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

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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-isoquinolinequinones have been isolated from marine sponges and from *Actinomycetes*.[1] In 1979, Faulkner and co-workers[2] 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[3] isolated renierol (**3**) from the hard blue sponge *Xestospongia caycedoi*. In addition, new isoquinolinequinone metabolites, renierol acetate (**4**) and renierol propionate (**5**), together with *N*-formyl-1,2-dihydrorenierol esters, have recently been isolated from the marine sponge *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*.[4]

Synthetic studies of these antibiotics have been conducted by four groups. Total synthesis of renierone (**1**) was completed by both Danishefsky[5] and Kubo.[6a,c] 7-Methoxy-1,6-dimethylisoquinoline-5,8-dione (**2**) was synthesized by Kubo,[6a,c] Liebskind,[7] and Molina.[8] In addition, total synthesis of renierol (**3**), renierol acetate (**4**), and renierol propionate (**5**) was reported by Kubo and co-workers.[6a,c,d] Recently, the Molina group[8] 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)[6] and by oxidative demethylation of a 5,7,8-trimethoxyisoquinoline derivative with Ag_2O (Liebskind group).[7] 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.[5,6,8]

We are currently interested in the synthetic development of biologically active, condensed heterocyclic compounds, including natural products based on the thermal electrocyclic reaction[9] of either hexatriene[9,10a] or azahexatriene systems[9—11] incorporating one double bond of the aromatic or heteroaromatic portion. In 1988—1989, we reported studies on the synthesis of simple isoquinolines[11a] and the total synthesis of aaptamine[11b] using the thermal electrocyclic reaction of 1-azahexatriene systems involving the benzene 1,2-bond. We wish to report new access to the highly substituted 5-oxygenated isoquinoline based on the thermal electrocyclic reaction of the 1-azahexatriene system, and the total syntheses of renierol (**3**), renierol acetate (**4**), and renierol propionate (**5**) 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**)[12] 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 benzaldehyde (**10**) was subjected to the Baeyer-Villiger reaction with *m*-chloroperbenzoic 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 triflate (**13**) (43% from **11**). The cross-coupling reaction of **13** with vinyl tributyltin in the presence of palladium dichlorobistriphenylphosphine gave the *o*-ethenylbenzaldehyde (**14**) (90%). The Grignard reaction of **14** with dimethylisopropyloxysilylmethylmagnesium chloride,[13] 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 (TBDMSCl) 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

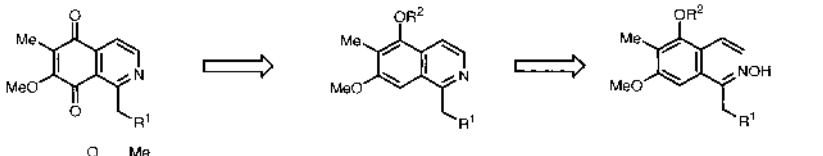

Chart 1

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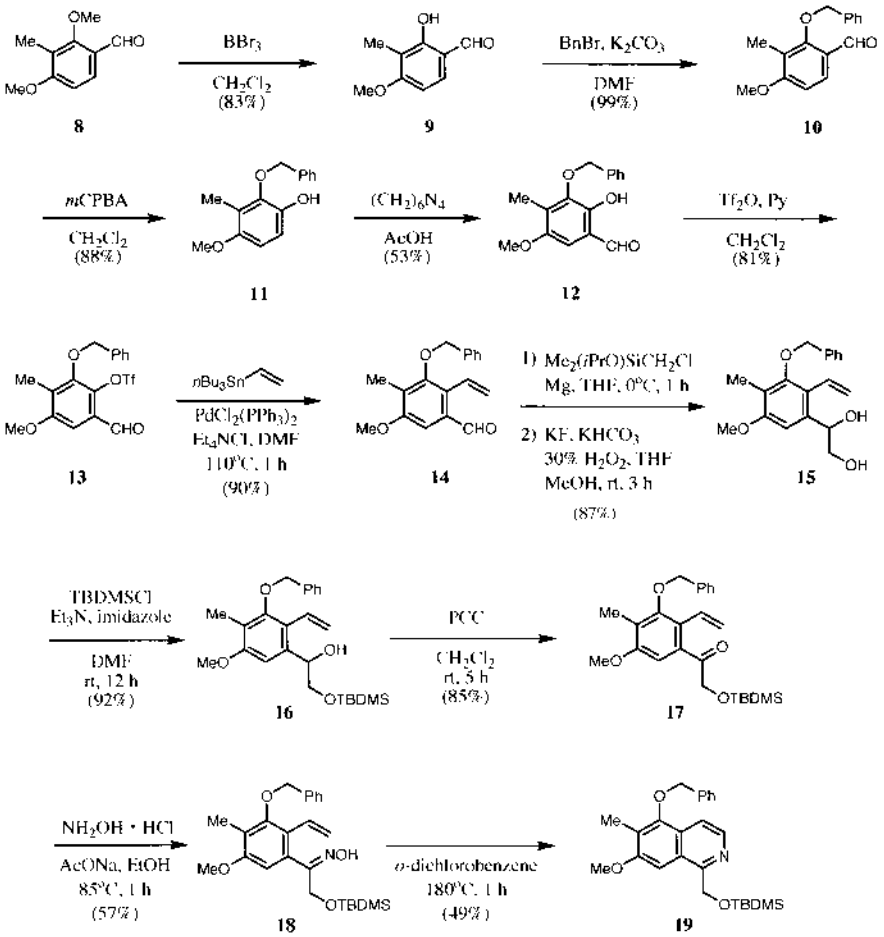

Chart 2

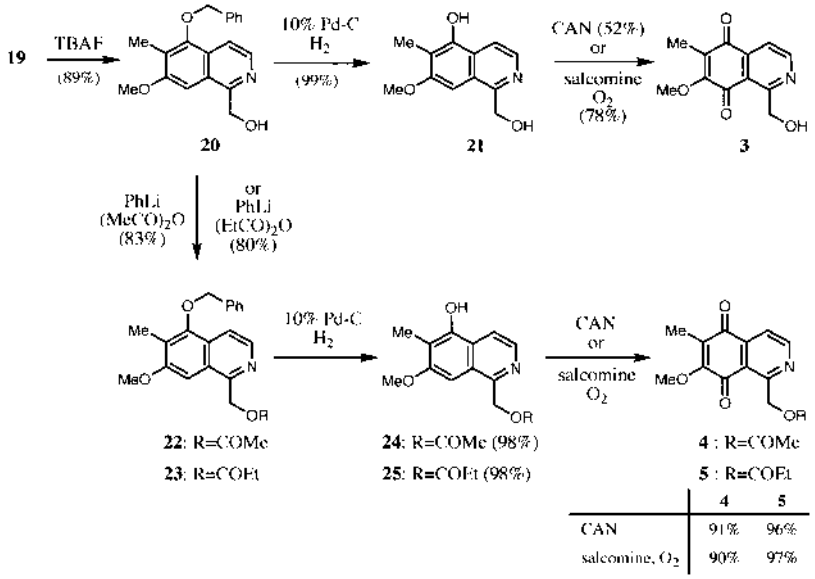

Chart 3

thermal electrocyclic reaction[10b,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).[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/H_2 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 *N*,*N*-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-azahexatriene 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.

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References and Notes

1) *a*) Arai T., Kubo A., "The Alkaloid," ed. by Brossi A., Academic Press, New York, Vol. 21, 1983, pp. 55—100; *b*) Christopherson C., *ibid*., Vol. 24, 1985, pp. 25—111; *c*) Thompson R. H., "Naturally Occurring Quinones," Chapman and Hall, London, 1987, Vol. III, pp. 633—671.
2) *a*) McIntire D. E., Faulkner D. J., Engen D. V., Clardy J., T*etrahedron Lett.*, **20**, 4163—4166 (1979); *b*) Flinke J. M., Faulkner D. J., *J. Am. Chem. Soc*., **104**, 265—269 (1982).
3) McKee T., Ireland C. M., *J. Nat. Prod*., **50**, 754—756 (1987).
4) *a*) de Silva E. D., Glavita N. K., 16th IUPAC International Symposium on the Chemistry of Natural Products, Kyoto, May 1988, Abstract Pa 8, p. 610; *b*) Ph. D. Dissertation of N. K. Gulavita, University of Hawaii.
5) Danishefsky S., Berman E., Cvetovich R., Minamikawa J., *Tetrahedron Lett.*, **21**, 4819—4822 (1980).
6) *a*) Kubo A., Nakahara S., *Chem. Pharm. Bull*., **29**, 595—596 (1981); *b*) Kubo A., Nakahara S., Inaba K., Kitahara Y., *ibid*., **33**, 2582—2584 (1985); *c*) *Idem*, *ibid*., **34**, 4056—4068 (1986); *d*) Kubo A., Kitahara Y., Nakahara S., *ibid.*, **37**, 1384—1386 (1989) and related references cited therein.
7) Iyer S., Liebskind S., *J. Am. Chem. Soc*., **109**, 2759—2770 (1987).
8) Molina P., Vidal A., Tover F., *Synthesis*, **1997**, 963—966.
9) *a*) Okamura W. H., de Lera A.R., "Comprehensive Organic Synthesis," ed. by Trost B. M., Freming I., Paquette L. A., Pergamon Press, New York, Vol. 5, 1994, pp. 697—750; *b*) Kawasaki T., Sakamoto M., *J. Indian Chem. Soc*., **71**, 443—457 (1994); *c*) Hibino S., Sugino E., "Advances in Nitrogen Heterocycles," ed. by Moody C. J., JAI Press, Greenwich, CT, 1995, Vol. 1, pp. 205—227.
10) *a*) Hagiwara H., Choshi T., Fujimoto H., Sugino E., Hibino S., *Chem. Pharm. Bull*., **46**, 1948—1949 (1998) and related references cited therein; *b*) Choshi T., Matsuya Y., Okida M., Inada K., Sugino E., Hibino S., *Tetrahedron Lett.*, **39**, 2341—2344 (1998) and related references cited therein.
11) *a*) Hibino S., Sugino E., Adachi Y., Nomi K., Sato K., *Heterocycles*, **28**, 275—282 (1989); *b*) Hibino S., Sugino E., Choshi T., Sato K., *J. Chem. Soc., Perkin Trans. 1*, **1988,** 2429—2432; *c*) Sugino E., Choshi T., Hibino S., *Heterocycles*, **50**, 543—559 (1999).
12) Godfrey I. M., Sargent M. V., *J. Chem. Soc*., *Perkin Trans. 1*, **1974**, 1353—1354.
13) Tamao R., Ishida N., *Tetrahedron Lett*., **25**, 4245—4248 (1984).
14) *a*) Joseph J. R. III, Callery P. S., Shulgin A. T., Castagnoli N., Jr., *J. Org. Chem*., **41**, 3627—3629 (1976); *b*) Syper L., Kloc K., Mlochowski J., Szulc Z., *Synthesis*, **1979**, 521—522; *c*) Kubo A., Kitahara Y., Nakahara S., Numata R., *Chem. Pharm. Bull*., **31**, 341—343 (1983); *d*) Kitahara Y., Nakai T., Nakahara S., Akazawa M., Shimizu M., Kubo A., *ibid.*, **39**, 2256$_A$\2263 (1991).
15) *a*) Bailes R. H., Calvin M., *J. Am. Chem. Soc*., **69**, 1886—1893 (1947); *b*) VanDort H. M., Geursen H. J. , *Recl. Trav. Chim. Pays-Bas*, **86**, 520—526 (1967); *c*) Hibino S., Weinreb S. M., *J. Org. Chem*., **42**, 232—236 (1977); *d*) Wakamatsu T., Nishi T., Ohnuma T., Ban Y., *Synth. Comm*., **14**, 1167—1173 (1984).