Total Synthesis of the Structure Proposed for Prekinamycin

Frank M. Hauser* and Maotang Zhou

Department of Chemistry, The University at Albany, State University of New York, Albany, New York 12222

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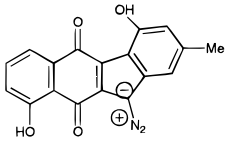
Synthetic work by several groups led to revision of the structure initially proposed for prekinamycin to **1**.[1] We



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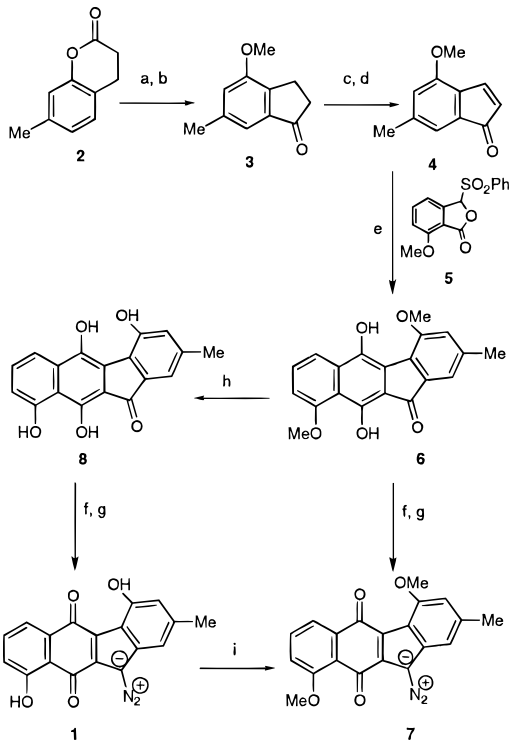
have achieved a brief regiospecific preparation of **1** based on use of our phthalide annelation methodology.[2] In accomplishing this preparation, we have established that the anion of the phthalide **5** readily undergoes condensations with indenones such as **4**, a class of compounds not previously investigated as acceptors.[3]

As indicated in Scheme 1, the indenone **4** needed for the phthalide annelation was prepared from the dihydrocoumarin **2**. Intramolecular Friedel−Crafts rearrangement[4] of **2** ($AlCl_3$/NaCl, 180 °C, 1 h), followed by methylation ($DMSO_4$, K_2CO_3, acetone), furnished **3** in 60% overall yield. As a class of compounds, indenones are unstable materials,[5] and attempted application of a procedure previously established to convert indanones to indenones[6] gave only a modest yield of **4** from **3**. Ultimately we were able to prepare **4** in satisfactory yield (75%) via conversion of **3** to the silyl enol ether (TMSTf, Et_3N), followed by treatment with $Pd(OAc)_2$.[7]

Condensation of the anion of the phthalide sulfone **5** with the indenone **4** regiospecifically furnished the benz[*b*]fluorene ketone **6** (73%). In initial work, **6** was converted to the hydrazone. Treatment with Fetizon's reagent (Ag_2CO_3 on Celite) in the presence of triethylamine oxidatively transformed both the hydroquinone to the quinone[8] and the hydrazone to the diazomethine moiety[9] (IR 2096 cm^{-1}), providing an overall one-pot, two-step conversion to **7** in 66% yield. Although the diazo compound **7** was reasonably stable, attempted cleavage of the *O*-methyl groups with BBr_3, TMSI, or $MgI_2{\cdot}OEt_2$ to afford **1** instead produced a complex mixture of decomposition products. On the basis of this finding, it appeared that O-demethylation would be required prior to introduction of the diazomethine moiety.

Scheme 1[a]



[a] Reagents: (a) NaCl/$AlCl_3$, Δ; (b) Me_2SO_4, K_2CO_3; (c) TMSTf, Et_3N; (d) $Pd(OAc)_2$; (e) **5**, LiOBu-*t*; (f) NH_2NH_2, EtOH; (g) Ag_2CO_3, Celite; (h) BBr_3; (i) MeI, DMF, K_2CO_3.

Treatment of **6** with BBr_3 gave **8**, which was sequentially reacted with hydrazine and Ag_2CO_3 on Celite to furnish **1**, the structure reported for prekinamycin.[10] The spectral properties (IR and ^1H NMR) for **1** were not identical with those reported in the literature.[11] However, the UV and ^1H NMR spectra were identical with another, previously uncharacterized metabolite from *Streptomyces murayamaensis*, thus implying that the spectral properties for the material identified as prekinamycin are in error. This finding has prompted a reinvestigation of the natural product reported to be **1**, and this work is described in the following communication.

Acknowledgment. We are indebted to Professor Steven Gould for providing the UV comparison of our synthetic **1** with the natural product previously assigned this structure and also for establishing that our material matches an uncharacterized kinamycin metabolite. This work was generously supported by the National Cancer Institute and the National Institute of General Medical Sciences of the National Institutes of Health.

Supporting Information Available: Experimental procedures and spectral data for all compounds (17 pages).

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(10) Because of insolubility, we were not able to fully characterize either the demethylated compound **8**, the hydrazone intermediate, or **1**. However, methylation of synthetic **1** afforded the methyl ether **7**, which we had been able to fully characterize. Furthermore, acetylation of **1** (Ac_2O, Py, DMAP) produced a characterizable diacetate and the spectral properties (IR, ^1H and ^{13}C NMR) of this compound were also not identical to the diacetate reported in the literature.[11]

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