New Regioselective Total Syntheses of Antibiotic Renierol, Renierol Acetate, and Renierol Propionate from the 5-Oxygenated Isoquinoline

Nagako KUWABARA, Hiroyuki HAYASHI, Noriko HIRAMATSU, Tominari CHOSHI, Eiichi SUGINO, and Satoshi HIBINO*

Graduate School of Pharmacy and Pharmaceutical Sciences, Faculty of Pharmacy and Pharmaceutical Sciences, Fukuyama University, Fukuyama, Hiroshima 729–0292, Japan.

Received September 20, 1999; accepted October, 25,1999

New total syntheses of renierol (3), renierol acetate (4), and renierol propionate (5) were completed by the synthesis of 5-oxygenated isoquinoline (6) based on the thermal electrocyclic reaction of the 1-azahexatriene system followed by regioselective oxidations of 5-hydroxyisoquinolines (6).

Key words renierol; renierol acetate; renierol propionate; regioselective synthesis; electrocyclic reaction; 5-oxygenated isoquinoline

During the past two decades, several naturally occurring 5,8-isooquinolinequinones have been isolated from marine sponges and from Actinomycetes. In 1979, Faulkner and co-workers reported the isolation and structural determination of renierone (1) and 7-methoxy-1,6-dimethylisoquinoline-5,8-dione (2), along with N-formyl-1,2-dihydrorenierone, from the marine sponge Reniera sp. Subsequently, McKee and Ireland isolated renierol (3) from the hard blue sponge Xestospongia caycedoi. In addition, new isooquinolinequinone metabolites, renierol acetate (4) and renierol propionate (5), together with N-formyl-1,2-dihydrorenierone esters, have recently been isolated from the marine sponge Xestospongia sp. and its associated nudibranch Jorunna funebris.

Synthetic studies of these antibiotics have been conducted by four groups. Total synthesis of renierone (1) was completed by both Danishefskys and Kubo. 7-Methoxy-1,6-dimethylisoquinoline-5,8-dione (2) was synthesized by Kubo, Liebskind, and Molina. In addition, total synthesis of renierol (3), renierol acetate (4), and renierol propionate (5) was reported by Kubo and co-workers. Recently, the Molina group also reported a formal synthesis of renierol (3) in conjunction with the synthesis of 2. Among the efforts by these groups, two regioselective syntheses of the isoquinolone-5,8-dione have been established by the oxidation of an 8-aminoisoquinoline derivative with potassium nitrosodisulfonate (Fremy’s salt) (Kubo group) and by oxidative demethylation of a 5,7,8-trimethoxyisoquinoline derivative with Ag2O (Liebskind group). However, it is difficult to find the regioselectivity of oxidative demethylation from the 5,7,8-trimethoxyisoquinoline to either the isoquinoline-5,8-dione or isoquinoline-7,8-dione in literatures.

We are currently interested in the synthetic development of biologically active, condensed heterocyclic compounds, including natural products based on the thermal electrocyclic reaction of either hexatriene or azahexatriene systems incorporating one double bond of the aromatic or heteroaromatic portion. In 1988–1989, we reported studies on the synthesis of simple isoquinolines and the total synthesis of aaptamine using the thermal electrocyclic reaction of 1-azahexatriene systems involving the benzene 1,2-bond. We wish to report new accesses to the highly substituted 5-oxygenated isoquinoline based on the thermal electrocyclic reaction of the 1-azahexatriene system, and the total syntheses of renierol, renierol acetate, and renierol propionate by regioselective oxidations.

Based on previous researchers’ results and our synthetic studies, we envisaged the synthesis of 5-hydroxy-1-hydroxy (or acyloxy)methylisoquinoline (6) as an efficient substrate for a new regioselective oxidation of the isoquinoline-5,8-dione antibiotics (1—5) based on a retrosynthetic analysis (Chart 1). The required substrate would be obtained by application of our methodology. For the preparation of a ketoxime (7), that is, a 1-azahexatriene system, we began with 2,4-dimethoxy-3-methylbenzaldehyde (8) and proceeded as follows. 2,4-Dimethoxy-3-methylbenzaldehyde (8) was treated with boron tribromide to produce the 2-hydroxybenzaldehyde (9) (83%), which was converted into the benzyl ether (10) (99%). The benzyl ether (10) was subjected to the Baeyer-Villiger reaction with m-chloroperoxybenzoic acid to give the phenol (11) (88%). The phenol (11) was subjected to the Duff reaction with hexamethylenetetramine in acetic acid, followed by treatment with trifluoromethanesulfonic anhydride to yield the trflate (13) (43% from 11). The cross-coupling reaction of 13 with vinyl tributyltin in the presence of palladium dichlorobis(triphenylphosphine) gave the o-ethylbenzaldehyde (14) (90%). The Grignard reaction of 14 with dimethylpropoxyxilylmagnesium chloride followed by treatment with potassium fluoride and 30% hydrogen peroxide, afforded the 1,2-diol (15) (87%). Selective protection of the 1,2-diol with tert-butyldimethylsilyl chloride (TBDMSI) produced the TBDMS ether (16) (92%), which was oxidized with pyridinium chlorochromate (PCC) to obtain the ketone (17). Subsequent treatment of the ketone with hydroxylamine afforded the ketoxime (18) as the 1-azahexatriene system (57%), which was subjected to the

![Chart 1](attachment:image.png)

* To whom correspondence should be addressed. © 1999 Pharmaceutical Society of Japan
thermal electrocyclic reaction\(^\text{10,11}\) in o-dichlorobenzene at 180 °C to furnish the desired 5-benzyloxyisoquinoline (19) (42%). Although it was found that the electrocyclic reaction of the highly substituted benzene (18) also proceeded, the yield of isoquinoline (19) was only marginally better than that of the simple o-alkenyl benzaldoxime (Chart 2).\(^\text{11a}\)

Deprotection of the TBDMS group of 19 was carried out by tetrabutylammonium fluoride (TBAF) to give the isoquinoline derivative (20) (89%) with the appropriate substituents. Subsequently, 1-hydroxymethylisoquinoline (20) was converted into the esters (22, 83% and 23, 80%) by treatment of the alcohol (20) with phenyl lithium and the corre-
sponding acid anhydride. Subsequent reductive cleavage of the benzyl ether (20, 22, and 23) with 10% Pd-C/H₂, gave the three 5-hydroxyisoquinolines (21, 24, and 25) as precursors of natural products in excellent yields (Chart 3).

Finally, regioselective oxidation of 5-hydroxyisoquinolines (21, 24, and 25) to isoquinoline-5,8-diones (3, 4, and 5) was examined by either cerium ammonium nitrate (CAN) [14] or N₃N-bis(salicylidene)ethylenediaminocobalt(II) (salcomine) [15] and oxygen. The oxidation of 21, 24, and 25 with CAN in an aqueous acetonitrile afforded the corresponding quinones in 52%, 91%, and 90% yields, respectively. On the other hand, the oxidation of 21, 24, and 25 with salcomine and oxygen in DMF gave the same quinones (3, 4, and 5) without any other products in 78%, 96%, and 97% yields (Chart 3). The spectroscopic evidence of these synthetic isoquinoline-5,8-diones (3, 4, and 5) was identical to that of reported data for the synthetic [6] and natural products. [3,4]

Thus the novel 5-oxygenated isoquinoline (19) could be synthesized by the thermal electrocyclic reaction of a 1-azaheptatriene system involving the benzene 1,2-bond. Further, the total syntheses of renierol (3), renierol acetate (4), and renierol propionate (5) were newly established by regioselective oxidation. It was demonstrated that the 5-hydroxyisoquinolines are novel efficient substrates for the regioselective total synthesis of isoquinoline-5,8-dione antibiotics.

Acknowledgment We wish to thank Professor A. Kubo for providing useful information concerning his synthetic work and natural products. This work was partly supported by a Grant-in-Aid for Encouragement of Young Scientists (No. 08772046 to T. Choshi) from the Ministry of Education, Science, Culture and Sport of Japan.

References and Notes