Synthesis of the Central Heterocyclic Skeleton of an Antibiotic, A10255

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The central heterocyclic skeleton (**13**) of an antibiotic, A10255, was synthesized by stepwise introduction of two groups into the 2,6-positions of 3-{(4-ethoxycarbonyl)-2-thiazolyl}-pyridine, *via* 17 steps in 4.8% total yield.

In addition to the thiopeptide antibiotics[1] including heterocycles such as pyridine, thiazole, indole rings, a new group comprising an oxazole ring such as berninamycin A,[2] sulfomycin I,[3] thioxamycin,[4] A10255 (**1**)[5] (Fig. 1) has been found in recent years. They exhibit strong inhibitory activity against gram-positive bacteria. For the total synthesis of A10255, we have already synthesized dehydopentapeptide in the ring structure,[6] and here, we would like to report the synthesis of the central skeleton common in the latter group of antibiotics, and useful for a total synthesis; 2-{2-(1-benzyloxycarbonylaminovinyl)-4-oxazolyl}-3-{(4-ethoxycarbonyl)-2-thiazolyl}pyridine-6-ethylcarbonate (**13**) from 3-{(4-ethoxycarbonyl)-2-thiazolyl}pyridine (**2**).[7]

As a similar compound, dimethylsulfomycinamate obtained by acidic methanolysis of sulfomycin I, which has a 2-{(2-acetyl)-4-oxazolyl} group in **13**, was synthesized from 5-hydroxy-2-methylpyridine *via* the final cross-coupling of the corresponding thiazole ring at the 3-position of the pyridine ring.[8] However, it's ambiguous that whether the cross-coupling method is applicable to a compound having an unstable substituents or not. We now describe a certain synthesis by using the stepwise procedure.

For introduction of the 2- and 6-substituents, the Reissert method was used. Thus, the oxidation of **2** with *m*-chloroperbenzoic acid (*m*-CPBA) gave the corresponding *N*-oxide (**3**), and then treatment of **3** with trimethylsilyl cyanide (TMSCN) gave the corresponding 6-cyanide (**4**), 4- and 2-isomers, in 62%, 15% and 19% yield, respectively. The cyano group of **4** was converted to an ethoxycarbonyl group (**5**) by successive treatment with sodium hydroxide in aqueous methanol and diethyl sulfate in DMF. By the use of the Reissert method again, the 2-hydroxyl group (**6**) was introduced into **5**, and after activation as the triflate, coupling reaction with vinyltributyltin gave the corresponding 2-vinyl derivative (**7**) successfully.

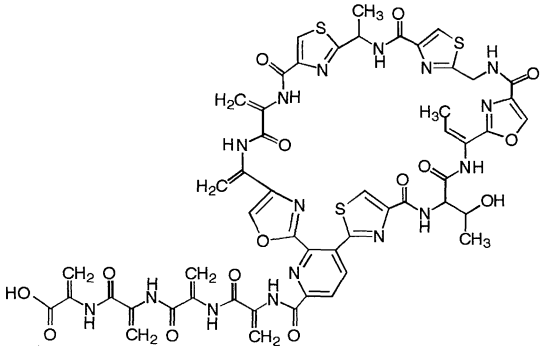
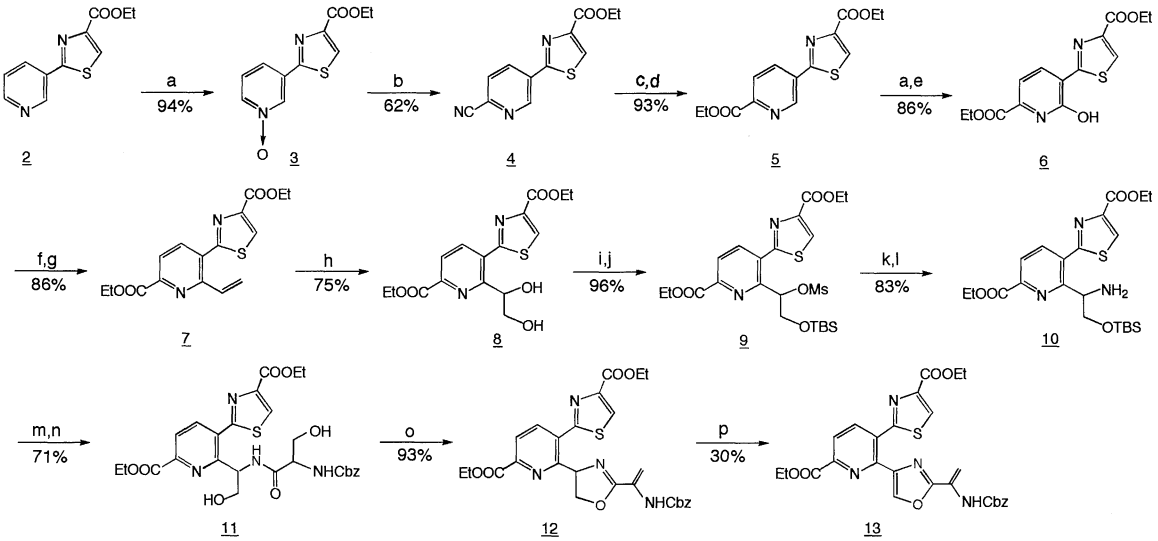


Figure 1. Structure of A10255G (1).

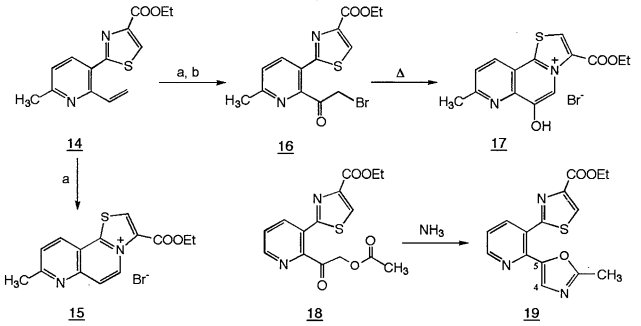
On the other hand, previous examinations of the conversion of a vinyl group into the 4-oxazolyl group indicated that the method applicable in our system is restricted. For example, treatment of newly synthesized 3-{(4-ethoxycarbonyl)-2-thiazol-



Reagents : a) m-CPBA/CH_2Cl_2, b) TMSCN/Et_3N-CH_3CN, c) H_2O-EtOH/NaOH, d) Et_2SO_4/DMF, e) 1. Ac_2O 2. NaOEt, f) Tf_2O, Et_3N-DMAP/CH_2Cl_2, g) CH_2=$CHSnBu_3$, LiCl, $(PPh_3)_4Pd$/THF, h) $KMnO_4$, $MgSO_4/H_2O$, i) TBSCl, Et_3N-DMAP/CH_2Cl_2, j) MsCl, DMAP/CH_2Cl_2, k) NaN_3/DMF, l) Pd-C,H_2/EtOH, m) *N*-Cbz-Serine, BOP/CH_3CN, n) AcOH-H_2O, o) Burgess reagent, p) NiO_2/Benzene.

Scheme 1. Synthesis of **13**.

yl}-6-methyl-2-vinylpyridine (**14**) with *N*-bromosuccinimide (NBS) at room temperature gave directly an intramolecular ring-closed compound (**15**). The intermediate bromohydrin could be actually isolated in the reaction at 0 °C, and it was further converted to the bromoacetyl derivative (**16**); however, oxazole ring formation with acetamide gave again a similar ring-closed product (**17**). An analogous compound was obtained by the interaction of nitrogen of the thiazole ring with a neighboring diazoacetyl group.[9] These facts indicated that the neighboring-group participation of nitrogen in the thiazole ring is unavoidable, when an halogenoacetyl intermediate is formed. Another attempted cyclization of the 2-acetoxyacetyl function of (**18**) with ammonia gave the rearranged 5-oxazolyl derivative (**19**), instead of the expected 4-oxazolyl derivative, as was reported by Yamamura *et al.*[10]



a) NBS-H_2O/DMSO (rt or 0 °C), b) MnO_2/Benzene.

Scheme 2. Unusual reaction in the formation of the oxazole ring.

Therefore, we selected another path way *via* an oxazoline derivative (**12**). Thus, oxidation of the vinyl group of **7** with $KMnO_4$ gave the corresponding diol (**8**), and the primary hydroxyl group was tentatively protected with a *t*-butyldimethylsilyl (TBS) group. Then, the secondary hydroxyl group was converted into an amino group *via* *O*-mesylation (**9**), azidation and reduction (**10**). Deprotection of the TBS group and condensation of the amino alcohol intermediate with *N*-benzyloxycarbonyl-L-serine (*N*-Cbz-serine) gave the corresponding amide (**11**). Treatment of **11** with the Burgess reagent[11] gave the corresponding oxazoline derivative (**12**) which was successfully oxidized to give 2-{2-(1-benzyloxycarbonylaminovinyl)-4-oxazolyl}-3-{(4-ethoxycarbonyl)-2-thiazolyl}pyridine-6-ethylcarbonate (**13**),[12] though the yield was not high.[13] The overall yield was modest ca. 4.8% in 17 steps; however, this work has opened a way to the total synthesis of A10255.

References and Notes

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13 All new products in this study gave satisfactory analytical results, and the data are as follows. **3**: mp 138-139 °C; MS (EI) *m/z*=250 $(M)^+$; ^{1}H NMR ($CDCl_3$/TMS): δ=1.44 (t, 3H, *J*=7.2Hz, CH_3), 4.46 (q, 2H, *J*=7.2Hz, CH_2O), 7.44 (dd, 1H, *J*=6.5, 8.1Hz, Py-5), 7.89 (d, 1H, *J*=8.1Hz, Py-4), 8.30 (d, 1H, *J*=6.5Hz, Py-6), 8.33 (s, 1H, Th-5), 8.88 (s, 1H, Py-2). **4**: mp 162.5-163.5 °C; MS (EI) *m/z*=258 $(M-1)^+$; ^{1}H NMR ($CDCl_3$): δ=1.45 (t, 3H, *J*=7.2Hz, CH_3), 4.48 (q, 2H, *J*=7.2Hz, CH_2O), 7.83 (d, 1H, *J*=7.8Hz, Py-5), 8.33 (s, 1H, Th-5), 8.50 (dd, 1H, *J*=1.9, 7.8Hz, Py-4), 9.30 (d, 1H, *J*=1.9Hz, Py-2). **5**: mp 122-123 °C; MS (EI) *m/z*=305 $(M-1)^+$; ^{1}H NMR ($CDCl_3$): δ=1.47, 1.50 (each t, 3H, *J*=7.2Hz, $CH_3\times2$), 4.51 (m, 4H, $CH_2O\times2$), 8.24 (d, 1H, *J*=8.6Hz, Py-5), 8.31 (s, 1H, Th-5), 8.51 (dd, 1H, *J*=2.4, 8.6Hz, Py-4), 9.29 (d, 1H, *J*=2.4Hz, Py-2). **6**: mp 187.5-188.5 °C; MS (EI) *m/z*=321 $(M-1)^+$; ^{1}H NMR ($CDCl_3$): δ=1.45 (m, 6H, $CH_3\times2$), 4.48 (m, 4H, $CH_2O\times2$), 7.21 (d, 1H, *J*=7.6Hz, Py-5), 8.33 (s, 1H, Th-5), 8.82 (d, 1H, *J*=7.6Hz, Py-4), 10.92 (br-s, 1H, OH). **7**: syrup; MS (EI) *m/z*=330 $(M-2)^+$; ^{1}H NMR ($CDCl_3$): δ=1.45 (m, 6H, $CH_3\times2$), 4.50 (m, 4H, $CH_2O\times2$), 5.69 (dd, 1H, *J*=1.6, 10.8Hz, vinyl), 6.68 (dd, 1H, *J*=1.6, 16.7Hz, vinyl), 7.42 (dd, 1H, *J*=10.8, 16.7Hz, vinyl), 8.07 (d, 1H, *J*=8.1Hz, Py-5), 8.17 (d, 1H, *J*=8.1Hz, Py-4), 8.38 (s, 1H, Th-5). **8**: mp 131-132 °C; MS (EI) *m/z*=366 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=1.45 (m, 6H, $CH_3\times2$), 4.01 (t, 1H, *J*=4.3Hz, C_2-OH), 4.07 (m, 2H, C_2-H×2), 4.45 (m, 4H, $CH_2O\times2$), 5.24 (d, 1H, *J*=7.6Hz, C_1-OH), 5.33 (m, 1H, C_1-H), 8.18 (d, 1H, *J*=8.6Hz, Py-5), 8.21 (d, 1H, *J*=8.6Hz, Py-4), 8.37 (s, 1H, Th-5). **9**: syrup; MS (EI) *m/z*=558 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=0.03 (s, 6H, Si-$CH_3\times2$), 0.78 (s, 9H, *t*-Bu), 1.47 (m, 6H, $CH_3\times2$), 3.20 (s, 3H, Ms), 4.34 (m, 2H, C_2-H×2), 4.53 (m, 4H, $CH_2O\times2$), 6.55 (m, 1H, C_1-H), 8.10 (d, 1H, *J*=8.4Hz, Py-5), 8.20 (d, 1H, *J*=8.4Hz, Py-4), 8.40 (s, 1H, Th-5). **10**: syrup; MS (EI) *m/z*=479 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=0.00 (s, 6H, Si-$CH_3\times2$), 0.82 (s, 9H, *t*-Bu), 1.44 (m, 6H, $CH_3\times2$), 3.01 (br-s, 2H, NH_2), 3.90, 3.97 (each dd, 2H, *J*=5.4, 10.8Hz, C_2-H), 4.46 (m, 4H, $CH_2O\times2$), 5.69 (m, 1H, C_1-H), 8.09 (s, 2H, Py-4,5), 8.33 (s, 1H, Th-5). **11**: syrup; MS (EI) *m/z*=585 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=1.40, 1.43 (each t, 3H, *J*=7.0 and 7.2Hz, $CH_3\times2$), 2.26 (br-s, 1H, OH), 3.74 (m, 1H, CH-serine), 3.89 (br-s, 1H, OH), 4.01 (m, 2H, CH_2-serine), 4.42 (m, 6H, $CH_2O\times2$, C_2-H×2), 5.30 (s, 2H, CH_2-Cbz), 5.92 (m, 1H, C_1-H), 6.03 (d, 1H, *J*=7.8Hz, NH), 7.32 (s, 5H, Ph-Cbz), 7.88 (d, 1H, *J*=8.6Hz, NH-serine), 8.04 (d, 1H, *J*=9.6Hz, Py-5), 8.11 (d, 1H, *J*=9.6Hz, Py-4), 8.34 (s, 1H, Th-5). **12**: mp 140-143 °C; MS (EI) *m/z*=550 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=1.42 (m, 6H, $CH_3\times2$), 4.44 (m, 4H, $CH_2O\times2$), 4.86 (dd, 1H, *J*=8.4, *J*=9.1Hz, Oxa-5a), 5.06 (dd, 1H, *J*=7.8, *J*=9.1Hz, Oxa-5b), 5.12 (s, 2H, CH_2-Cbz), 5.52 (s, 1H, vinyl), 6.05 (dd, 1H, *J*=7.8, *J*=8.4Hz, Oxa-4), 6.11 (s, 1H, vinyl), 7.32 (m, 6H, NH, Ph-Cbz), 8.11 (s, 2H, Py-4,5), 8.30 (s, 1H, Th-5). **13**: syrup.; MS (EI) *m/z*=548 $(M)^+$; ^{1}H NMR ($CDCl_3$): δ=1.38, 1.47 (each t, 3H, *J*=7.0Hz, $CH_3\times2$), 4.42, 4.51 (eachq, 2H, *J*=7.0Hz, $CH_2O\times2$), 5.17 (s, 2H, $PhCH_2$), 5.57 (s, 1H, vinyl), 6.08 (s, 1H, vinyl), 7.15 (br-s, 1H, NH), 7.36 (s, 5H, Ph), 8.14 (s, 1H, Oxa-5), 8.17 (d, 1H, *J*=7.8Hz, Py-4), 8.23 (d, 1H, *J*=7.8Hz, Py-5), 8.27 (s, 1H, Th-5).