Natural Product Synthesis

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Asymmetric Total Synthesis of the Epoxykinamycin FL-120 B′**

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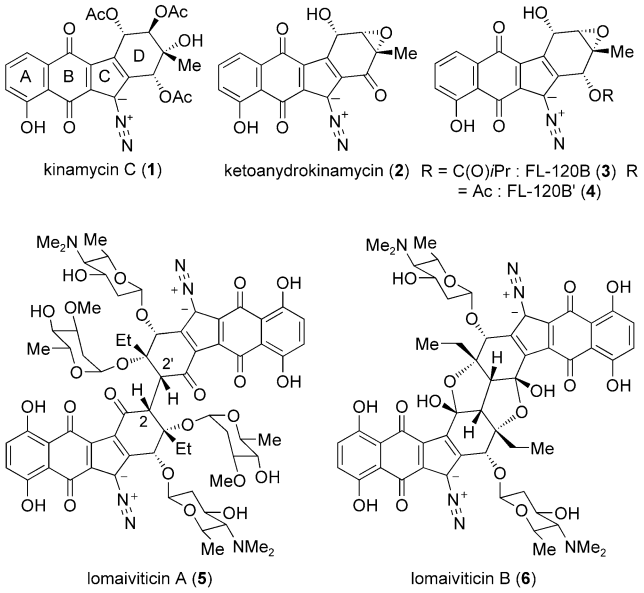
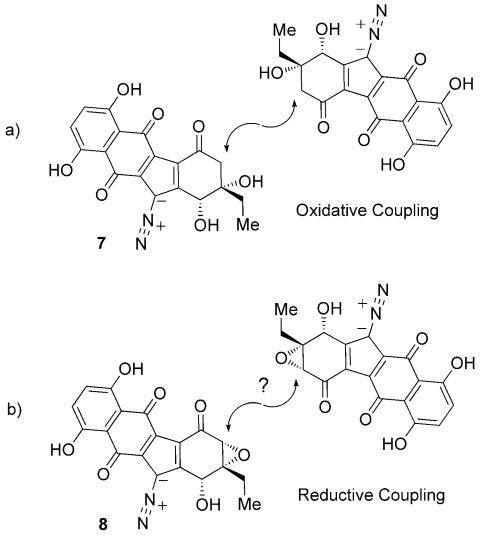
Diazobenzofluorene natural products are a family of structurally complex molecules with a tetracyclic (ABCD) framework bearing a diazo moiety, a functionality rarely found in nature (Scheme 1).[1] Members of this family differ in the levels of functionalization of the cyclohexene moiety (D ring). Kinamycin C (**1**),[2] which is biosynthetically[3] derived from the epoxide-containing ketoanhydrokinamycin (**2**),[4] contains a D ring with four contiguous stereocenters. Other epoxykinamycins include FL-120B (**3**) and the closely related FL-120B′ (**4**).[5] Monomeric diazobenzofluorenes have been shown to exhibit antitumor properties.[2,6] Numerous studies have suggested that these biological activities may result from damage to DNA mediated by bioreductive pathways, thus leading to loss of the diazo functional group.[6b,7] This unique family of natural products gained significant attention upon isolation of the dimeric diazobenzofluorenes lomaiviticins A (**5**) and B (**6**) by He et al. in 2001.[8] Demonstrated to be DNA-damaging agents, the lomaiviticins were found to display antibiotic acitivity against Gram-positive bacteria and potent cytotoxicity in several cancer cell lines. The C_2-symmetric lomaiviticins may originate from the C2–C2′ linkage of precursors that closely resemble the monomeric kinamycins.



Scheme 1. Representative diazobenzofluorene natural products.

Since 2006, numerous research groups have reported total syntheses of monomeric diazobenzofluorene natural products[9] as well as studies towards the dimeric lomaiviticins.[10] Recently, Herzon et al. reported a remarkable 11-step synthesis of the lomaiviticin aglycon.[11] Their dimerization approach utilizes an oxidative homocoupling of a silyl enol ether derived from a protected monomer, which resembles **7** (Scheme 2a). Given the abundance of diazobenzofluorene natural products bearing an epoxide or oxygenated functionality at the C2-position, we believe that a biosynthetic precursor to the lomaiviticins may also be depicted by the proposed monomer **8** (Scheme 2b). This dimerization process may result from a reductive epoxide-opening[12] event leading to a pivotal carbon–carbon bond formation.[13] In this regard, we report the total synthesis of FL-120B′ (**4**) and development of methods to prepare diazobenzofluorenes with intact epoxides; these methods may also allow future access to the lomaiviticins and related compounds.



Scheme 2. Biomimetic approaches to the lomaiviticins.

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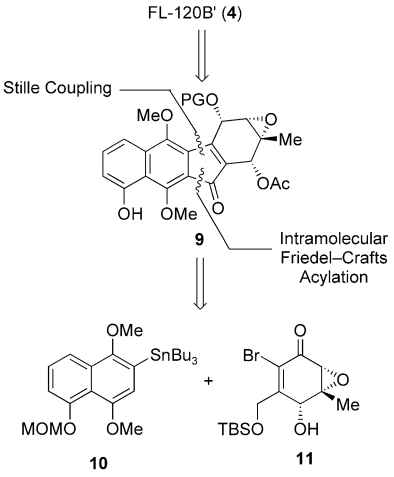
In our retrosynthetic analysis, we believed that the installation of the diazo group of FL-120B′ (**4**) could be achieved by a two-step process starting from a benzofluorenone intermediate such as **9** (Scheme 3). This strategy would first involve the formation of a sulfonylhydrazone from a

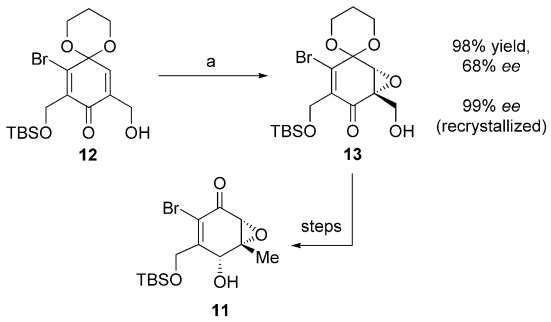


Scheme 3. Retrosynthesis for FL-120B′ (**4**). PG = protecting group, MOM = methoxymethyl, TBS = *tert*-butyldimethylsilyl.

ketone precursor and subsequent oxidation with spontaneous desulfination of the hydrazone to form the requisite diazo functionality.[9c–e] The synthesis of **9** may be achieved from the naphthalene fragment **10** and epoxide **11** utilizing Stille coupling and intramolecular Friedel–Crafts acylation using reaction conditions previously described in the synthesis of kinamycin C by our group.[9b]

In our prior synthesis,[9b] asymmetric nucleophilic epoxidation (D-DIPT, Ph_3COOH, and NaHMDS)[14] was utilized to access chiral, nonracemic **11**. Unfortunately, high levels of enantioselectivity were not achieved on a larger scale. However, Sharpless asymmetric epoxidation of quinone monoketal **12** was performed on a 4.4 g scale to provide **13** in 98% yield with moderate enantioselectivity (68% *ee*; Scheme 4).[15] A single recrystallization provided **13** in high enantiomeric excess (99% *ee*). Epoxide **13** was further elaborated to our desired epoxyketone fragment **11** as previously reported.[9b]

For the synthesis of the AB ring subunit, quinone **14**[9b] was reduced and subsequently methylated to provide bromonaphthalene derivative **15** (Scheme 5). Stannylation[16] of **15** afforded aryl stannane **10**. Stille coupling[17] of stannane **10** and bromide **11** afforded epoxyketone **16** in excellent yield (90%) as a 1.5:1 mixture of atropisomers,[18] as indicated by ^{1}H NMR analysis.[19] Acetylation of **16** followed by reduction with Super-Hydride ($LiHBEt_3$) provided allylic alcohol **17** as a single diastereomer.[19] At this stage in the synthesis, three protecting groups for the secondary alcohol of substrate **17** were explored. Alcohol **17** was masked as acetate (Ac), 4-azidobutyrate ($C(O)(CH_2)_3N_3$),[20] and *tert*-butoxycarbonyl (Boc) groups to provide protected intermediates **18a**, **18b**, and **18c**, respectively. Desilylation[21] of **18a–c** and oxidation with Dess–Martin periodinane[22] gave aldehydes **19a–c**.

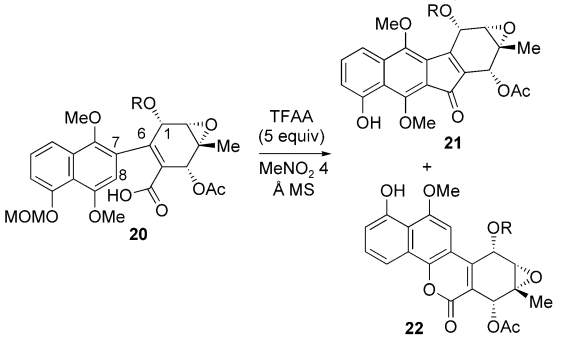


Scheme 4. Enantioselective synthesis of epoxide **13**. a) *t*BuOOH (2.0 equiv), $Ti(OiPr)_4$ (0.10 equiv), L-DIPT (0.13 equiv), 4 Å M.S., CH_2Cl_2, 0°C, 60 h. DIPT = diisopropyl tartrate, M.S. = molecular sieves.

Oxidation with $NaClO_2$[23] afforded carboxylic acids **20a–c** for evaluation in the pivotal intramolecular Friedel–Crafts acylation to form the tetracyclic framework of FL-120B′.

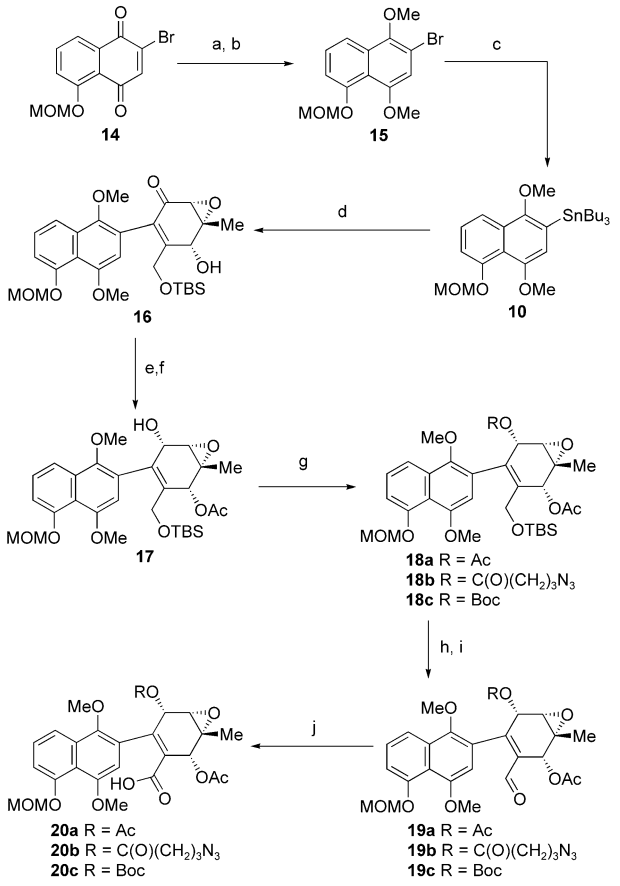
Treatment of carboxylic acids **20a–c** with trifluoroacetic anhydride (TFAA) in a variety of solvents and at different temperatures gave varying ratios of the desired ketone products **21** and lactone by-products **22** (Table 1). By adding TFAA to a preheated (80°C) solution of **20a** (R = Ac) in nitromethane, as the optimal solvent, a 10:1 (determined by ^{1}H NMR analysis of the reaction mixture) mixture of C-acylation to O-acylation products (**21a**/**22a**) was observed.

Table 1: Studies on the intramolecular Friedel–Crafts acylation.



Entry	Substrate	T [°C][a]	Selectivity (**21**/**22**)[b]	Yield [%][c] of **21**	Yield [%][c] of **22**
1	**20a** (R=Ac)[d]	80	10:1	89	8
2	**20b** (R=C(O)$(CH_2)_3N_3$)[d]	23	4:1	58	15
3	**20b**[d]	50	>20:1	81	–
4	**20b**	80	>20:1	84	–
5	**20c** (R=Boc)[e]	80	>20:1	72[f]	–

[a] TFAA was added to the reaction mixture at the indicated temperature. [b] Selectivity was measured by ^{1}H NMR analysis of the reaction mixture. [c] Yields are for isolated products after column chromatography on silica gel. [d] The crude reaction mixture was further treated with TFA for complete MOM deprotection. [e] Treatment with pyridine[24] in EtOH was required to deprotect trifluoroacetylated intermediates. [f] The Boc group was cleaved during reactions: R = H. TFAA = trifluoroacetic anhydride, TFA = trifluoroacetic acid.



Scheme 5. Forward synthesis to carboxylic acids **20a–c**. a) $Na_2S_2O_4$ (6.0 equiv), Et_2O, H_2O, RT, 10 min; b) MeI (6.0 equiv), K_2CO_3 (6.5 equiv), DMF, 0 °C→RT, 18 h, 66% yield (2 steps); c) $(SnBu_3)_2$ (1.3 equiv), $[Pd(PPh_3)_4]$ (0.1 equiv), toluene, 110 °C, 48 h, 74%; d) **11** (1.0 equiv), **10** (1.1 equiv), $[Pd_2(dba)_3]\cdot CHCl_3$ (0.1 equiv), $AsPh_3$ (0.3 equiv), CuCl (0.6 equiv), *i*Pr_2NEt (1.1 equiv), MeCN, 72 °C, 3 h, 90% yield; e) Ac_2O (30 equiv), pyr, RT, 6 h; f) Super-Hydride ($LiHBEt_3$; 2.1 equiv), THF; 74% (2 steps) g) **18a**: Ac_2O (30 equiv), pyr, RT, 3 h, 96%; **18b**: $ClC(O)(CH_2)_3N_3$ (1.1 equiv), CH_2Cl_2/pyr, 0 °C, 1 h, 73%; **18c**: Boc_2O (5.0 equiv), DMAP (5.5 equiv), CH_2Cl_2, RT, 4 h, 93%; h) HF·pyr (excess), THF/pyr, 0 °C, 15–20 h; i) DMP (2.0 equiv), pyr (2.1 equiv), CH_2Cl_2, RT, 3–5 h, 73–88% (2 steps); j) $NaClO_2$ (9 equiv), NaH_2PO_4 (8 equiv), 2-methyl-2-butene (excess), *t*BuOH/H_2O, 0 °C→RT, 2–3 h, 78–90%. Boc = *t*-butoxycarbonyl, dba = dibenzylideneacetone, DMAP = *N*,*N*-dimethyl-4-aminopyridine, DMF = *N*,*N*-dimethylformamide, DMP = Dess–Martin periodinane, pyr = pyridine.

Higher ratios (**21**/**22**) were observed with use of the bulkier azidobutyrate ($C(O)(CH_2)_3N_3$) and Boc groups (>20:1; Table 1, entries 3–5).[19] Interestingly, we found that higher reaction temperatures were required to achieve higher selectivities and yields for the desired ketone products. For example, treatment of **20b** with TFAA at RT gave a 4:1 (**21b**/**22b**) selectivity and a 58% yield for ketone **21b** (Table 1, entry 2). The ratio was significantly increased to >20:1 when the reaction was performed at 50 °C and 80 °C affording **21b** in 81% and 84% yields, respectively (Table 1, entries 3 and 4).[19]

These results may be accounted for by the observation that acid substrates **20a–c** were found to exist as a mixture of atropisomers (1.2–1.6:1 mixture by ^{1}H NMR analysis). Variable temperature (VT) ^{1}H NMR experiments indicated that the atropisomers equilibrate upon warming (H8 proton shows coalescence at 80 °C; Figure 1), and the barrier to rotation ($\Delta G^{\ddagger}$) for acid **20b** was calculated to be 18 kcal mmol^{-1}.[25]

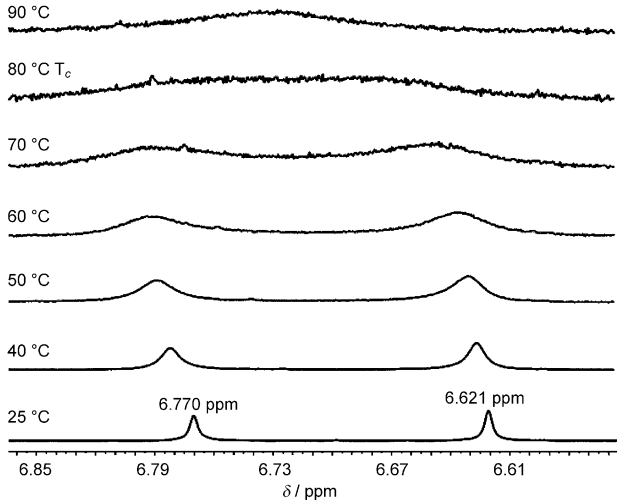
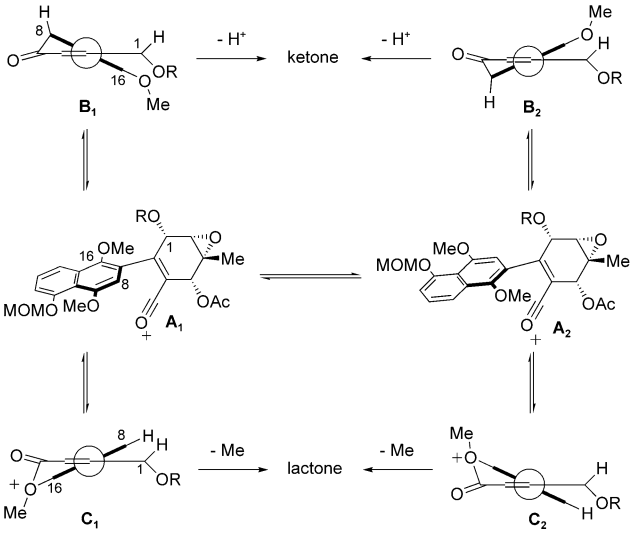


Figure 1. Variable temperature (VT) ^{1}H NMR (500 MHz, CD_3NO_2) stackplot of acid **20b**.

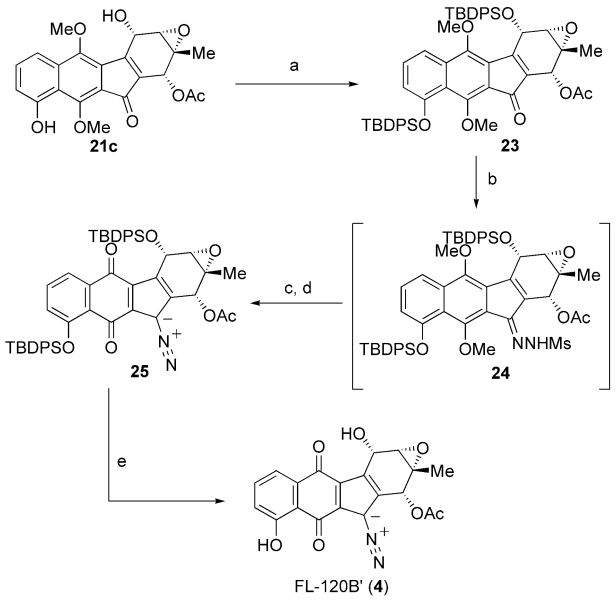
This significant barrier to rotation may be directly correlated to the atropisomeric acylium intermediates $\mathbf{A_1}$ and $\mathbf{A_2}$ (Scheme 6). At lower temperatures, $\mathbf{A_1}$ and $\mathbf{A_2}$ may not freely equilibrate and independently may give mixtures of intermediates $\mathbf{B_1}/\mathbf{C_1}$ and $\mathbf{B_2}/\mathbf{C_2}$, respectively (Scheme 6; partial structures shown for clarity).[19,26] At higher temperatures, $\mathbf{A_1}$ and $\mathbf{A_2}$ may rapidly equilibrate, thus leading to a thermodynamically favored ketone intermediate. We believe that ketone intermediate $\mathbf{B_2}$ should be energetically preferred owing to an unfavorable steric interaction between the C16 aryl methoxy and C1 protected alcohol in intermediate $\mathbf{B_1}$. In



Scheme 6. Proposed cyclization manifolds for intramolecular Friedel–Crafts acylation and lactone formation.

intermediate $\mathbf{B_2}$, the interaction between the C16 aryl methoxy and H1 is minimized and upon rearomatization affords the observed ketone products.

To complete the synthesis of FL-120B′, ketone **21c**, derived from Boc-protected acid **20c**, was protected using TBDPSCl to afford the bis(silylated) ketone **23** (Scheme 7). Initial attempts using various Lewis and Bronsted acids to form mesylhydrazone **24** failed to retain the sensitive epoxide moiety. Ultimately, trifluoroacetic acid (TFA) proved to be a



Scheme 7. Completion of FL-120B′ (**4**). a) TBDPSCl (15 equiv), imid (20 equiv), DMAP (0.5 equiv), CH_2Cl_2, RT, 20 h, 84%. b) $MsNHNH_2$ (25 equiv), TFA (8 equiv), *i*PrOH/H_2O, 72 h; c) CAN (3 equiv), CH_3CN/pH 7 buffer, 0°C, 1 h; d) NEt_3 (10 equiv), CH_2Cl_2, RT, 1 h, 16% (3 steps); e) HF·pyridine (excess), THF, 0°C→RT, 3 h, 51%. CAN = cerium(IV) ammonium nitrate, imid = imidazole, Ms = methanesulfonyl, TBDPS = *tert*-butyldiphenylsilyl.

suitable Bronsted acid with a non-nucleophilic counteranion to promote sulfonylhydrazone formation to **24**. Oxidation of **24** with ceric(IV) ammonium nitrate (CAN) provided the desired quinone, which was followed by partial spontaneous desulfination to provide the desired diazobenzofluorene product **25**. Treatment of the mixture with NEt_3 provided full conversion to **25**.[9d] In addition to **25**, the parent ketone **23** was reformed (12% for three steps) through an oxidative or hydrolytic process.[27] With protected **25** in hand, desilylation with HF·pyridine cleanly gave FL-120B′ (**4**). For comparison, a four-step semisynthesis of **4** from the closely related FL-120B (**3**) was also achieved.[19] Synthetic and semisynthetic FL-120B′ gave matching ^{1}H NMR and IR spectra as well as TLC and HPLC retention values. Furthermore, similar optical rotations for synthetic ($[\alpha]_D^{23} = -132°$) and semisynthetic ($[\alpha]_D^{23} = -128°$) FL-120B′ allowed assignment of the absolute configuration for both FL-120B (**3**) and FL-120B′ (**4**) as depicted in Scheme 1.

In summary, an asymmetric synthesis of FL-120B′ has been achieved using Sharpless asymmetric epoxidation, Stille cross-coupling, and intramolecular Friedel–Crafts reactions as key steps. Notably, the high reaction temperatures utilized for Friedel–Crafts acylation allowed selective formation of an intermediate that led to the desired ketone products in a process likely involving atropisomers. The synthesis of FL-120B′ represents the first total synthesis of an epoxide-containing, diazobenzofluorene natural product. Studies involving evaluation of reductive coupling of epoxykinamycins to access the lomaiviticins and related compounds will be reported in due course.

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