SYNTHESSES OF NEW IMMunosUPPRESSIVE MYRIOcin ANALOGS, 2-EPi-MYRIOcin, Z-14-DEOxOMYRIOcin, AND NORDEOxOMYRIOcINS: 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 6Z-form product(14 : n=12, 74.9%) and 6E-form product(14 : n=12, 10.7%). Treatment of the 6Z-form(14 : n=12) with p-TsOH-H2O

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2-deoxy-d-glucose (3)

1. \( \text{CHO} \) → 4
   - a) \( \text{CHO} \) → 5
     - b) \( \text{CHO} \) → 6
   - c) \( \text{CHO} \) → 7
   - d) \( \text{CHO} \) → 8
   - e) \( \text{CHO} \) → 9

9 \( (E : Z = 1 : 6) \)

10 \( (E : Z = 4 : 1) \)

13

15

16

17 : n=12 (14-deoxomyriocin)
18 : n=9
19 : n=6
20 : n=3
21 : n=12 (Z-14-deoxomyriocin)
22 : n=9
23 : n=6
24 : n=3

a) 1) NaClO₂ / NH₄SO₄ / dioxane-\( \text{H}_2\text{O} \), 2) TsOH / H₂O / MeOH; b) 1) H₂ / 10\% Pd-C / EtOH, 2) BzCl / Py; c) 1\% NaOMe / MeOH, 2) PCC / CH₂Cl₂; d) n-BuLi / t-BuOH-THF; e) hv/ PhSSPh / cyclohexane; f) HPLC separation; g) p-TsOH / H₂O / 70\% aq. EtOH; h) 1N NaOH

i) n-BuLi / THF
afforded the lactone (16: n=12, 77.4%), which was subjected to alkaline treatment to yield Z-14-deoxymyricin (21)\(^3\) in 60.1% yield. Similarly, 14-deoxymyricin (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-deoxymyricins (6E-form: 18, 19, 20; 6Z-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 myricin analogs (11, 17-24) and Z-myricin (22) on mouse allogeneic mixed lymphocyte reaction were examined in comparison with those of myricin (1) and 14-deoxymyricin (17). As shown in Table 1, Z-14-deoxymyricin (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-myricin (11) shows almost as potent immunosuppressive activity as myricin (1), the stereostructure at 2-position of the amino acid moiety in 1 does not affect the activity. 2) Trinor-deoxymyricins (18, 22) exhibit potent activity similar to myricin (1) and Z-myricin (2), but their activities were less than those of 14-deoxymyricin (17) and E-14-deoxymyricin (21), respectively, while hexanor- and nonanor-deoxymyricins (19, 20, 23, 24) show a little activity. Based on this evidence, long carbon chain (n=29) bonded to the amino acid moiety is essential to the activity. 3) When the activities for myricin analogs with twenty-membered carbon chains were compared, 6Z-isomers have more potent activity than 6E-ones. 4) Comparison of the activities for 6E-nor-deoxymyricins (18-20) with those for 6Z-nor-deoxymyricins (22-24) shows that, in the case of the nor-deoxymyricins, each 6Z-isomer has less activity than 6E-isomer. We are currently working on the further characterization of structure-activity relationships and detailed investigation of immunosuppressive activity for synthesized myricin analogs.

**REFERENCES AND NOTES**


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-Myricin (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-Deoxymyricin (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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