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The Synthesis of Fragment A of an Antibiotic, Nosiheptide †

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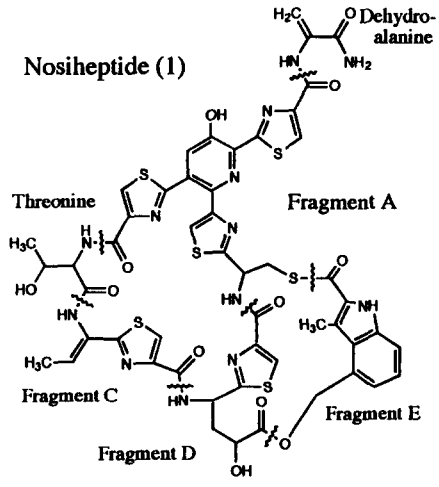
Abstract: Fragment A derivative (13) of nosiheptide, useful for the total synthesis, was obtained by stepwise introduction of the 2,5-bis{(4-ethoxycarbonyl)-2-thiazolyl} groups and 6-{(2-substituted)-4- thiazolyl} group into 3-hydroxy-5-cyanopyridine(3). The total yield was 7.6% via 14 steps. © 1997 Published by Elsevier Science Ltd.

Nosiheptide (1)

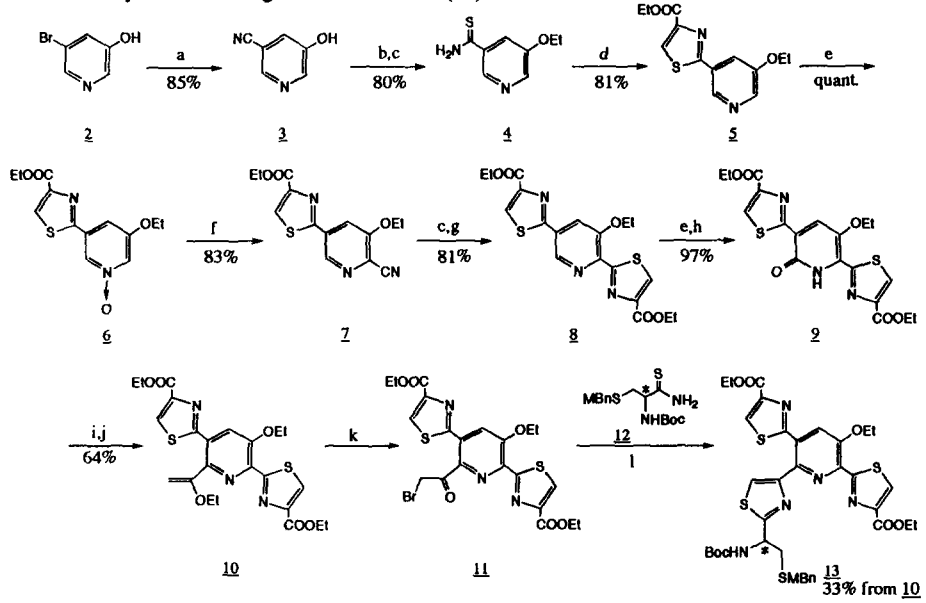


Nosiheptide (1)[1] is a bicyclic peptide antibiotic composed of heterocyclic fragments C, D, E, A, L-threonine, and dehydroalanine, and we have already synthesized fragments C[2], D[3], E[4] and their peptides[5]. Now, we would like to report the synthesis of the central skeleton, fragment A derivative (13). The skeleton includes pyridine and three thiazole rings: 2,5-bis{4-carboxy)-2-thiazolyl}-6-{(2-substituted)-4-thiazolyl}-3-hydroxypyridine. As a similar skeleton, micrococcinic acid[6] of micrococcin P was synthesized by the coupling method of the individual heterocyclic ring system; however, we have used the stepwise procedure as follows (Scheme 1).

† This paper is dedicated to Prof. Dr. Hans Paulsen in honor of his 75th birthday.

Treatment of 5-bromo-3-hydroxypyridine (2)[7] with copper(I) cyanide gave the corresponding 5-cyanide (3), and then the cyano group was converted to the thiazolyl group by the Hantzsch method. Thus, the *O*-ethylation with diethyl sulfate and thioamidation with hydrogen sulfide gave 3-ethoxy-5-pyridylthioamide (4) which was condensed with ethyl bromopyruvate to give 3-ethoxy-5-{(4-ethoxycarbonyl)-4-thiazolyl}pyridine (5). For the introduction of the second thiazolyl group, cyanation with the Reissert method was tried. Oxidation of **5** with m-chloroperbenzoic acid (m-CPBA) gave the corresponding *N*-oxide (6), and then treatment with trimethylsilyl cyanide (TMSCN) gave the corresponding regioisomers in 83% and 9% yields, respectively. Fortunately, the structure of the minor product was proved to be the undesirable 6-cyanide by X-ray analysis (Fig. 1).

Scheme 1. Synthesis of Fragment A derivative (13).



a) CuCN/DMF, b) Et_2SO_4-K_2CO_3/DMF, c) H_2S/Py-Et_3N, d) $BrCH_2COCOOEt$/EtOH, e) m-CPBA/CH_2Cl_2, f) TMSCN-Et_3N/MeCN, g) 1:$BrCH_2COCOOEt$ -K_2CO_3/THF, 2:TFAA-Py/THF, h) Ac_2O, i) Tf_2O-i-$PrNEt_2$/DMAP-CH_2Cl_2, j) CH_2=CHOEt-Pd$(AcO)_2$-dppp-Et_3N/DMF, k) NBS-H_2O/THF, l) EtOH. MBn : *p*-Methoxybenzyl.

Then, 2-cyanide (7) was converted into the 2,5-bisthiazolyl derivative (8), in which the modified Hantzsch method[8] was used for cyclization of the thiazolyl group. For the activation of the 6-position of **8**, the second Reissert method was applied to **8** with m-CPBA and subsequent acetylation with acetic anhydride gave the corresponding pyridone (9) directly. The intermediate, 6-acetate, could be isolated in the reverse order of reactions: **7**→*N*-oxide→6-acetate→2-cyanide →**9**. After activation of **9** as the 6-*O*-triflate, coupling reaction with ethyl vinyl ether[9] in the presence of Pd-catalysts gave the corresponding 6-1-ethoxyvinyl derivative (10), which was

successively converted into bromoacetyl derivative (11) with *N*-bromosuccinimide (NBS) in good yield.

Finally, condensation of **11** with *N*-t-butoxycarbonyl-*S*-*p*-methoxybenzyl-L-cystein thioamide (12), which was derived in a similar pathway with the corresponding *S*-benzyl derivative[10], gave fragment A derivative, 3-ethoxy-2,5-bis(4-ethoxycarbonylthiazolyl-2)-6-{2-(1*S*-t-butoxycarbonylamino-2-*p*-methoxybenzylthio)ethylthiazolyl-4}pyridine (13)[11].

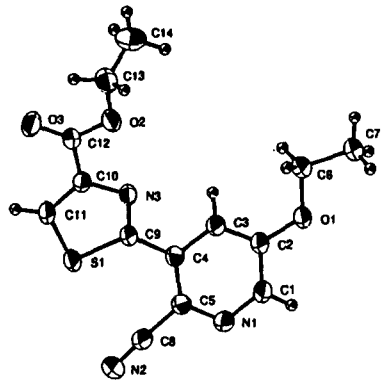


Fig. 1. ORTEP drawing of the molecular structure of 6-isomer of 7.

Although fragment A obtained by acid hydrolysis of the authentic nosiheptide was the corresponding 6-{(2-acetyl)-4-thiazolyl} pyridine, **13** synthesized in the present work is a valuable building block for the total synthesis of nosiheptide.

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References and Notes

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11. All new products in this study gave satisfactory analytical results, and data are as follows. **5**; mp. 68-69°C; MS(EI): *m/z* 277 (M-1)$^+$; ^{1}H-NMR ($CDCl_3$): δ 1.45(t, 3H, J =7.2Hz, ester-CH_3), 1.47(t, 3H, J =7.0Hz, ether-CH_3), 4.18(q, 2H, J =7.0Hz, ether-CH_2), 4.43(q, 2H, J =7.2Hz, ester-CH_2), 7.86(dd, 1H, J =2.0, 2.5Hz, Py-4), 8.22(s, 1H, Th-5), 8.38(d, 1H, J =2.5Hz, Py-6), 8.73(d, 1H, J =2.0Hz, Py-2). **6**; mp. 123.5-125.5°C; MS(EI): *m/z* 293 (M-1)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.44(t, 3H, J =7.2Hz, ester-CH_3), 1.47(t, 3H, J =6.9Hz, ether-CH_3), 4.15(q, 2H, J =6.9Hz, ether-CH_2), 4.46(q, 2H, J =7.2Hz, ester-CH_2), 7.51(dd, 1H, J =1.5, 2.0Hz, Py-4), 8.00(dd, 1H, J =1.5, 2.0Hz, Py-6), 8.26(s, 1H, Th-5), 8.47(t, 1H, J =1.5Hz, Py-2). **7**; mp. 158-159°C; MS(EI): *m/z* 302(M-1)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.45(t, 3H, J =7.2Hz, ester-CH_3), 1.56(t, 3H, J =7.0Hz, ether-CH_3), 4.33(q, 2H, J =7.0Hz, ether-CH_2), 4.48(q, 2H, J =7.2Hz, ester-CH_2), 8.04(d, 1H, J =1.7Hz, Py-4), 8.33(s, 1H, Th-5), 8.74(d, 1H, J =1.7Hz, Py-6). **6-isomer of 7**; mp.159-160.5°C; MS(EI): *m/z* 302(M-1)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.49(t, 3H, J =7.2Hz, ester-CH_3), 1.55(t, 3H, J =6.9Hz, ether-CH_3), 4.26(q, 2H, J =6.9Hz, ether-CH_2), 4.48(q, 2H, J =7.2Hz, ester-CH_2), 7.99(d, 1H, J =2.5Hz, Py-4), 8.39(s, 1H, Th-5), 8.43(d, 1H, J =2.5Hz, Py-6). **8**; mp. 167-168°C; MS(EI): *m/z* 432(M-2)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.45(t, 6H, J =6.9Hz, ester-CH_3), 1.67(t, 3H, J =6.9Hz, ether-CH_3), 4.39-4.51(m, 6H, CH_2×3), 8.11(d, 1H, J =1.5Hz, Py-4), 8.28(s, 1H, Th-5), 8.36(s, 1H, Th-5), 8.84(d, 1H, J =1.5Hz, Py-6). **9**; mp.229-231°C; MS(EI): *m/z* 448(M-2)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.45(t, 6H, J =7.2Hz, ester-CH_3×2), 1.59(t, 3H, J =6.9Hz, ether-CH_3), 4.38-4.49(m, 6H, CH_2×3), 8.30, 8.33(each s, 1H, Th-5×2), 8.72(s, 1H, Py-4), 10.56(br s, 1H, NH). **10**; sirup; MS(EI): *m/z* 502(M-2)$^+$; ^{1}H-NMR($CDCl_3$): δ 1.10(t, 3H, J=6.9Hz, ethoxyvinyl CH_3), 1.44(t, 6H, J=6.9Hz, ester-CH_3×2), 1.64(t, 3H, J =6.9Hz, ether-CH_3), 3.81(q, 2H, J =6.9Hz, ethoxyvinyl CH_2), 4.43-4.51(m, 7H, CH_2×3 + vinyl CH), 4.88(d, 1H, J =2.0Hz, vinyl CH), 7.94(s, 1H, Py-4), 8.30, 8.33(each s, 1H, Th-5×2). **11**; ^{1}H-NMR($CDCl_3$): δ 1.45(t, 6H, J =7.0Hz, ester-CH_3×2), 1.67(t, 3H, J =6.9Hz, ether-CH_3), 4.33-4.51(m, 6H, CH_2×3), 4.93(s, 2H, $BrCH_2$), 7.84(s, 1H, Py-4), 8.36, 8.37(each s, 1H, Th-5×2). **12**; sirup; $[\alpha]_D$-11.4° (*c* 1.0, MeOH); ^{1}H-NMR($CDCl_3$): δ 1.45(s, 9H, t-Bu), 2.84-2.99(m, 2H, SCH_2), 3.74(s, 2H, $PhCH_2$), 3.80(s, 3H, OCH_3), 4.47(q, 1H, J=7.0Hz, CH), 5.41(br d, 1H, NH), 6.85(d, 2H, J =6.5Hz, Ph-3,5), 7.27(d, 2H, J=6.5Hz, Ph-2,6), 7.52(br s, 1H, NH), 7.68(br s, 1H, NH). **13**; sirup; $[\alpha]_D$-13.9° (*c* 1.05, MeOH); ^{1}H-NMR($CDCl_3$): δ 1.42(t, 6H, J =6.9Hz, ester-CH_3×2), 1.47(s, 9H, t-Bu), 1.67(t, 3H, J =6.9Hz, ether-CH_3), 2.72-2.89(m, 2H, SCH_2), 3.61(s, 2H, $PhCH_2$), 3.79(s, 3H, OCH_3), 4.35-4.49(m, 6H, CH_2 ×3), 5.08(m,1H, CH), 5.39(br d, 1H, J =7.9Hz, NH), 6.83(d, 2H, J =8.7Hz, Ph-3,5), 7.85(d, 2H, J =8.7Hz, Ph-2,6), 7.85(s, 1H, Th-5), 7.91(s, 1H, Py-4), 8.17, 8.33(each s, 1H, Th-5×2).

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