SUMMARY OF Ph.D. DISSERTATION

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Title

Total Synthesis of Siomycin A, a Representative of the Thiostrepton Family of Peptide Antibiotics

Abstract

In 1955, thiostrepton was isolated from the culture broth of *Streptomyces azureus* by the Squibb group. Other structurally related antibiotics, the siomycins, the thiopeptins, Sch 18640, and Sch 40832, were also isolated. The characteristic structure of this thiostrepton family of peptide antibiotics is the bicyclic structure containing a tetrasubstituted dehydropiperidine and/or piperidine moiety, a tetrasubstituted dihydroquinoline moiety, four thiazole moieties, a thiazoline moiety, dehydroamino acid moieties, and a dihydroxyisoleucine moiety. These antibiotics show high activities against Gram-positive bacteria, mycobacteria, and human malaria parasite. Also these antibiotics show immunosuppressive properties. Siomycin A was selected as a synthetic target and divided into the five segments, segments A, B, C, D, and E. The coupling of these five segments and the two cyclization reactions finished the total synthesis of siomycin A.

The segment A (the dehydropiperidine portion) was synthesized featuring the coupling between the azomethine ylide and the enantiopure sulfinimine, the subsequent stereoselective reduction of the 6-membered imine, and the regioselective dehydrogenation of the piperidin ring.

The segment B (the pentapeptide portion), containing the dihydroxyisoleucine, thiazoline, and dehydroamino acid, was synthesized featuring the β-lactone opening by phenylselenylation, the vinylzinc addition to the chiral sulfinimine, the Wipf oxazoline–thiazoline conversion method, and the oxidative *syn*-elimination of the phenylseleno group.

The segment C (the dihydroquioline portion) was synthesized featuring the modified Reissert–Henze reaction, the homolytic heteroaromatic substitution reaction, the one-pot olefination via the new Matsumura–Boekelheide rearrangement using trifluoromethanesulfonic anhydride and triethylamine, the Katsuki asymmetric epoxidation, the stereoselective addition reaction controlled by the stereocenter of the peri-position, and the regioselective opening of the epoxide function with the L-valine derivertive using catalytic $Yb(OTf)_3$.

The segments D and E (the dehydropeptide portions) was synthesized from two phenylselenoalanines.

The consecutive coupling of the segments A, C, and D followed by cyclization between the segments A and D afforded the monocyclic core portion (A–C–D) of siomycin A. Finally the total synthesis of siomycin A was achieved by the coupling of this portion and the segment B, followed by the one-pot regioselective cyclization of the resulting coupling product and amidation of the segment E onto the cyclization product.