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

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Abstract

Turn up the heat: An asymmetric total synthesis of the epoxykinamycin FL-120B' is reported. The synthesis establishes a route to epoxide-containing diazobenzofluorenes which could potentially serve as monomers to the dimeric lomaiviticins. Key steps include Sharpless asymmetric epoxidation, Stille coupling, and intramolecular Friedel-Crafts acylation of atropisomeric carboxylic acids at elevated temperatures to construct the FL-120B' core structure.

Keywords

antitumor agents; natural products; Friedel-Crafts; atropisomerism; total synthesis

Diazobenzofluorene natural products are a family of structurally complex molecules with a tetracyclic (ABCD) framework bearing a diazo moiety - a functionality sparsely found in Nature (Figure 1).[1] Members of this family differ in levels of functionalization of the cyclohexene moiety (D ring). Kinamycin C (**1**),[2] 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 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 and coworkers 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 C(2)-C(2') linkage of precursors that closely resemble the monomeric kinamycins.

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 and coworkers have reported a remarkable 11-step synthesis of the lomaiviticin aglycon.[11] Their dimerization approach utilizes an oxidative homo-coupling of a silyl enol ether derived from a protected monomer resembling **7** (Figure

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2, *a*). Given the abundance of diazobenzofluorene natural products bearing an epoxide or oxygenated functionality at the C(2) position, we believe that a biosynthetic precursor to the lomaiviticins may also be depicted by proposed monomer **8** (Figure 2, *b*). This dimerization process may result from a reductive epoxide opening[12] event leading to pivotal carbon-carbon bond formation.[13] In this regard, we report the total synthesis of FL-120B' (**4**) and development of methodologies to prepare diazobenzofluorenes with intact epoxides which may allow future access to the lomaiviticins and related compounds.

In our retrosynthetic analysis, we believed that diazo installation of FL-120B' (**4**) could be derived from a two-step process from a diazobenzofluorenone intermediate such as **9** (Figure 3). This strategy would first involve sulfonylhydrazone installation to a ketone precursor and a subsequent oxidation with spontaneous desulfination of the hydrazone to form the requisite diazo functionality.[9c–e] The synthesis of **9** may be achieved from naphthalene fragment **10** and epoxide **11** utilizing a Stille coupling and intramolecular Friedel-Crafts acylation using conditions previously described in our group's synthesis of kinamycin C.[9b]

In our prior synthesis,[9b] asymmetric nucleophilic epoxidation (*D*-DIPT, Ph_3COOH, and NaHMDS)[14] was utilized to access chiral, non-racemic **11**. Unfortunately, high levels of enantioselectivity were not achieved on a larger scale. However, Sharpless asymmetric epoxidation ($Ti(O\textit{i}\text{-}Pr)_4$, *L*-DIPT, and *t*-BuOOH) of quinone monoketal **12** was performed on a 4.4 g scale to provide **13** in 98% yield with moderate enantioselectivity (68% ee) (Scheme 1).[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 ($Na_2S_2O_4$) and subsequently methylated (MeI) to provide bromonaphthalene derivative **15** (Scheme 2). Stannylation ($(SnBu_3)_2$, $Pd(PPh_3)_4$)[16] of **15** afforded aryl stannane **10**. Stille coupling ($Pd_2(dba)_3{\cdot}CHCl_3$, CuCl, $AsPh_3$, $\textit{i}\text{-}Pr_2NEt$)[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 ^1H 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 *t*-butoxycarbonyl (Boc) groups to provide protected intermediates **18a**, **18b**, and **18c**, respectively. Desilylation (HF·pyridine)[21] of **18a–c** and oxidation with Dess-Martin periodinane[22] gave aldehydes **19a–c**. 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 byproducts **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 (crude ^1H NMR analysis) mixture of *C*-acylation to *O*-acylation products (**21a** : **22a**) was observed. Higher ratios (**21** : **22**) were observed with the use of the bulkier azidobutyrate ($C(O)(CH_2)_3N_3$) and Boc groups (>20 : 1) (Entries 3–5, Table 1).[19] Interestingly, we found that higher reaction temperatures were required to achieve higher selectivities and yields for desired ketones products. For example, subjecting **20b** to TFAA at rt gave a 4 : 1 (**21b** : **22b**) selectivity and a 58% yield for ketone **21b** (Entry 2, Table 1). The ratio was significantly increased (>20 : 1) when the reaction was performed at 50 °C and 80 °C affording **21b** in 81% and 84% yields, respectively (Entries 3 and 4, Table 1).[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 (H(8) proton shows coalescence at 80 °C, Figure 4) in which the barrier to rotation ($\Delta G^{\ddagger}$) for acid **20b** was calculated to be 18 kcal/mmol.[25] This significant barrier to rotation may be directly correlated to atropisomeric acylium intermediates $\mathbf{A_1}$ and $\mathbf{A_2}$ (Scheme 3). 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 (partial structures shown for clarity).[19,26] At higher temperatures, $\mathbf{A_1}$ and $\mathbf{A_2}$ may rapidly equilibrate leading to a thermodynamically-favored ketone intermediate. We believe that ketone intermediate $\mathbf{B_2}$ should be energetically preferred due to an unfavorable steric interaction between the C(16) aryl methoxy and C(1) protected alcohol in intermediate $\mathbf{B_1}$. In intermediate $\mathbf{B_2}$, the interaction between the C(16) aryl methoxy and H(1) 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 (TBDPSCl) to give *bis*-silylated ketone **23** (Scheme 4). Initial attempts to form mesylhydrazone **24** failed to retain the sensitive epoxide moiety using various Lewis and Bronsted acids. Ultimately, trifluoroacetic acid (TFA) proved to be a suitable Bronsted acid with a non-nucleophilic counteranion to promote hydrazone formation to **24**. Oxidation of **24** with ceric (IV) ammonium nitrate (CAN) provided the desired quinone with partial spontaneous desulfination to the desired diazo product. 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·pyrdine cleanly gave FL-120B' (**4**). For comparison, a 4-step semi-synthesis of **4** from the closely related FL-120B (**3**) was also achieved.[19] Synthetic and semi-synthetic 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 semi-synthetic ($[\alpha]_D^{23} = -128°$) FL-120B' allowed assignment of the absolute configuration for both FL-120B (**3**) and FL-120B' (**4**) as depicted in Figure 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, high reaction temperatures utilized for Friedel-Crafts acylation allowed selective formation of an intermediate that led to desired ketone products in a process likely involving atropisomeric intermediates. The completion 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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References

1. For a recent review on diazo natural products, see: Nawrat CC, Moody CJ. Nat. Prod. Rep. 2011; 28:1426–1444. [PubMed: 21589994]
2. (a) Ito S, Matsuya, T T, Omura S, Otani M, Nakagawa A. J. Antibiot. 1970; 23:315–317. [PubMed: 5458310] b) Hata T, Omura S, Iwai Y, Nakagawa A, Otani M. J. Antibiot. 1971; 24:353–359.

[PubMed: 5091211] c) Omura S, Nakagawa A, Yamada H, Hata T, Furusaki A. Chem. Pharm. Bull. 1973; 21:931–940. [PubMed: 4727361]

3. For a review on the biosynthesis of diazobenzofluorene natural products, see: Gould SJ. Chem. Rev. 1997; 97:2499–2509. [PubMed: 11851467]
4. Cone MC, Seaton PJ, Halley KA, Gould SJ. J. Antibiot. 1989; 42:179–188. [PubMed: 2925509] b) Seaton PJ, Gould SJ. J. Antibiot. 1989; 42:189–197. [PubMed: 2925510]
5. Lin HC, Chang SC, Wang NL, Chang LR. J. Antibiot. 1994; 47:675–680. [PubMed: 8040072] b) Young J-J, Ho SN, Ju WM, Chang LR. J. Antibiot. 1994; 47:681–687. [PubMed: 8040073]
6. (a) Hasinoff BB, Wu X, Yalowich JC, Goodfellow V, Laufer RS, Adedayo O, Dmitrienko GI. Anti-Cancer Drugs. 2006; 17:825–837. [PubMed: 16926632] (b) O'hara KA, Wu X, Patel D, Liang H, Yalowich JC, Chen N, Goodfellow V, Adedayo O, Dmitrienko GI, Hasinoff BB. Free Radical Biol. Med. 2007; 43:1132–1144. [PubMed: 17854709]
7. (a) Feldman KS, Eastman KJ. J. Am. Chem. Soc. 2005; 127:15344–15345. [PubMed: 16262378] (b) Feldman KS, Eastman KJ. J. Am. Chem. Soc. 2006; 128:12562–12573. [PubMed: 16984207] (c) Ballard TE, Melander C. Tetrahedron Lett. 2008; 49:3157–3161.(d) Khdour O, Skibo EB. Org. Biomol. Chem. 2009; 7:2140–2154. [PubMed: 19421453] (e) Heinecke CL, Melander C. Tetrahedron Lett. 2010; 51:1455–1458.
8. He H, Ding D, Bernan VS, Richardson AD, Ireland CM, Greenstein M, Ellestad GA, Carter GT. J. Am. Chem. Soc. 2001; 123:5362–5363. [PubMed: 11457405]
9. (a) Hauser FM, Zhou M. J. Org. Chem. 1996; 61:5722.(b) Lei X, Porco JA Jr. J. Am. Chem. Soc. 2006; 128:14790–14791. [PubMed: 17105273] (c) Kumamoto T, Kitani Y, Tsuchiya H, Yamaguchi K, Seki H, Ishikawa T. Tetrahedron. 2007; 63:5189–5199.(d) Birman VB, Zhao Z, Guo L. Org. Lett. 2007; 9:1223–1225. [PubMed: 17328553] (e) Nicolaou KC, Li H, Nold AL, Pappo D, Lenzen A. J. Am. Chem. Soc. 2007; 129:10356–10357. [PubMed: 17676854] (f) Woo CM, Lu L, Gholap SL, Smith DR, Herzon SB. J. Am. Chem. Soc. 2010; 132:2540–2541. [PubMed: 20141138] (g) Kimura S, Kobayashi S, Kumamoto T, Akagi A, Sato N, Ishikawa T. Helv. Chim. Acta. 2011; 94:578–591.
10. (a) Nicolaou KC, Denton RM, Lenzen A, Edmonds DJ, Li A, Milburn RR, Harrison ST. Angew. Chem. 2006; 118:2130–2135.Nicolaou KC, Denton RM, Lenzen A, Edmonds DJ, Li A, Milburn RR, Harrison ST. Angew. Chem. Int. Ed. 2006; 45:2076–2081.(b) Zhang W, Baranczak A, Sulikowski GA. Org. Lett. 2008; 10:1939–1941. [PubMed: 18410121] (c) Krygowski ES, Murphy-Benenato K, Shair MD. Angew. Chem. 2008; 120:1704–1708.Krygowski ES, Murphy-Benenato K, Shair MD. Angew. Chem. Int. Ed. 2008; 47:1680–1684.(d) Nicolaou KC, Nold AL, Li H. Angew. Chem. 2009; 121:5974–5977.Nicolaou KC, Nold AL, Li H. Angew. Chem. Int. Ed. 2009; 48:5860–5863.(e) Gholap SL, Woo CM, Ravikumar PC, Herzon SB. Org. Lett. 2009; 11:4322–4325. [PubMed: 19719089] (f) Lee HG, Ahn JY, Lee AS, Shair MD. Chem. Eur. J. 2010; 16:13058–13062. [PubMed: 20976820]
11. Herzon SB, Lu L, Woo CM, Gholap SL. J. Am. Chem. Soc. 2011; 133:7260–7263. [PubMed: 21280607]
12. For an analogous reductive epoxide opening for dynemicin A, see: Sugiura Y, Shiraki T, Konishi M, Oki T. Proc. Natl. Acad. Sci, U.S.A. 1990; 87:3831–3835. [PubMed: 2339123]
13. For reductive dimerization of anthracycline antitumor drugs, see: Gaudiano G, Koch TH. Chem. Res. Toxicol. 1991; 4:2–16. and references therein. [PubMed: 1912296]
14. Li C, Johnson RP, Porco JA Jr. J. Am. Chem. Soc. 2003; 125:5095–5106. [PubMed: 12708860]
15. For Sharpless asymmetric epoxidation of an electron deficient quinone monoketal, see: Clark DA, Riccardis FD, Nicolaou KC. Tetrahedron. 1994; 50:11391–11426.
16. Azizian H, Eaborn C, Pidcock A. J. Organomet. Chem. 1981; 215:49–58.
17. Bobe F, Tunoori AR, Niestroj AJ, Gronwald O, Maier ME. Tetrahedron. 1996; 52:9485–9498.
18. For reviews on atropisomerism, see: Bringmann G, Mortimer AJP, Keller PA, Gresser MJ, Garner J, Breuning M. Angew. Chem. Int. Ed. 2005; 44:5384–5427. Clayden J, Moran WJ, Edwards PJ, LaPlante SR. Angew. Chem. Int. Ed. 2009; 48:6398–6401. Bringmann G, Gulder T, Gulder TAM, Breuning M. Chem. Rev. 2011; 111:563–569. [PubMed: 20939606]
19. See Supporting Information for complete details.
20. Kusumoto S, Sakai K, Shiba T. Bull. Chem. Soc. Jpn. 1986; 59:1296–1298.

21. Carreira EM, Du Bois J. J. Am. Chem. Soc. 1995; 117:8106–8125.
22. (a) Dess DB, Martin JC. J. Org. Chem. 1983; 48:4155–4156.(b) Ireland RE, Liu L. J. Org. Chem. 1993; 58:2899.
23. (a) Lindgren BO, Nilsson T. Acta. Chem. Scand. 1973; 27:888–890.(b) Kraus GA, Taschner MJ. J. Org. Chem. 1980; 45:1175–1176.(c) Bal BS, Childers WE Jr, Pinnick HW. Tetrahedron. 1981; 37:2091–2096.
24. Takatani M, Matsuo I, Ito Y. Carbohydr. Res. 2003; 338:1073–1081. [PubMed: 12706973]
25. For a recent review on the use of dynamic NMR spectroscopy for conformational analysis, see: Casarini D, Lunazzi L, Mazzanti A. Eur. J. Org. Chem. 2010:2035–2056.
26. For intramolecular Friedel-Crafts acylation of separable atropisomers giving different ketone and lactone product distributions, see: Yonemoto K, Nakai Y, Yamamoto G, Oki M. Chem. Lett. 1985:1739–1742.
27. For CAN-mediated oxidation of hydrazones, see: Bird JW, Diaper DGM. Can. J. Chem. 1969; 47:145–150.

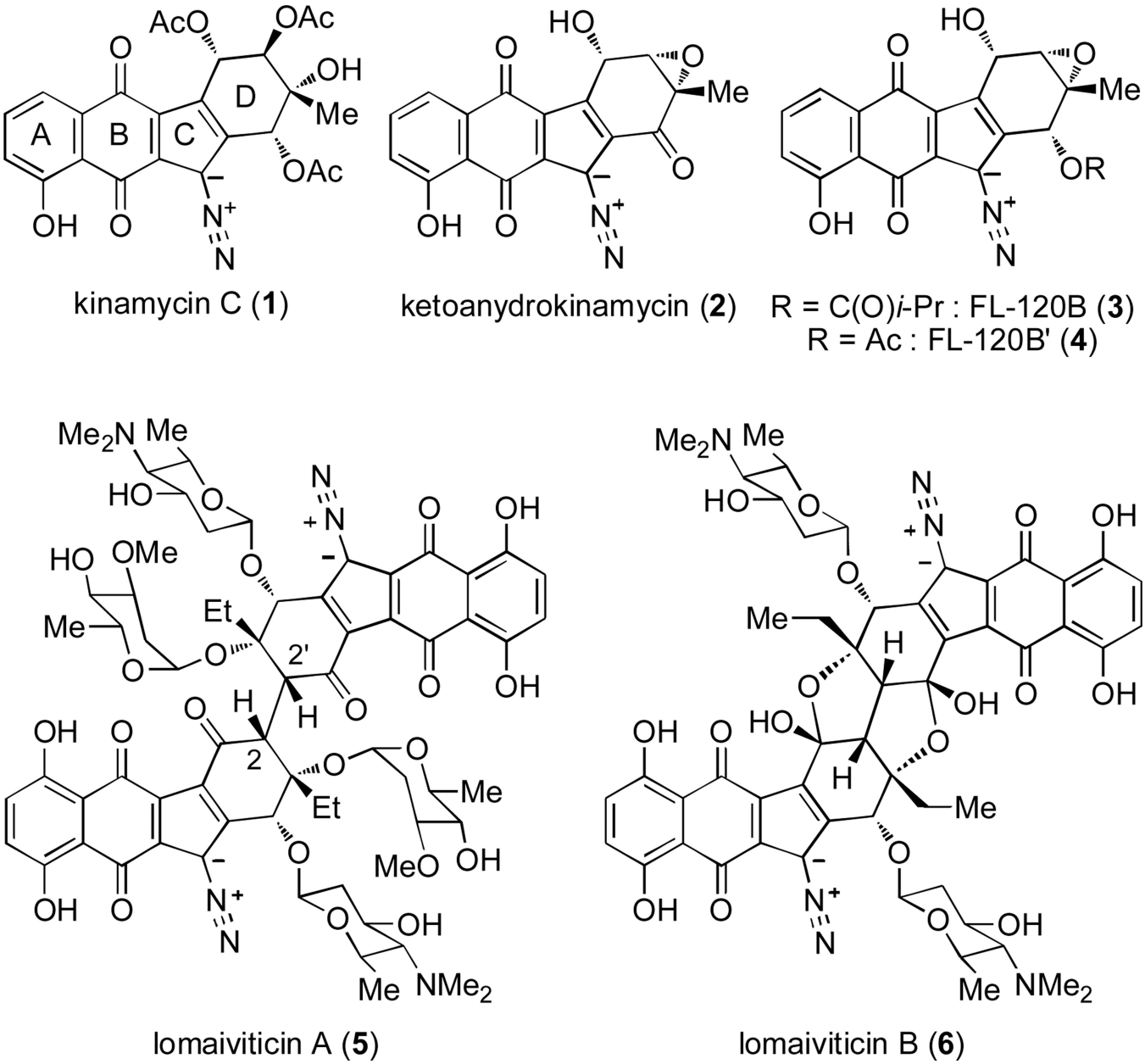


Figure 1.
Representative diazobenzofluorene natural products.

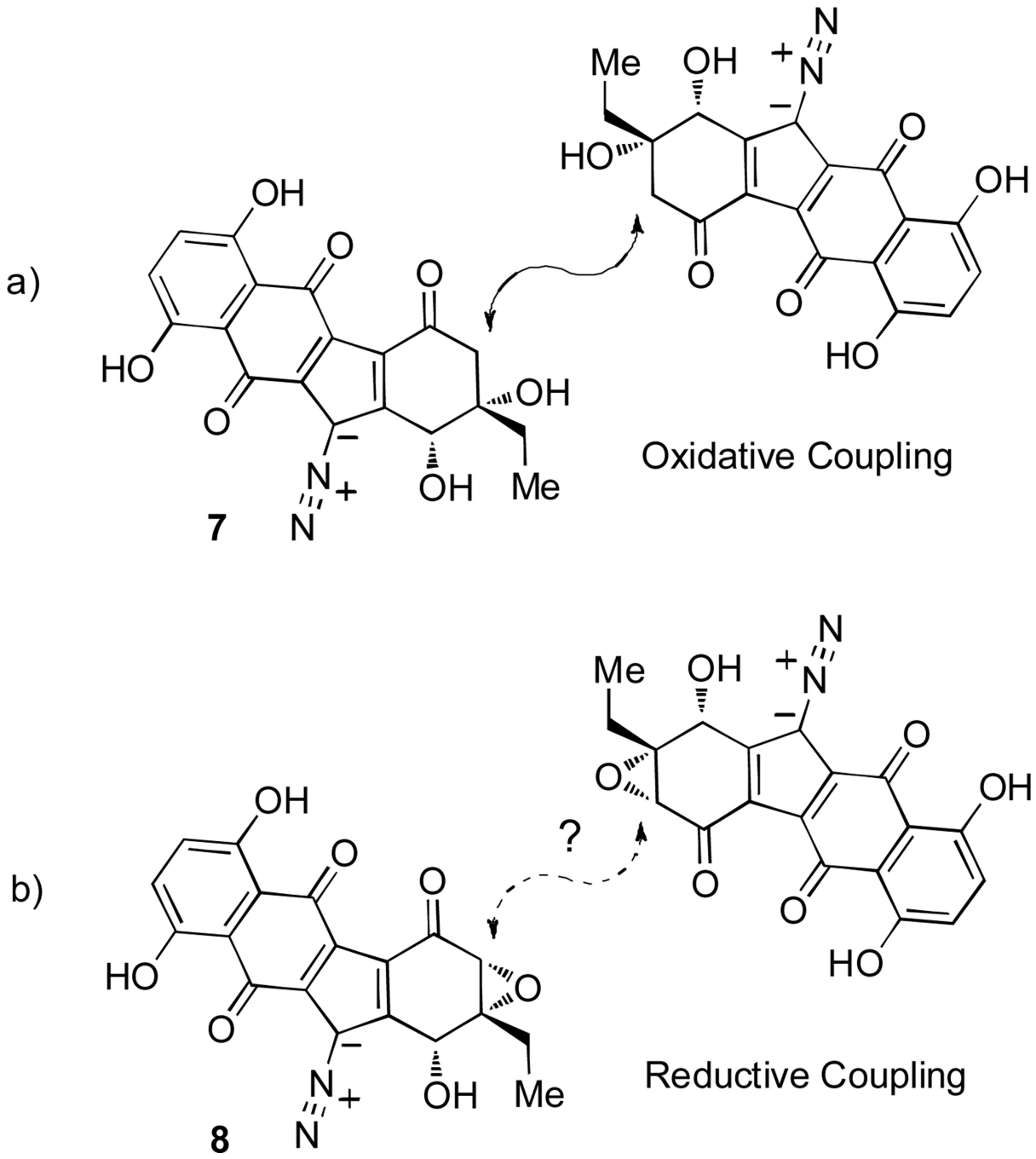


Figure 2.
Biomimetic approaches to the lomaiviticins.

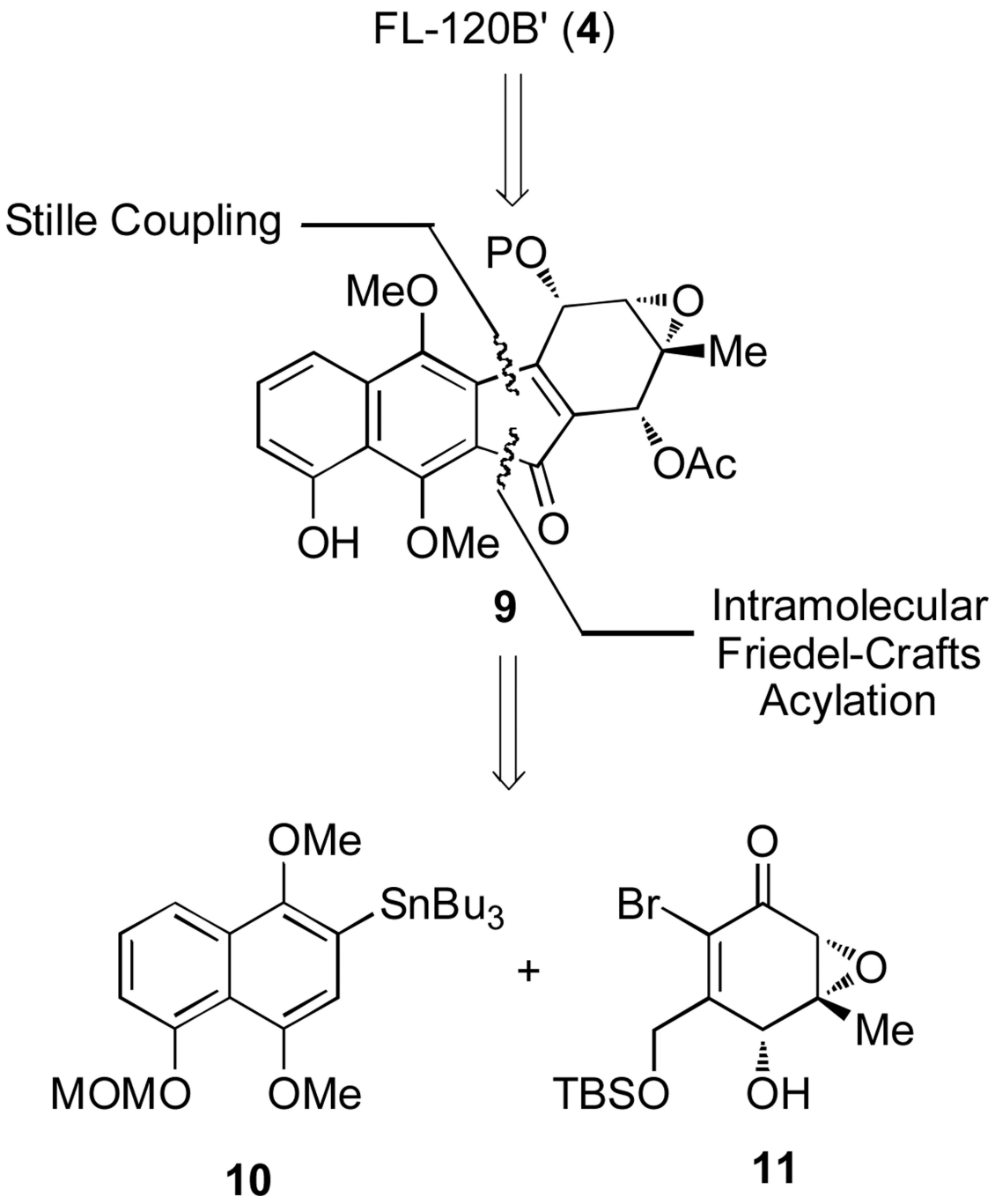


Figure 3.
Retrosynthesis for FL-120B' (**4**). P = protecting group, MOM = methoxymethyl. TBS = *t*-butyldimethylsilyl.

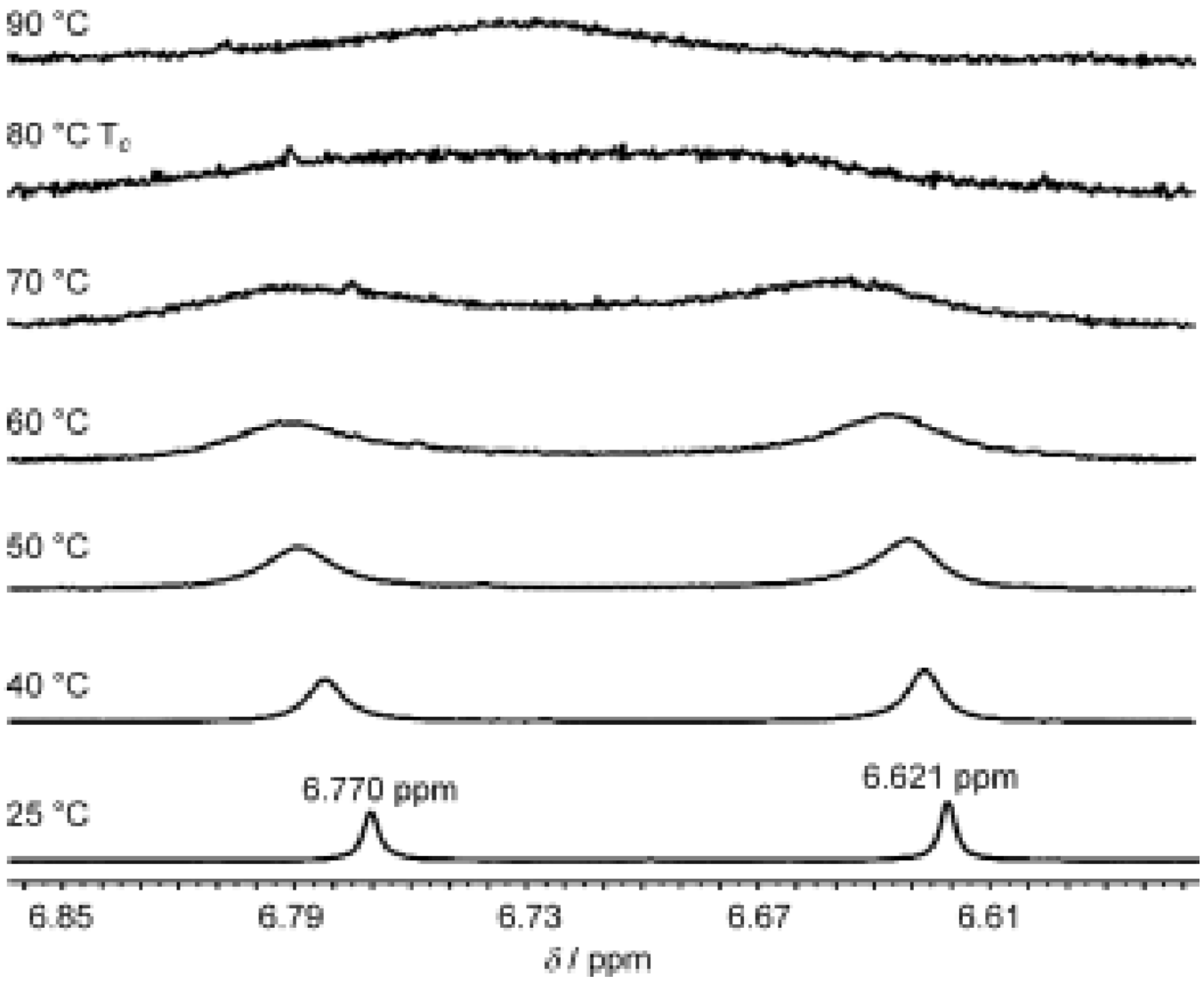
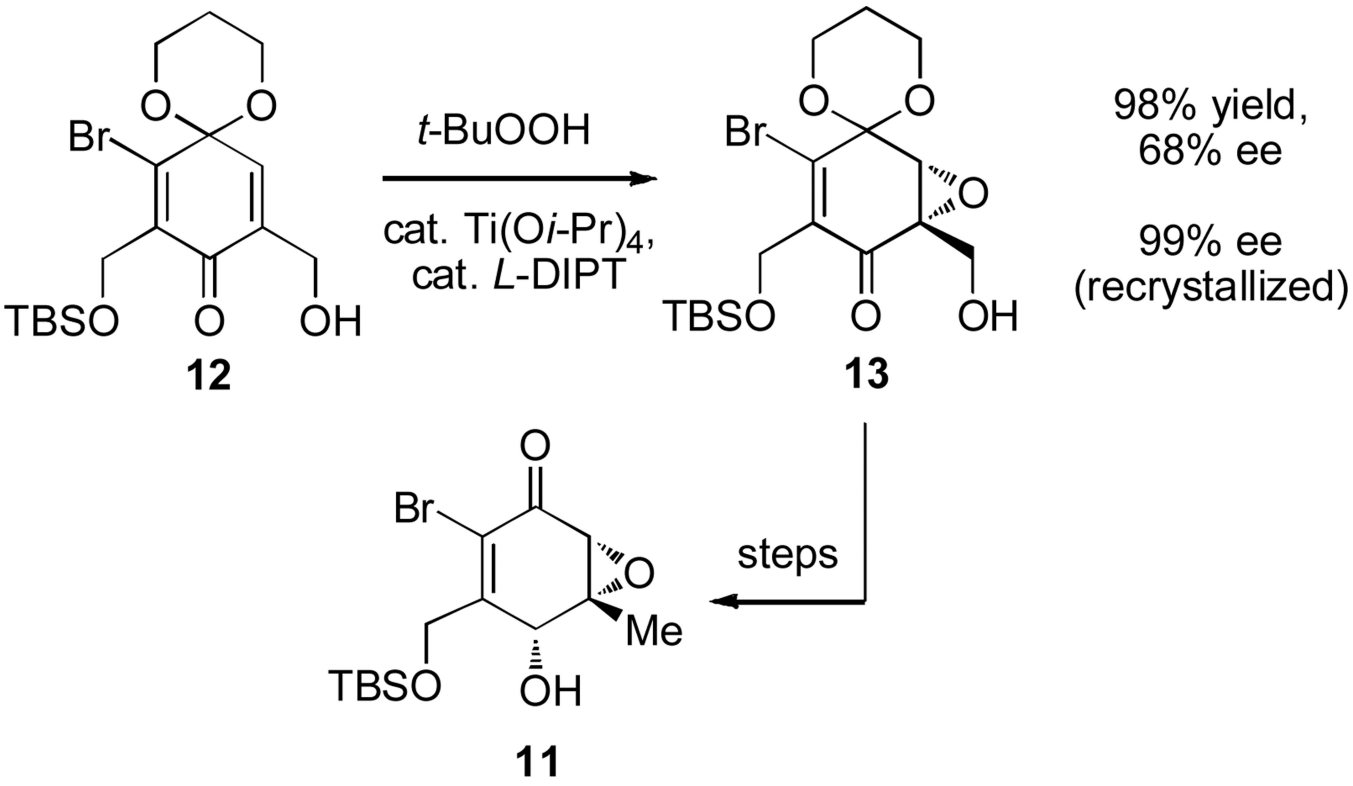
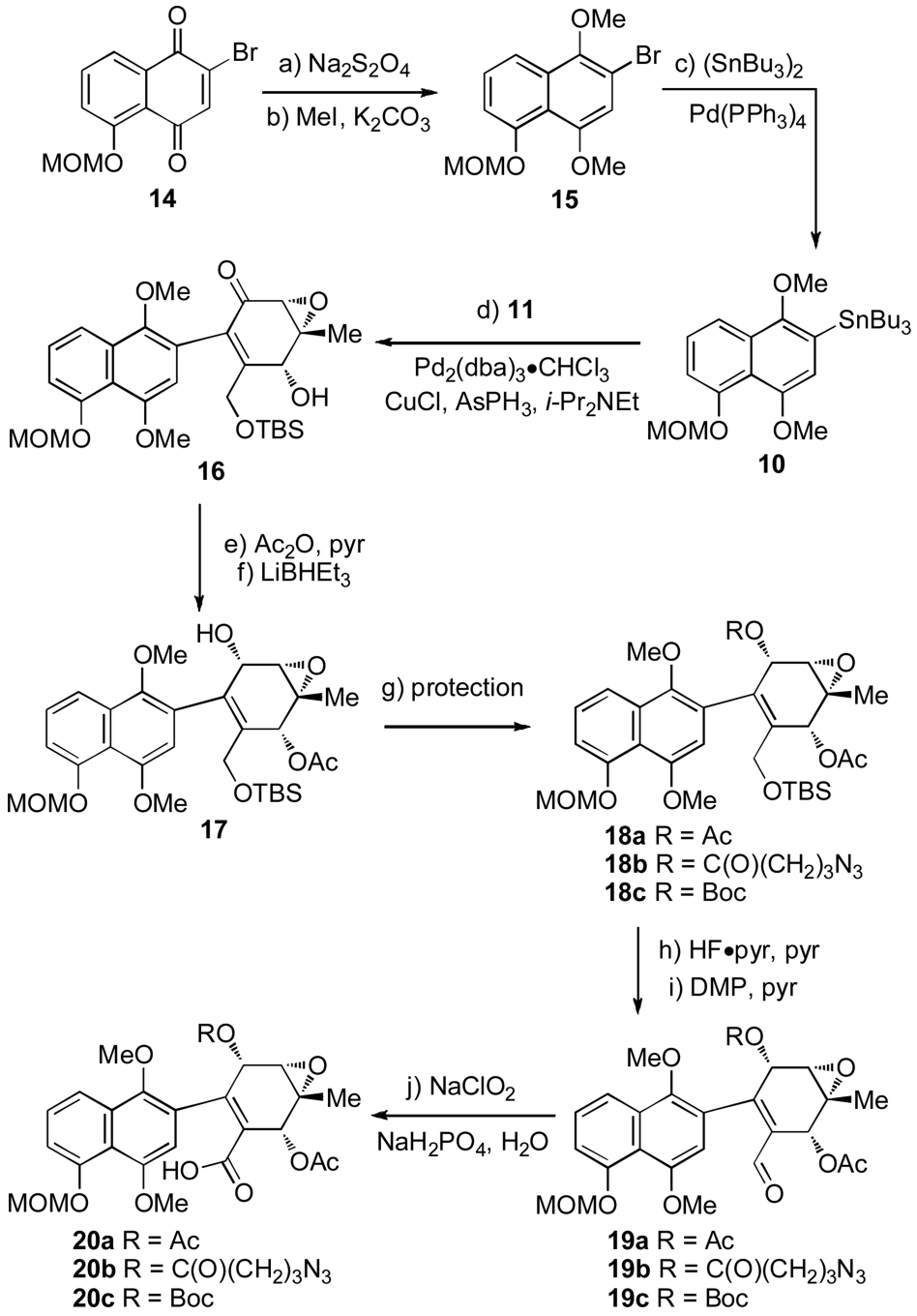


Figure 4.
Variable temperature (VT) ^{1}H NMR (500 MHz, CD_3NO_2) stackplot of acid **20b**.



Scheme 1.

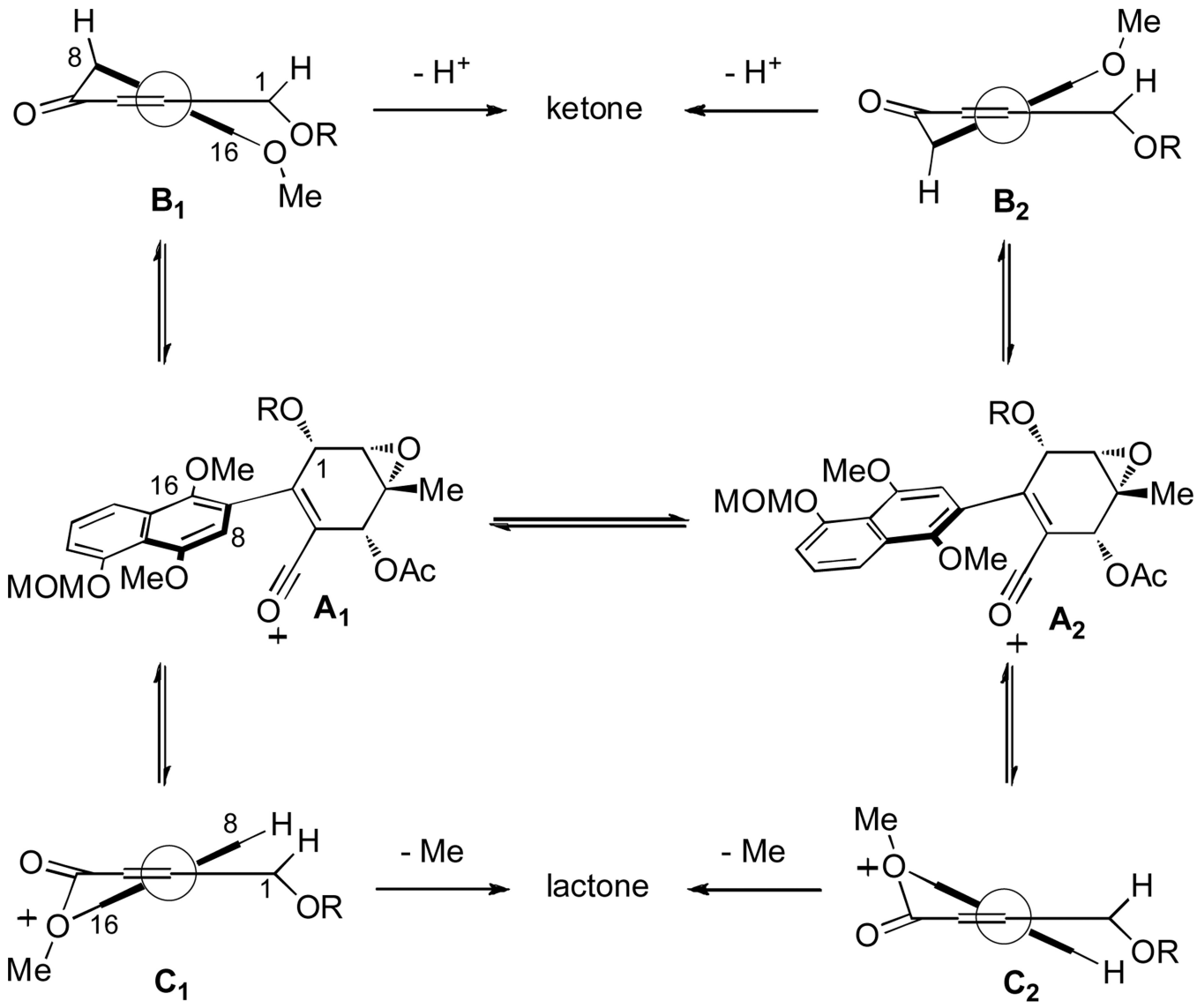
Enantioselective synthesis of epoxide **13.** *t*-BuOOH (2.0 equiv), Ti(O*i*-Pr)$_4$ (0.10 equiv), *L*-DIPT (0.13 equiv), 4Å MS, CH_2Cl_2, 0 °C, 60 h. DIPT = diisopropyl tartrate, MS = molecular sieves.



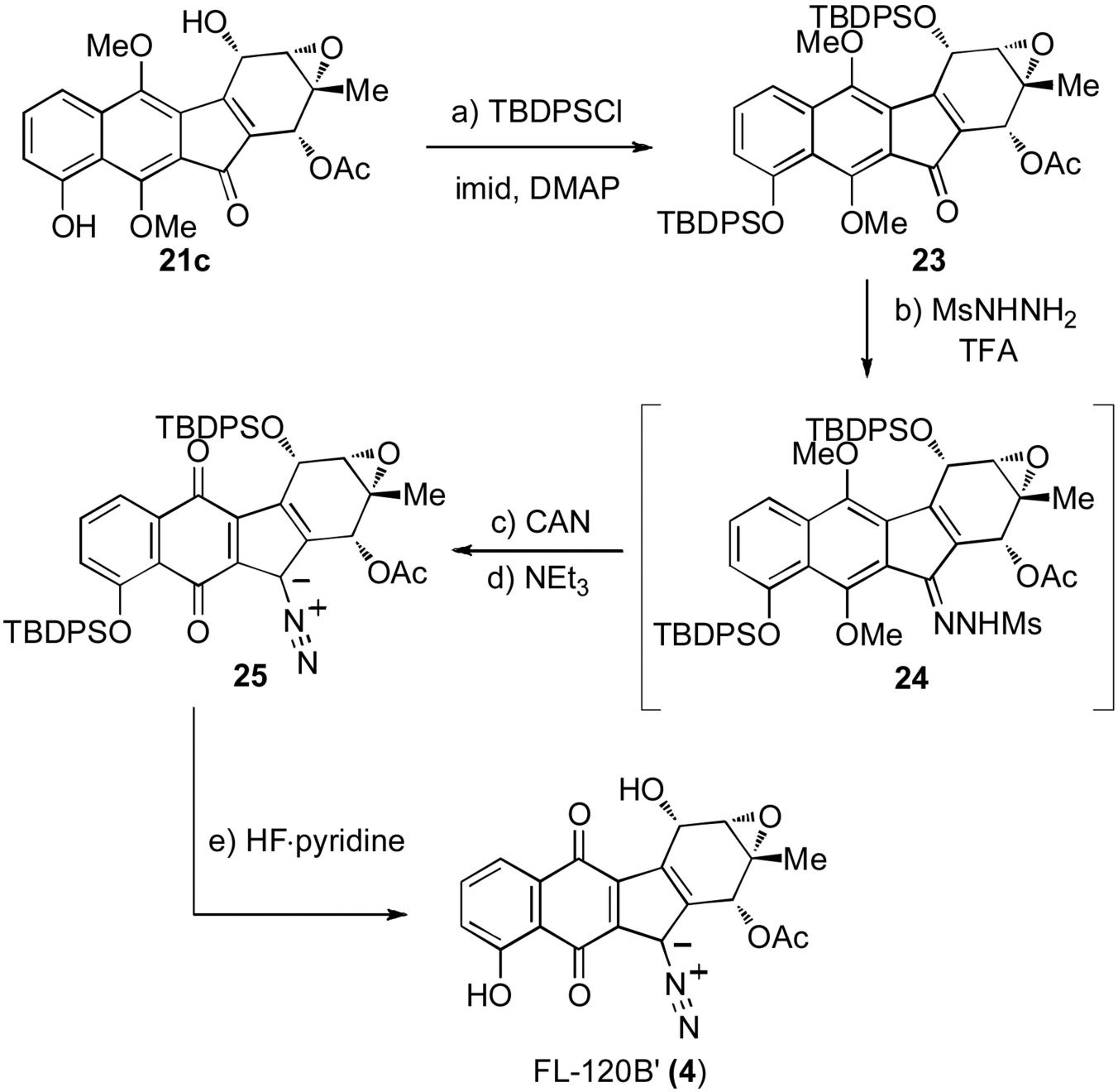
Scheme 2.

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), $Pd_2(dba)_3$·$CHCl_3$ (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%. Dba = dibenzylideneacetone, DMF = *N,N*-dimethylformamide, pyr = pyridine, Boc = *t*-butoxycarbonyl, DMAP = *N,N*-dimethyl-4-aminopyridine, DMP = Dess-Martin periodinane.



Scheme 3.
Proposed cyclization manifolds for intramolecular Friedel-Crafts acylation and lactone formation.

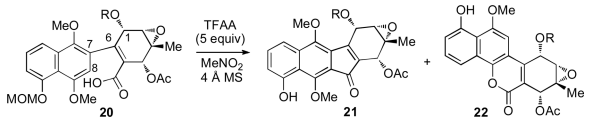


Scheme 4.

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%. TBDPS = *t*-butyldiphenylsilyl, imid = imidazole, Ms = methanesulfonyl, CAN = cerium (IV) ammonium nitrate.

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 crude ^{1}H NMR analysis.

[c] Yields are based on isolation from silica gel column chromatography.

[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 trifluroacetylated intermediates.

[f] Boc group was cleaved during reactions: R = H. TFAA = trifluoroacetic anhydride, TFA = trifluoroacetic acid.