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Total Synthesis of the Diazobenzofluorene Antibiotic (−)-Kinamycin C[1]

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The kinamycins represent a family of structurally unique natural products containing a highly oxygenated cyclohexene ring and an unusual diazobenzofluorene moiety (Figure 1).[2] Four kinamycin antibiotics, A−D, were isolated in 1970 from the culture broth of *Streptomyces murayamaensis* sp. nov. by Omura and co-workers.[3] These monomeric compounds display strong inhibition of Gram-positive bacteria. Kinamycin C **1** also showed antitumor activity.[3] Other kinamycins include the biosynthetic precursor prekinamycin **2**[4] and the epoxide-containing FL-120B **3**.[5] The structural assignment of the kinamycins has been the subject of revision. Kinamycin C **1** was initially characterized as a *N*-cyanobenzo[b]-carbazole.[6] In 1994, Gould[7] and Dmitrienko[8] independently revised its structure to contain a diazobenzofluorene moiety based on X-ray and NMR analysis, as well as synthetic studies. Although the novel and challenging chemical structures of the kinamycins, as well as their interesting biological activities, have prompted a number of synthetic and mechanistic investigations,[2,9] total syntheses of the kinamycins have not been reported to date. Herein, we report the first enantioselective total synthesis of kinamycin C.

Our retrosynthetic analysis for kinamycin C **1** is illustrated in Figure 2. Because of the labile nature of the diazo function, we planned to install this moiety at a late stage. Kinamycin C **1** may be derived from oxidation and diazo formation of the MOM-protected benzofluorene ketone precursor **4**. Compound **4** should be available through intramolecular Friedel−Crafts cyclization of carboxylic acid **5**. Acid **5** may be accessed via Stille cross-coupling of vinyl bromide **6** (fragment A) and MOM-protected arylstannane **7** (fragment B). Fragment A **6** may be derived from epoxyketone precursor **8**, which may be obtained from tartrate-mediated asymmetric nucleophilic epoxidation of quinone monoketal **9** using methodology developed in our laboratory.[10] Fragment B **7** may be readily accessed from the commercially available 1, 5-napthalenediol.

The synthesis of fragment A (**6**) began with the readily available 2-bromo-3,6-dihydroxy-benzaldehyde **10**[11] (Scheme 1).[12] Selective methylation,[13] followed by reduction, provided **11** (85%). Hypervalent iodine oxidation of **11**, followed by transketalization and silyl protection, afforded quinone monoketal **12** (72% yield, three steps). As the literature was sparse with regard to Baylis−Hillman reactions of quinone monoketal substrates,[14] we evaluated new protocols for this transformation. After extensive evaluation, we identified a modification of conditions reported by Aggarwal[15] employing Et_3P as nucleophilic activator which afforded quinone monoketal **9** in 70% yield. With **9** in hand, we evaluated the critical hydroxyl-directed, asymmetric nucleophilic epoxidation.[10] After careful reaction optimization, we identified satisfactory conditions for tartrate-mediated asymmetric nucleophilic epoxidation to generate epoxide **8** in 94% yield and 90% ee. In contrast, Sharpless asymmetric epoxidation of **9** ($Ti(^iPrO)_4$, *D*-DIPT, ^{t}BuOOH)[16] provided **8** in 85% yield (70% ee). The absolute stereochemistry of **8** was confirmed by X-ray crystallographic analysis of the derived diol **13**.[12]

Further elaboration of epoxyalcohol **8** was initiated by hydroxyl-directed reduction[17] to afford a diol as a single diastereomer, which was subsequently subjected to selective mesylation of the primary alcohol to yield **14**. (Scheme 2).[18] Reductive demesylation cleanly afforded **15** (95%).[19] Selective removal of the cyclic ketal using

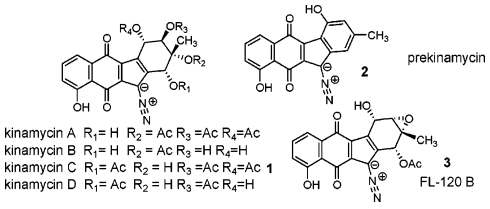


Figure 1. The kinamycin family of natural products.

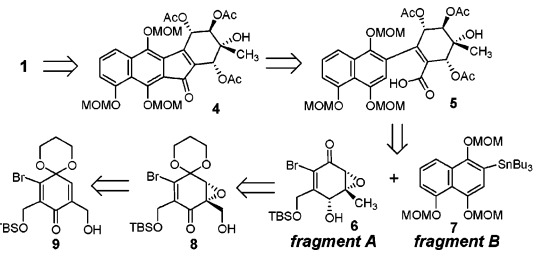
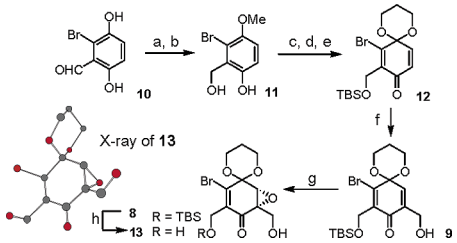


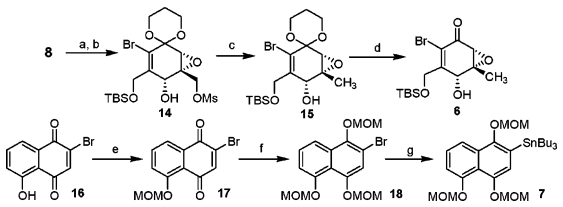
Figure 2. Retrosynthetic analysis.

Scheme 1[a]



[a] Conditions: (a) Me_3O-BF_4, proton sponge, 4 Å MS, CH_2Cl_2, room temp, 12 h, 85%; (b) $NaBH_4$, EtOH, 0 °C, 1 h, 99%; (c) $PhI(OAc)_2$, MeOH, room temp, 30 min; (d) 1, 3-propanediol, BF_3-Et_2O, DME, room temp, 3 h; (e) TBSCl, imid. CH_2Cl_2, room temp, 6 h, 72% for three steps; (f) $(CH_2O)_n$, $La(OTf)_3$, $N(CH_2CH_2OH)_3$, Et_3P, CH_2Cl_2, −20 °C, 6 h, 70%; (g) Ph_3COOH, NaHMDS, *D*-DIPT, 4 Å MS, toluene, −65 °C, 72 h, 94%, 90% ee; (f) Et_3N-3HF, CH_3CN, room temp, 12 h, 98%.

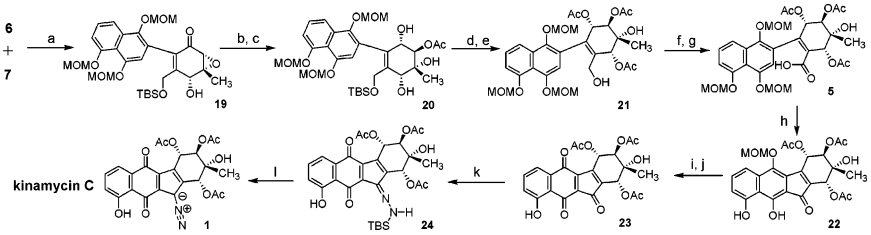
Scheme 2[a]



[a] Conditions: (a) $Me_4NBH(OAc)_3$, AcOH, CH_3CN, 0 °C, 24 h, 90%; (b) MsCl, collidine, CH_2Cl_2, 5 °C, 8 h, 85%; (c) Super-Hydride, DCE, 60 °C, 30 min, 95%; (d) K-10 clay, CH_2Cl_2, room temp, 4 h, 90%; (e) MOMCl, DIEA, CH_2Cl_2, room temp, 3 h, 85%; (f) $Na_2S_2O_4$, Et_2O, then MOMCl, DIEA, CH_2Cl_2, room temp, 24 h, 70%; (g) $Pd(PPh_3)_4$, $Bu_3SnSnBu_3$, toluene, 110 °C, 24 h, 70%.

10.1021/ja066621v CCC: $33.50

Scheme 3[a]



[a] Conditions: (a) $Pd_2(dba)_3$, $AsPh_3$, CuCl, DIEA, CH_3CN, 70 °C, 4 h, 70%; (b) Super-Hydride, THF, - 78 °C, 1 h, 80% (dr >10 :1); (c) $Ti(O^iPr)_4$, $^nBu_4NOAc$, 4 Å MS, CH_2Cl_2, room temp, 10 h, 60%; (d) Ac_2O, pyridine, room temp, 2 h; (e) Et_3N-3HF, CH_3CN, room temp, 12 h, 67% for two steps; (f) TPAP, NMO, CH_2Cl_2, room temp, 20 min; (g) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, room temp, 12 h, 88% for two steps; (h) TFAA, DCE, 4 Å MS, room temp, 1 h, 90%; (i) CBr_4, ^iPrOH, 84 °C, 1 h; (j) Pd/C, air, EtOAc, room temp, 30 min, 70% for two steps; (k) TBSNHNHTBS, $Sc(OTf)_3$, CH_2Cl_2; (l) $PhIF_2$, 2-chloropyridine, CH_2Cl_2, 35% for two steps.

K-10 clay[20] cleanly afforded the desired epoxyketone **6** (fragment A) in 90% yield. The synthesis of fragment B (**7**) was initiated from readily available 1,5-naphthoquinone **16** (Scheme 2).[21] Protection of **16** using MOMCl/DIEA afforded naphthalenedione **17**, which was subsequently reduced with $Na_2S_2O_4$ and further protected to generate **18**. Stannylation of aryl bromide **18** ($Pd(PPh_3)_4$, bis-(tributyltin))[22] afforded the desired arylstannane **7** (70%).

With both fragments A and B in hand, we initiated studies on fragment coupling (Scheme 3). Through extensive reaction evaluation, we identified a suitable condition ($Pd_2(dba)_3$, $AsPh_3$, CuCl, DIEA)[23] to afford the desired coupling product **19** (70%). Compound **19** was found to have two major rotamers (2:1) by ^{1}H-NMR analysis.[12] Further reduction of **19** with Super-Hydride afforded the *syn*-epoxyalcohol (80%, 10:1 dr),[12] which was subjected to the epoxide-opening[24] using $Ti(^iPrO)_4$ and $^nBu_4NOAc$ to generate triol **20** (60%, >10:1 dr). Acylation of **20**, followed by deprotection of the silyl ether, provided alcohol **21**. Sequential oxidations of **21** using TPAP[25] and $NaClO_2$[26] provided carboxylic acid **5** (88%, 2 steps).

Next, we examined the feasibility for an intramolecular Friedel−Crafts cyclization for construction of the C-ring. Evaluation of a number of different conditions revealed that TFAA[27] efficiently mediated the desired Friedel−Crafts annulation to generate cyclization product **22** (90%). In addition, two MOM protecting groups were also removed in a regioselective fashion under the reaction conditions.[12] MOM deprotection,[28] followed by oxidation of the hydroquinone using Pd/C-air,[29] afforded ketoquinone **23**. Condensation of **23** with 1,2-bis(*tert*-butyldimethylsilyl)hydrazine generated **24**, which was treated with $PhIF_2$ to install the diazo functionality[30] and complete the total synthesis of kinamycin C **1**. Synthetic **1** was confirmed to be identical with data reported for natural kinamycin C[12] by ^{1}H and ^{13}C NMR spectra, mass spectrum, IR, $[\alpha]_D$, HPLC, and TLC R_f values in three solvent systems.[12]

In conclusion, we have accomplished the first enantioselective total synthesis of the complex diazobenzofluorene natural product (−)-kinamycin C. The synthesis relies on a directed, asymmetric nucleophilic epoxidation process to establish the desired stereochemistry of the complex D-ring subunit. Further studies toward the synthesis of diazobenzofluorene natural products as well as biological evaluation of kinamycin C and congeners will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds; X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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