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Total Synthesis of Kinamycins C, F, and J

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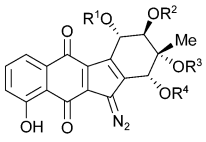
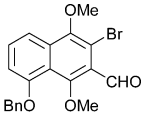
The kinamycins (e.g., A−D, F and J, **1a**−**1f**, Figure 1) are a series of naturally occurring compounds endowed with intriguing molecular architectures and potent biological properties, including antibiotic and antitumor activities.[1] These novel diazofluorene-containing compounds defied chemical synthesis[2] since their initial disclosure by Omura et al. in 1970[1] until the first total synthesis of kinamycin C by Porco et al. in late 2006,[3] and of methyl-kinamycin C by the Kumamoto−Ishihawa group in 2007.[4] We now report our enantioselective total synthesis of kinamycins C, F, and J through a convergent strategy that is both enantioselective and expedient.





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1a: kinamycin A: R^1 = H, R^2 = Ac, R^3 = Ac, R^4 = Ac
1b: kinamycin B: R^1 = H, R^2 = H, R^3 = Ac, R^4 = H
1c: kinamycin C: R^1 = Ac, R^2 = Ac, R^3 = H, R^4 = Ac
1d: kinamycin D: R^1 = H, R^2 = Ac, R^3 = H, R^4 = Ac
1e: kinamycin F: R^1 = H, R^2 = H, R^3 = H, R^4 = H
1f: kinamycin J: R^1 = Ac, R^2 = Ac, R^3 = Ac, R^4 = Ac

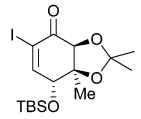

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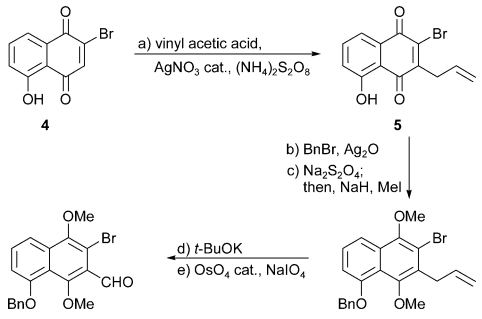
Figure 1. Structures of kinamycins A−D, F, and J (**1a**−**1f**) and of key building blocks **2** and **3**.

The unique carbocyclic skeleton of the kinamycin molecule is boldly defined by its fluorenone structural motif that could, in principle, be forged through the union of key building blocks **2** and **3** (Figure 1) by a strategy featuring an Ullmann-type coupling followed by an intramolecular benzoin-like condensation and further elaboration. Cognizant of the sensitivity of the diazo group, we left its installation toward the end of the designed synthetic sequence, although we harbor aspirations to reach as many kinamycin congeners as possible from a common intermediate through the deployment of suitable conditions.

The construction of the building block **2** (see Scheme 1) began with **4**,[5] whose allylation with vinyl acetic acid in the presence of $(NH_4)_2S_2O_8$ and cat. $AgNO_3$[6] proceeded smoothly to afford naptho-quinone **5** in 75% yield, an intermediate that was suitably protected as its dimethoxy benzyl form **6** [(i) BnBr, Ag_2O, 92% yield; (ii) $Na_2S_2O_4$; NaH, MeI, 82% yield]. The latter compound was then converted to the desired fragment, bromo-aldehyde **2**, by first conjugating its olefinic bond (*t*-BuOK, 98% yield) and then oxidatively cleaving it (OsO_4, $NaIO_4$, 84% yield).

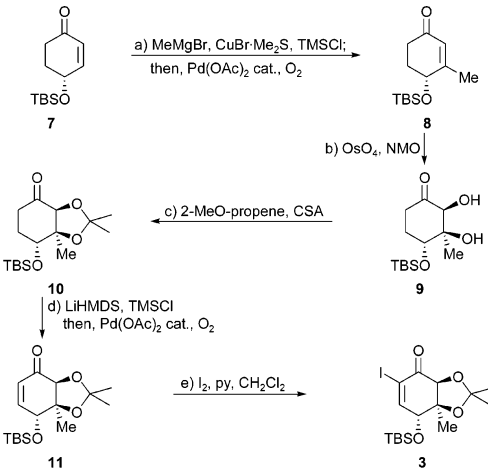
The construction of the other required fragment, iodo-enone **3**, in its enantiomerically pure form was carried out as summarized in Scheme 2. Thus, the readily available enone **7** (≥80% ee)[7] was elaborated into its methylated derivative **8** through a two-step sequence involving conjugate addition of a methyl group and trapping (MeMgBr, CuBr·Me_2S, TMSCl), followed by Saegusa oxidation[8] of the resulting silyl enol ether [$Pd(OAc)_2$ cat., O_2, 90% overall yield]. The latter compound was then stereoselectively dihydroxylated (OsO_4 cat., NMO, 76% yield after three recrystal-

Scheme 1. Construction of Bromo-aldehyde **2**[a]



[a] Reagents and conditions: (a) vinylacetic acid (1.3 equiv), $AgNO_3$ (0.3 equiv), $(NH_4)_2S_2O_8$ (2.0 equiv), $MeCN/H_2O$, 2:1, 65 °C, 3 h, 75%; (b) BnBr (2.0 equiv), Ag_2O (1.0 equiv), CH_2Cl_2, 25 °C, 18 h, 92%; (c) $Na_2S_2O_4$ (5.0 equiv), $Et_2O/EtOAc/H_2O$, 10:1:10, , 25 °C, 30 min; NaH (2.1 equiv), MeI (2.2 equiv), DMF, −15 °C, 1 h, 82%; (d) *t*-BuOK (2.0 equiv), THF, 0 °C, 2 h, 98%; (e) OsO_4 (0.01 equiv), $NaIO_4$ (2.4 equiv), THF/H_2O, 2:1, 70 °C, 18 h, 84%. Abbreviations: DMF = dimethylformamide, Bn = benzyl, THF = tetrahydrofuran.

Scheme 2. Construction of Iodo-enone **3**[a]



[a] Reagents and conditions: (a) MeMgBr (3.0 M in Et_2O, 2.0 equiv), CuBr·Me_2S (0.1 equiv), THF/HMPA, 10:1, −78 °C, 30 min; enone **8** (1.0 equiv), TMSCl (2.5 equiv), −78 °C, 30 min; −78 → 25 °C, 30 min; then, $Pd(OAc)_2$ (0.1 equiv), DMSO, O_2 (1 atm), 18 h, 25 °C, 90%; (b) OsO_4 (0.02 equiv), NMO (1.5 equiv), Me_2CO/H_2O, 10:1, 25 °C, 45 min, 76% after 3 recrytallizations, >98% ee; (c) 2-MeO-propene (10.0 equiv), CSA (0.02 equiv), THF, 25 °C, 18 h, 95%; d) LiHMDS (1.0 M in THF, 3.0 equiv), TMSCl (3.0 equiv), THF, 0 °C, 30 min; then, $Pd(OAc)_2$ (0.1 equiv), DMSO, O_2 (1 atm), 25 °C, 18 h, 84%; (e) I_2 (3.0 equiv), CH_2Cl_2:py, 1:2, 25 °C, 30 min, 92%. Abbreviations: TBS = *tert*-butyldimethylsilyl, HMPA = hexamethyl phosphoramide, TMS = trimethylsilyl, DMSO = dimethylsulfoxide, NMO = *N*-methylmorpholine-*N*-oxide, CSA = camphorsulfonic acid, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, py = pyridine.

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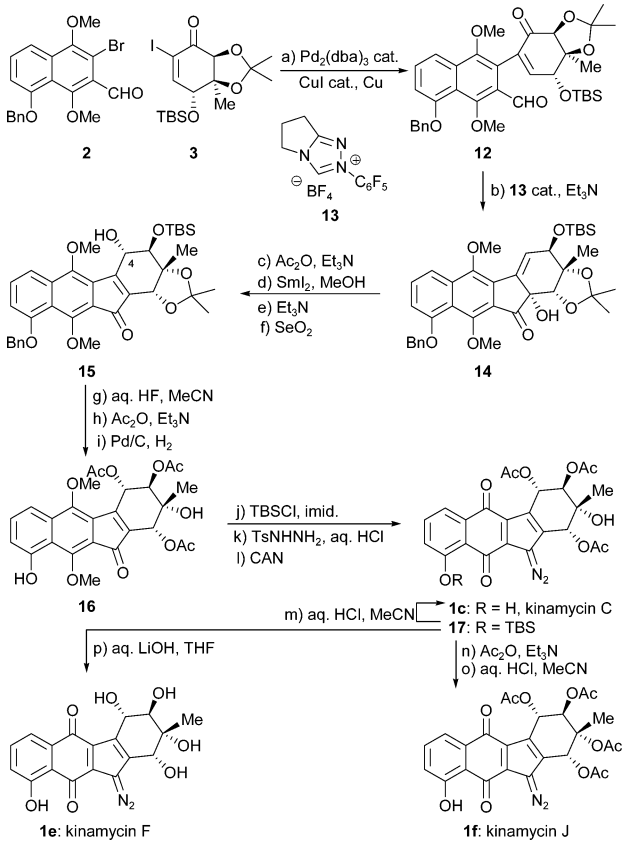
Scheme 3. Total Synthesis of Kinamycin C (**1c**)[a]



[a] Reagents and conditions: (a) **2** (1.5 equiv), **3** (1.0 equiv), $Pd_2(dba)_3$ (0.1 equiv), CuI (0.4 equiv), Cu (10.0 equiv), DMSO, 65 °C, 2.5 h, 83%; (b) **13** (0.2 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 45 °C, 4 h, 78%; (c) Ac_2O (10.0 equiv), Et_3N (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 20 h, 95%; (d) SmI_2 (2.0 equiv), MeOH (5.0 equiv), THF, −78 °C, 10 min; (e) Et_3N (2.0 equiv), CH_2Cl_2, 25 °C, 1 h, 81% over two steps; (f) SeO_2 (1.2 equiv), 1,4-dioxane, 110 °C, 9 h, 72%; (g) aq HF/MeCN, 3:10, 25 °C, 3 h; (h) Ac_2O (10.0 equiv), Et_3N (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 20 min, 89% over two steps; (i) 10% Pd/C (10% w/w), EtOAc/AcOH, 300:1, H_2 (1 atm), 25 °C, 3 h, 99%; (j) TBSCl (5.0 equiv), imid. (6.0 equiv), DMF, 25 °C, 3 h, 94%; (k) $TsNHNH_2$ (5.0 equiv), 1 M aq HCl/*i*-PrOH, 1:40, 25 °C, 18 h, ca. 4:1 mixture of isomers, 95%; (l) CAN (3.0 equiv), MeCN/pH 7 buffer, 10:1, 0 °C, 1 h, 42%; m) 1 M aq HCl/MeCN, 1:2, 25 °C, 3 h, 95%; n) Ac_2O (10.0 equiv), Et_3N (10.0 equiv), DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 2 h; o) 1 M aq HCl/MeCN, 1:2, 25 °C, 3 h, 80% over two steps; p) 0.2 M aq LiOH/THF, 1:2, 25 °C, 1 h, 92%. Abbreviations: dba = dibenzylideneacetone, DMAP = 4-dimethylaminopyridine, imid. = imidazole, Ts = tosyl, CAN = cerium ammonium nitrate.

lizations, ≥98% ee) to furnish vicinal diol **9**, whose protection as an acetonide (2-methoxypropene, CSA) gave **10** in 95% yield. Exposure of ketone **10** to LiHMDS−TMSCl, followed by treatment of the resulting silyl enol ether with catalytic amounts of $Pd(OAc)_2$ in the presence of oxygen, led to enone **11** in 84% yield. Finally, iodination of **11** (I_2, py) furnished the desired iodo-enone **3** in 92% yield.

Available in multigram quantities, fragments **2** and **3** were coupled under modified Ullmann conditions (Cu, CuI cat., $Pd_2(dba)_3$ cat.)[9] to afford coupling product **12** in 83% yield (Scheme 3). The latter entered into a benzoin-type reaction in the presence of the Rovis catalyst **13**,[10] yielding hydroxyketone **14** as an inconsequential ca. 3:1 mixture of diastereomers in 78% yield. Alcohol **14** (mixture of isomers) was then acylated (Ac_2O, Et_3N, DMAP, 95% yield) and exposed to SmI_2[11] in the presence of MeOH and then Et_3N to cleave the acetate and migrate the double bond into conjugation (81% yield over the two steps). Allylic oxidation of the resulting fluorenone with SeO_2 provided, stereoselectively, alcohol **15** in 72% yield. The TBS and acetonide groups were then removed from **15** through the action of aq HF in MeCN, and the resulting tetraol was selectively tri-acetylated (Ac_2O, Et_3N, DMAP, 89% overall yield for the two steps), and then debenzylated (H_2, 10% Pd/C) to afford advanced fluorenone **16** in 99% yield. Finally, temporary protection of the phenolic group (TBSCl, imid., 94% yield) followed by tosyl hydrazone formation [$TsNHNH_2$, aq HCl, ca. 4:1 mixture of isomers (inconsequential), 95% yield][4] and oxidation (CAN) led to TBS-protected kinamycin C (**17**) in 42% yield. Exposure of the latter compound to aq HCl in MeCN furnished kinamycin C (**1c**) in 95% yield. Acetylation of **17** (Ac_2O, Et_3N, DMAP), followed by TBS−ether cleavage (aq HCl, MeCN) provided kinamycin J (**1f**) in 80% yield over the two steps, while LiOH-mediated removal of all protecting groups from **17** led to kinamycin F (**1e**) in 92% yield. The spectroscopic data of synthetic kinamycins C, F, and J were consistent with those reported for the natural compounds.[1]

The described chemistry provides an expedient and flexible entry into the kinamycin family of antitumor antibiotics and promises to be useful in the total synthesis of their more complex dimeric cousins, the lomaiviticins.[12]

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Note Added after ASAP Publication. A correction to ref 9 was made in the version published on August 9, 2007.

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

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