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Development of a Convergent Entry to the Diazofluorene Antitumor Antibiotics: Enantioselective Synthesis of Kinamycin F

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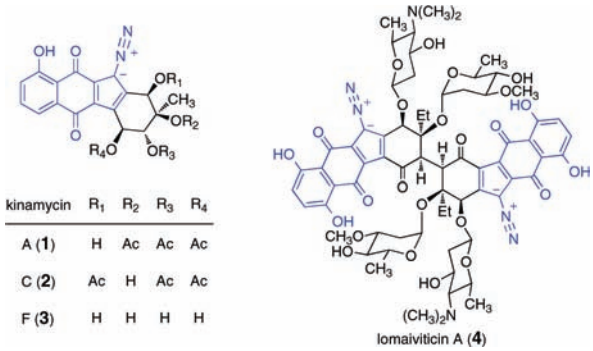
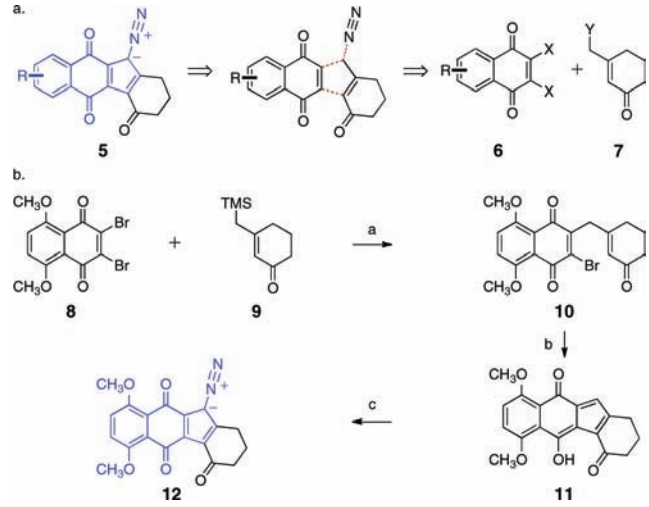
The kinamycins (**1**−**3**) and lomaiviticin A (**4**) are complex bacterial metabolites with broad-spectrum anticancer and antimicrobial activities.[1] Members of this class have demonstrated submicromolar inhibitory potencies against over 60 different cancer cell lines,[1f,2] and both Gram-positive and Gram-negative bacteria.[1d,f] In the kinamycin series, studies have suggested that kinamycin F (**3**) is the active agent formed in vivo from **1** and **2** via acetate hydrolysis.[3] The biological activity of these compounds is thought to arise from reductive cleavage of DNA.[1f,3,4] The isolates **1**−**4** are the first natural products known to contain a diazonapthoquinone function (diazofluorene, blue in **1**−**4**). This functional group has been established as reactive under reductive conditions,[5] but a clear understanding of the role of this reactivity in the cytotoxic effects of these metabolites has not yet been realized.



Stereoselective syntheses of kinamycin C (**2**) have been reported by Porco and Nicolaou.[6] Nicolaou has also completed syntheses of kinamycins F (**3**) and J (not shown).[6b] We describe herein a short and distinct route to **3** that features a powerful and potentially general method for construction of the diazofluorene function. Our strategy is outlined in Scheme 1a. Retrosynthetically, the generic construct **5** is disassembled by cleavage of two key carbon−carbon bonds of the cyclopentadiene substructure, to give the napthoquinone and cyclohexenone precursors **6** and **7**, respectively. Several different transformations to effect the proposed bond constructions could be envisioned; however, regiocontrol in the individual bond-forming events was a concern. The optimal timing for introduction of the diazo function was also not known.

After much experimentation, a three step-sequence to effect this annulation was realized, as exemplified by synthesis of the diazofluorene **12** (Scheme 1b). In the first step, a mixture of 2,3-dibromo-5,8-dimethoxynapthoquinone (**8**)[7] and 3-(trimethylsilylmethyl)-cyclohex-2-en-1-one (**9**)[8] is treated with tris(diethylamino)sulfonium trimethyldifluorosilicate [TASF(Et)][9] to form the

Scheme 1. (a) Proposed Annulation Strategy to Construct the Diazofluorene Function of the Kinamycins (**1**−**3**) and Lomaiviticin A (**4**) and (b) Synthesis of the Model Diazofluorene **12**[a]



[a] Conditions: (a) TASF(Et), CH_2Cl_2, −78 °C, 85%. (b) $Pd(OAc)_2$, polymer-supported PPh_3, Ag_2CO_3, toluene, 80 °C, 40%. (c) TfN_3, DIPEA, CH_3CN, 24 °C, 81%.

product (**10**) of 1,4-addition−elimination to the napthoquinone **8** (85%). In the second step, solutions of the addition product (**10**) are heated in the presence of palladium acetate, triphenylphosphine, and silver carbonate to form the tetracyclic product **11** (40%). The mechanism of the second step of this sequence may share parallels with Heck[10] or palladium-mediated carbonyl α-arylation reactions.[11,12] An alternate pathway comprising formation of a pentadienyl anion, electrocyclic ring closure, and elimination of bromide may also be operative.[13] This transformation is highly efficient (as determined by LC/MS and ^{1}H NMR analysis of the unpurified reaction mixtures), but we have observed that the product (**11**) forms a chromatographically stable complex to palladium,[14] preventing quantitative isolation of material. In the final step, the diazo function is introduced by treatment of solutions of the cyclization product (**11**) with excess trifluoromethanesulfonyl azide[15] and *N*,*N*-diisopropylethylamine (81%).

With the key annulation strategy established, our efforts then focused on synthesis of kinamycin F (**3**, Scheme 2). Our synthetic route begins with Birch reduction of 3-(tri*iso*-propylsilyloxy)-toluene (**13**) to form the cyclohexadiene derivative **14** (>99%). Regioselective asymmetric dihydroxylation[16] followed by protection of the resulting vicinal diol function forms the acetonide **15** (48%). The acetonide (**15**) is transformed to the enone **16** by a two-step sequence (57%). The enone (**16**) is readily recrystallized (ethanol) to 97% optical purity. Copper-mediated 1,4-

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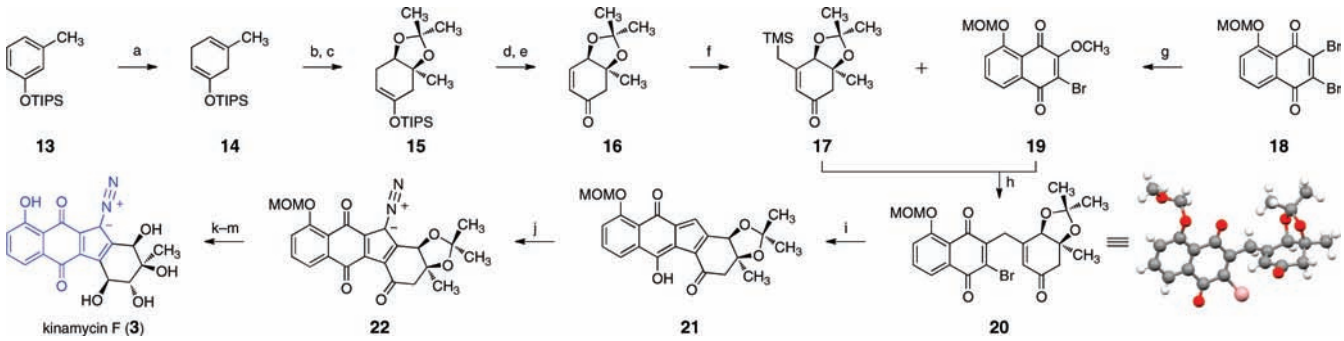
Scheme 2. Enantioselective Synthesis of Kinamycin F (**3**)[a]



[a] Conditions: (a) Na, NH_3, *t*-BuOH, THF, −78→−33→−78 °C, >99%. (b) AD-mix-β, $CH_3SO_2NH_2$, *t*-$BuOCH_3$-*t*-BuOH-H_2O, −12 °C, 55%, 66% ee. (c) 2,2-dimethoxypropane, PPTS, DMF, 24 °C, 88%. (d) CsF, PhSeCl, DMF, −50 °C, 69%. (e) H_2O_2, pyridine, CH_2Cl_2, 24 °C, 83%. (f) $TMSCH_2MgCl$, CuI, HMPA, Et_3N, TMSCl, THF, −30→−60→−78 °C; $Pd(OAc)_2$, CH_3CN, 24 °C, 88%. (g) Na_2CO_3, CH_3OH, 65 °C, 96%. (h) TASF(Et), CH_2Cl_2, −78 °C, 79%. (i) $Pd(OAc)_2$, polymer-supported PPh_3, Ag_2CO_3, toluene, 80 °C, 66%. (j) TfN_3, DIPEA, CH_3CN, 24 °C, >99%. (k) TIPSOTf, DIPEA, CH_2Cl_2, 0 °C; DMDO, CH_2Cl_2−CH_3OH,−40 °C, 76%. (l) BH_3•THF, THF, −20 °C, 58%. (m) AcCl, CH_3OH, −12→0 °C, 65%.

addition of trimethylsilylmethylmagnesium chloride followed by palladium-mediated oxidation then forms the β-(trimethylsilylmethyl)-cyclohexenone **17** (88%).

To complete the first step of the annulation, a mixture of the cyclohexenone (**17**) and *O*-(methoxymethyl)-2-bromo-3- methoxyjuglone (**19**; prepared in three steps, see Supporting Information) is treated with TASF(Et) to form the γ-alkylation product **20** (79%). The methoxy substituent was installed to impart electronic bias to the napthoquinone; its presence was critical, as efforts to couple the enone (**17**) directly with *O*-(methoxymethyl)-2,3-dibromojuglone (**18**) formed products arising from competitive addition to the 2-position of the quinone. The key cyclization and diazo transfer steps proceed smoothly to form the diazofluorene **22** (66%). To complete the synthesis, the diazofluorene (**22**) is functionalized by a three-step sequence comprising α-oxidation,[17] carbonyl reduction,[18] and global deprotection, to provide synthetic kinamycin F (**3**), indistinguishable from an authentic sample obtained by saponification of kinamycin C (**2**).[1d]

Our route to kinamycin F (**3**) proceeds in 12 linear steps from silyl ether **13**. The annulation strategy we describe allows for the synthesis of substituted diazofluorenes of potentially wide variability in three steps from simple precursors. *Ortho*-quinone methide intermediates resembling **11** and **21** have been postulated to form in vivo from the kinamycins,[4,5b,d,e] and our approach provides a straightforward synthetic pathway to such compounds.

Acknowledgment. We thank Dr. Christopher Incarvito for x-ray analysis of **20** and the Miller group for use of their HPLC. D.S. is a Yale Undergraduate Dean's Research Fellow. Kinamycin C (**3**, NSC 138425) was obtained from the NCI/DTP Open Chemical Repository (http://dtp.cancer.gov). Financial support from Yale University and Eli Lilly is gratefully acknowledged.

Supporting Information Available: Experimental procedures and detailed characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Control experiments indicated that palladium complex, phosphine, and base were all required for efficient conversion of **10**.

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(14) In experiments employing free PPh_3, we observed the formation of (**11**)$PdPPh_3$ (LC/MS and isotope modeling). Efforts to displace the product (**11**) from palladium using dppf or acach were unsuccessful.

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(17) Oxidation of the enoxysilane of **22** (DMDO) affords the corresponding α-hydroxyketone, presumably by cleavage of an intermediate silyloxy epoxide. The borane-mediated reduction of silyloxy epoxides was recently reported: Lim, S. M.; Hill, N.; Myers, A. G. *J. Am. Chem. Soc.* **2009**, *131*, 5763.

(18) Only trace amounts of hydroquinone were observed in the reaction mixture (LC/MS analysis), suggesting the reduction proceeds by hydride delivery from an in situ generated borinic ester.

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