*O*-*p*-methoxybenzyl derivative, whereas the condition in the presence of CF_3COOH in THF was used for the 1-*O*-*p*-methoxybenzyl derivative. [11] In this case, treatment of **6** with $NaBH_3CN$ and CF_3COOH in THF gave the 1-*O*-*p*-methoxybenzyl-4, 6-*O*-isopropylidene derivative without the desired migration. Swern oxidation of **7** afforded the 6-aldehyde (**8**), which was converted to the chiral α, α-disubstituted amino acid derivative **9** [12] by successive treatment with $NaClO_2$ and NH_2SO_3H in dioxane-H_2O followed by CH_2N_2 methylation. Deprotection of *p*-methoxybenzyl group in **9** with DDQ in CH_2Cl_2-H_2O [13] and subsequent Swern oxidation furnished the 1-aldehyde (**10**).



a) 1) DMP / *p*-TsOH·H_2O / DMF, 2) $NaBH_4$ / EtOH, 3) *p*-anisyldimethylacetal / *p*-TsOH·H_2O / DMF, b) Swern Oxid., c) CH_2Cl_2 / LDA / THF, d) NaN_3 / 15-crown-5 / HMPA, e) 1) $NaBH_4$ / EtOH, 2) MOMCl / *i*-Pr_2EtN / CH_2Cl_2, f) 1) H_2 / 10% Pd-C / EtOH, 2) BzCl / Py., g) $NaBH_3CN$ / TMSCl / CH_3CN, h) 1) $NaClO_2$ / NH_2SO_3H / dioxane-H_2O, 2) CH_2N_2 / Et_2O, i) 1) DDQ / CH_2Cl_2-H_2O, 2) Swern Oxid., j) **11** / *n*-BuLi / *t*-BuOH-THF, k) hν / PhSSPh / cyclohexane, l) *p*-TsOH·H_2O / 70% aq. EtOH, m) 1N NaOH.

Wittig reaction with the 1-aldehyde (**10**) and the phosphonium salt (**11**) [2c] in the presence of *n*-BuLi in *t*-BuOH-THF afforded a geometric mixture (**12**) (*E*:*Z*=*ca.* 1:3).[14] The photochemical geometrical isomerization reaction of **12** in the presence of diphenyldisulfide proceeded with deketalization at 14 position to provide the *E*-isomer (**13**)[15] as a major product and the Z-isomer (**14**). Treatment of **13** with *p*-TsOH·H_2O furnished N-benzoylanhydromyriocin (**15**). Finally, removal of the benzoyl group and lactone ring cleavage of **15** with 1N NaOH afforded myriocin (**16**) [16] in 5.1% overall yield from 2-deoxy-D-glucose, which was identified with an authentic sample by TLC, mp, $[\alpha]_D$, IR and ^{1}H NMR (CD_3OD).

On the other hand, the Z-lactone derivative (**17**, 50%) was prepared efficiently from **12** together with **15** (17%) by acid treatment, and then **17** was converted to a new analog of myriocin named Z-myriocin (**18**).[17] We are currently working on further application of this method to the synthesis of other congeners of myriocin (**16**).

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9) All new compounds (**1**, **2**, **4** ~ **8**, **10** ~ **12**, **14**, **15**, **17**) were characterized by physicochemical properties, and full characteristics will be presented in a full paper. The molecular composition of the compound (**3**, **9**, **13**, **18**) given the chemical formula was determined by high-resolution FAB-MS measurement.

10) **3**, white powder, $[\alpha]_D^{24}$ -26.0° ($CHCl_3$), $C_{18}H_{24}O_6Cl_2$,[9] IR ($CHCl_3$) : 3447, 1617, 1588, 1520 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 1.33 (br d, J=*ca.* 13.0Hz, 2-eq.H), 2.48 (dddd, J=4.0, 12.5, 12.5, 12.5Hz, 2-ax.H), 3.77 (d, J=11.9Hz, 6-ax.H), 4.11 (d, J=11.9Hz, 6-eq.H), 3.99 (ddd, J=2.6, 12.5, 12.5Hz, 1-ax.H), 4.20 (d, J=2.3Hz, 4-H), 4.30 (ddd, J=1.3, 4.0, 12.5Hz, 1-eq.H), 4.49 (ddd, J=2.3, 2.3, 12.5Hz, 3-H).

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12) **9**, colorless oil, $[\alpha]_D^{24}$ +32.3° ($CHCl_3$), $C_{28}H_{37}NO_9$, IR (film) : 1750, 1667, 1613, 1582, 1514 cm^{-1}. ^{1}H NMR ($CDCl_3$) : δ 1.94-2.05 (m, 2-H_2), 3.61-3.68 (m, 1-H_2), 4.15, 4.40 (ABq, J=10.2Hz, 7-H_2), 4.39-4.48 (m, 3, 4-H).

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14) The composition of the *E* and Z-isomers in the mixture was confirmed by HPLC analysis.

15) **13**, colorless oil, $[\alpha]_D^{24}$ +38.9° ($CHCl_3$), $C_{34}H_{53}NO_8$,[9] IR (film) : 1750, 1717, 1669, 1244, 1046 cm^{-1}. ^{1}H NMR (C_6D_6) : δ 0.92 (t, J=6.9Hz, 20-H_3), 2.06 (t-like, 13, 15-H_2), 4.35, 4.85 (ABq, J=9.6Hz, 1-H_2), 4.67 (ddd, J=4.0, 7.6, 7.6Hz, 4-H), 4.99 (d, J=7.6Hz, 3-H), 5.69 (dt, J=5.6, 15.2Hz, 7-H), 5.81 (dt, J=6.3, 15.2Hz, 6-H).

16) **16**, white powder, $[\alpha]_D^{24}$ +4.57° (MeOH), IR (KBr) : 3186, 1709, 1688, 1057, 970 cm^{-1}. ^{1}H NMR (CD_3OD) : δ 0.90 (t, J=6.9Hz, 20-CH_3), 1.22-1.58 (m, CH_2 x 8), 1.96-2.04 (m, 8-H_2), 2.27 (dd, J=6.6, 6.6Hz, 5-H_2), 2.44 (t-like, J=*ca.* 7.3Hz, 13, 15-H_2), 3.76 (s, 3-H), 3.82(t, J=6.6Hz, 4-H), 3.83, 3.97 (ABq, J=10.6Hz, 1-H_2), 5.39 (dt, J=6.6, 15.5, 6-H), 5.53 (dt, J=6.6, 15.5, 7-H)

17) **18**, colorless fine crystals, mp 180-182°C, $[\alpha]_D^{24}$ +12.2° (MeOH), $C_{21}H_{39}NO_6$,[9] IR (KBr) : 3387, 1715, 1663, 1046, 727 cm^{-1}. ^{1}H NMR (CD_3OD) : δ 0.90 (t, J=6.6Hz, 20-H_3), 1.21-1.57 (m, CH_2 x 8), 2.01-2.14 (m, 8-H_2), 2.33 (dd, J=7.3, 7.3Hz, 5-H_2), 2.44 (t-like, J=*ca.* 7.3Hz, 13, 15-H_2), 3.78 (s, 3-H), 3.85 (t, J=7.3Hz, 4-H), 3.85, 3.99 (ABq, J=10.9Hz, 1-H_2), 5.36 (dt, J=7.3, 10.9Hz, 6-H), 5.48 (dt, J=7.3, 10.9Hz, 7-H).

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