

SYNTHESES OF NEW IMMUNOSUPPRESSIVE MYRIOCIN ANALOGS, 2-EPI-MYRIOCIN, 14-DEOXYMYRIOCIN, Z-14-DEOXYMYRIOCIN, AND NOR-DEOXYMYRIOCINS : THEIR STRUCTURE-ACTIVITY RELATIONSHIPS

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Eight new myriocin analogs, 2-*epi*-myriocin, Z-14-deoxomyriocin, and nor-deoxomyriocins, and a known myriocin derivative, 14-deoxomyriocin, were synthesized from 2-deoxy-D-glucose *via* common intermediates in previous myriocin and Z-myriocin syntheses. The immunosuppressive activities of new myriocin analogs and Z-myriocin on mouse allogeneic mixed lymphocyte reaction were examined, and, by comparing with those of myriocin and 14-deoxomyriocin, some structure-activity relationships have been found.

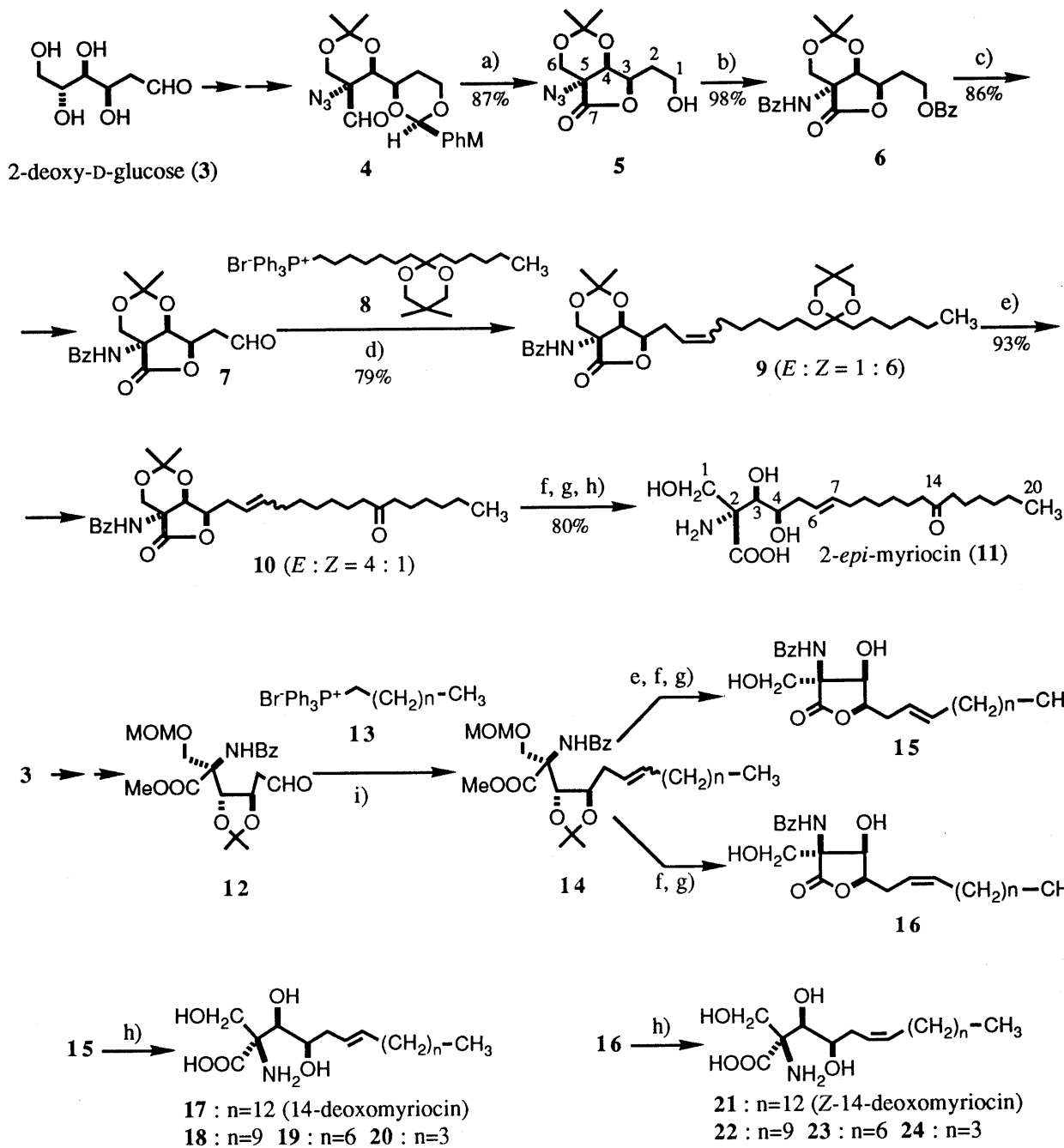
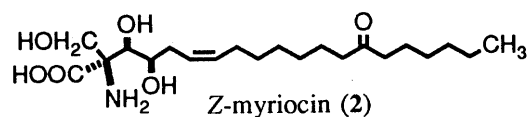
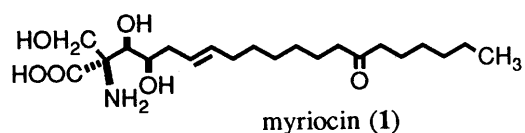
KEYWORDS myriocin; 2-*epi*-myriocin; Z-14-deoxomyriocin; nor-deoxomyriocin; immunosuppressive activity; structure-activity relationship

In the course of our studies on the effective utilization of natural carbohydrates as optically pure starting materials,¹⁾ we have developed a versatile method for synthesizing a novel immunosuppressant, myriocin(1) together with its new analog, Z-myriocin(2).²⁾ This synthetic pathway comprised a stereoselective formation of the chiral α , α -disubstituted amino acid structure in myriocin(1) and Z-myriocin(2) from the isopropylidene ketone, which was prepared from 2-deoxy-D-glucose(3), using a modified Darzen reaction as a key step. Recently, immunosuppressive activity of myriocin(1) was reported to be almost two orders of magnitude more effective than cyclosporin A.³⁾ Furthermore, by comparison of the immunosuppressive activities for myriocin derivatives with that for myriocin(1), some relationships between their structures and activity have been reported, and 14-deoxomyriocin(17) have been found to show 5 to 10-fold more potent immunosuppressive activity than 1.⁴⁾

As our continuing synthetic studies aimed at the development of a new immunosuppressant, we have synthesized new myriocin analogs from carbohydrates.⁵⁾ In this paper, we describe the syntheses of eight new myriocin analogs such as 2-*epi*-myriocin(11), Z-14-deoxomyriocin(21), and nor-deoxomyriocins(18~20, 22~24), and the known myriocin derivative 14-deoxomyriocin(17). In addition, the immunosuppressive activity of those myriocin analogs and Z-myriocin(2) was examined in comparison with those of myriocin(1) and 14-deoxomyriocin(17) in order to investigate the structure-activity relationships.

The synthesis of 2-*epi*-myriocin(11) started with the azido-aldehyde(4), which was the common synthetic intermediate in previous myriocin(1) and Z-myriocin(2) syntheses from 2-deoxy-D-glucose(3).¹⁾ By oxidation of an aldehyde group in 4 with NaClO₂ in the presence of NH₂SO₃H in aq. dioxane and subsequent selective removal of the 1,3-*p*-methoxybenzylidene group with *p*-TsOH·H₂O, the 7, 3-lactone(5)⁶⁾ was obtained. Reduction of an azide group in 5 followed by benzoylation yielded the dibenzoate(6), which was converted to the 1-aldehyde(7) by successive de-*O*-benzoylation with 1% NaOMe-MeOH and PCC oxidation in CH₂Cl₂. Wittig reaction of 7 with the phosphonium salt(8)²⁾ in the presence of *n*-BuLi in *t*-BuOH-THF afforded the geometric mixture(9) (*E* : *Z* = 1 : 6). The photochemical geometrical isomerization reaction of 9 in the presence of diphenyldisulfide proceeded along deketalization at 14-position to provide a geometric mixture(10) (*E* : *Z* = 4 : 1). By the HPLC separation of 10 followed by deprotection and hydrolysis of the lactone ring, 2-*epi*-myriocin(11)⁷⁾ was obtained in 11.0% overall yield from 2-deoxy-D-glucose(3).

Furthermore, 14-deoxomyriocin(17), Z-14-deoxomyriocin(21), and nor-deoxomyriocins(18~20, 22~24) were synthesized from the α , α -disubstituted amino acid derivative(12) which was also the synthetic intermediate of myriocin(1) and Z-myriocin(2).²⁾ Namely, Wittig reaction of 12 with the phosphonium salt(13 : *n*=12) gave the geometric mixture(14 : *n*=12) (*E* : *Z* = 1 : 7) which was subjected to HPLC separation to yield 6*Z*-form product(14 : *n*=12, 74.9%) and 6*E*-form product(14 : *n*=12, 10.7%). Treatment of the 6*Z*-form(14 : *n*=12) with *p*-TsOH·H₂O



a) 1) NaClO₂/NH₂SO₃H/ dioxane-H₂O, 2) *p*-TsOH·H₂O/ MeOH; b) 1) H₂/ 10% Pd-C/ EtOH, 2) BzCl/ Py.; c) 1) 1% NaOMe/ MeOH, 2) PCC/ CH₂Cl₂; d) *n*-BuLi/ *t*-BuOH-THF; e) *hν*/ PhSSPh/ cyclohexane; f) HPLC separation; g) *p*-TsOH·H₂O/ 70% aq. EtOH; h) 1N NaOH
i) *n*-BuLi/ THF

Table I. Suppressive Effects of Myriocin(1) and Its Analogs(2, 11, 17~24) on Mouse Allogeneic Mixed Lymphocyte Reaction

Compounds	IC ₅₀ (μM)
myriocin (1)	0.00929
Z-myriocin (2)	0.00323
2- <i>epi</i> -myriocin (11)	0.00939
14-deoxomyriocin (17)	0.000662
Z-14-deoxomyriocin (21)	0.000457
<i>E</i> -trinor-deoxomyriocin (18)	0.00592
<i>E</i> -hexanor-deoxomyriocin (19)	4.38
<i>E</i> -nonanor-deoxomyriocin (20)	57.9
Z-trinor-deoxomyriocin (22)	0.00907
Z-hexanor-deoxomyriocin (23)	10.2
Z-nonanor-deoxomyriocin (24)	236

afforded the lactone(16 : n=12, 77.4%), which was subjected to alkaline treatment to yield Z-14-deoxomyriocin(21)⁸⁾ in 60.1% yield. Similarly, 14-deoxomyriocin(17)⁴⁾ was efficiently prepared from 15, obtained by successive photochemical geometrical isomerization(*E* : *Z* = 4 : 1) of 14(n=12, *E* : *Z* = 1 : 7), HPLC separation, and deprotection steps. According to a similar procedure from 12 to 17 and 21, various nor-deoxomyriocins(6*E*-form : 18, 19, 20 ; 6*Z*-form : 22, 23, 24) were synthesized from 12 and the phosphonium salts(13 : n=9, 6, 3) via the lactones(15 or 16 ; n=9, 6, 3).

The effects of those synthesized myriocin analogs(11, 17~24) and Z-myriocin(2) on mouse allogeneic mixed lymphocyte reaction were examined in comparison with those of myriocin(1) and 14-deoxomyriocin(17). As shown in Table I, Z-14-deoxomyriocin(21)

showed the most potent suppressive activity on mouse allogeneic mixed lymphocyte reaction, and the following structure-activity relationships were found. 1) Since 2-*epi*-myriocin(11) shows almost as potent immunosuppressive activity as myriocin(1), the stereostructure at 2-position of the amino acid moiety in 1 does not affect the activity. 2) Trinor-deoxomyriocins(18, 22) exhibit potent activity similar to myriocin(1) and Z-myriocin(2), but their activities were less than those of 14-deoxomyriocin(17) and *E*-14-deoxomyriocin(21), respectively, while hexanor- and nonanor-deoxomyriocins(19, 20, 23, 24) show a little activity. Based on this evidence, long carbon chain (n ≥ 9) bonded to the amino acid moiety is essential to the activity. 3) When the activities for myriocin analogs with twenty-membered carbon chains were compared, 6*Z*-isomers have more potent activity than 6*E*-ones. 4) Comparison of the activities for 6*E*-nor-deoxomyriocins(18~20) with those for 6*Z*-nor-deoxomyriocins(22~24) shows that, in the case of the nor-deoxomyriocins, each 6*Z*-isomer has less activity than 6*E*-isomer. We are currently working on the further characterization of structure-activity relationships and detailed investigation of immunosuppressive activity for synthesized myriocin analogs.

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- 6) All new compounds[5~7, 11, 15(n=12, 9, 6, 3), 16(n=12, 9, 6, 3), 18~24] were characterized by physicochemical properties, and full characteristics will be presented in our full paper. The molecular composition of the compounds given the chemical formula was determined by high-resolution FAB-MS measurement.
- 7) 2-*epi*-Myriocin(11), colorless fine crystals, mp 182-184°C, [α]_D +107°(MeOH), C₂₁H₃₉NO₆, IR(KBr) : 3197, 1711, 1671, 1032, 972 cm⁻¹, ¹H NMR(CD₃OD, δ) : 0.90(t, J=6.6, 20-H₃), 2.29(dd, J=6.9, 6.9, 5-H₂), 2.44(t-like, 13, 15-H₂), 3.78, 3.91(ABq, J=11.2, 2-CH₂OH), 3.80(t, J=6.9, 4-H), 4.00(s, 3-H), 5.40(dt, J=6.9, 16.1, 6-H), 5.54(dt, J=6.9, 16.1, 7-H), positive FAB-MS(m/z) : 402(M+H)⁺.
- 8) Z-14-Deoxomyriocin(21), colorless fine crystals, mp 163-165°C, [α]_D -14.9°(MeOH), C₂₁H₄₁NO₅, IR(KBr) : 3431, 1632, 1458, 1387, 1262 cm⁻¹, ¹H NMR(DMSO-d₆, δ) : 0.85(t, J=5.9, 20-H₃), 1.24(22H, br s), 1.99(m, 8-H₂), 2.19(m, 5-H₂), 3.55(t-like, 4-H), 3.56, 3.68(ABq, J=10.8, CH₂OH), 3.60(br s, 3-H), 5.36(2H, m, 6, 7-H), negative FAB-MS(m/z) : 386(M-H)⁻.

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