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Benzo[*b*]fluorenes via Indanone Dianion Annulation. A Short Synthesis of Prekinamycin

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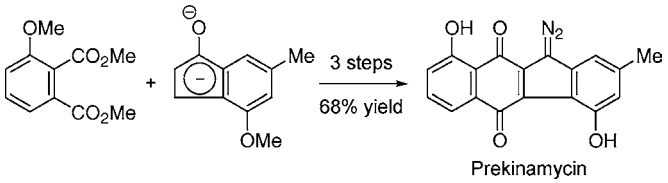
ABSTRACT



A rapid construction of benzo[*b*]fluorenones via reaction of 1-indanone dianions with phthalate diesters is described. Its utility is illustrated with a concise synthesis of prekinamycin.

The benzo[*b*]fluorene family of natural products comprises two major subgroups: the kinamycin antibiotics **1** and their aromatic congeners, **2**−**5**,[1] and the dimeric lomaiviticins **6** (Figure 1). Kinamycins[2,3] are strongly active against Gram-positive bacteria. Lomaiviticins, in addition to their potent antibacterial activity, exhibit powerful cytotoxicity against a wide range of cancer cell lines.[4]

Synthetic efforts in this area have resulted in the preparation of several naturally occurring aromatic benzo[*b*]fluorenes[5−7] and model compounds.[8,9] The first total synthesis of kinamycins has been published only recently.[10,11] The challenges posed by the stereochemical complexity of lomaivi-

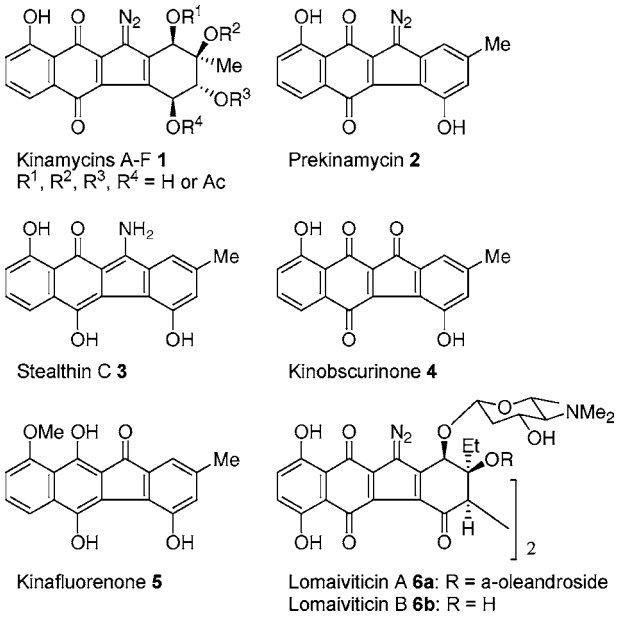


Figure 1. Benzo[*b*]fluorene natural products.

(1) For reviews of biosynthesis, history of structure determination, and synthetic studies, see: (a) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499. (b) Marco-Contelles, J.; Molina, M. T. *Curr. Org. Chem.* **2003**, *7*, 1433. (c) Kumamoto, T.; Ishikawa, T.; Omura, S. *J. Synth. Org. Chem. Jpn.* **2004**, *62*, 49.

(2) Isolation of kinamycins, their antibiotic activity, and the original structure determination: (a) Ito, S.; Matsuya, T.; Omura, S.; Otani, M.; Nakagawa, A.; Takeshima, H.; Iwai, Y.; Ohtani, M.; Hata, T. *J. Antibiot.* **1970**, *23*, 315. (b) Hata, T.; Omura, S.; Iwai, Y.; Nakagawa, A.; Otani, M.; Ito, S.; Matsuya, T. *J. Antibiot.* **1971**, *24*, 353. (c) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1971**, *19*, 2428. (d) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1973**, *21*, 931.

(3) Structure revision of kinamycins: (a) Gould, S. J.; Tamayo, N.; Melville, C. R.; Cone, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 2207. (b) Mithani, S.; Weeratunga, G.; Taylor, N. J.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **1994**, *116*, 2209.

(4) He, H.; Ding, W.-D.; Bernan, V. S.; Richardson, A. D.; Ireland, C. M.; Greenstein, M.; Ellestad, G. A.; Carter, G. T. *J. Am. Chem. Soc.* **2001**, *123*, 5362.

(5) Synthesis of prekinamycin: Hauser, F. M.; Zhou, M. *J. Org. Chem.* **1996**, *61*, 5722.

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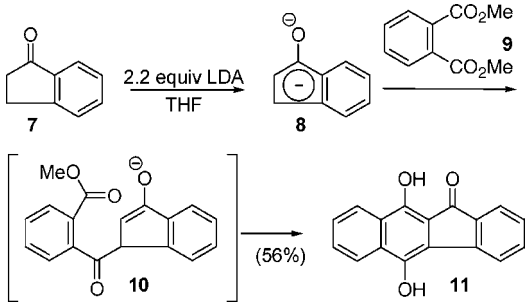
ticins still remain to be overcome.[12] Conceivably, both kinamycins and lomaiviticins could be accessed via oxidative dearomatization of aromatic precursors in a manner reminiscent of their probable biosynthesis.[1a] To explore the biogenetically patterned approach to these targets, we required a concise and flexible synthesis of the benzo[*b*]-fluorenone core. Although a number of synthetic approaches to this tetracycle have been described in the literature,[5−8] the existing schemes were deemed to be too lengthy to be suitable for the preparation of an early synthetic intermediate.

In this communication, we report a new method for the synthesis of functionalized benzo[*b*]fluorene derivatives, which compares favorably with the earlier routes. To demonstrate its utility, we also describe a short and high-yielding total synthesis of prekinamycin.[13] Apart from its significance as the direct biosynthetic precursor of kinamycins, prekinamycin and its derivatives have recently been used to elucidate the mechanism of action of diazobenzofluorene antibiotics.[14]

We realized that 5,10-dihydroxy-benzo[*b*]fluoren-11-one **11**,[8a,b,15] containing the essential structural elements of kinafluorenone **5**, could be assembled in a single step via sequential bisacylation of indanone dianion **8**[16] with a phthaloyl biselectrophile, e.g., dimethyl phthalate **9** (Scheme 1). It is surprising that this exceedingly simple approach to the benzo[*b*]fluorene natural products has not been previously described.[17] Because both of the requisite starting materials

Scheme 1. Synthesis of the Model Benzo[*b*]fluorenone **11**



were commercially available chemicals, the idea was immediately put to the test. A solution of the dianion generated by treatment of 1-indanone with 2.2 equiv of LDA was treated with dimethyl phthalate producing a bright purple solution. Upon the usual workup, the orange tetracycle **11** was isolated in 46% yield by precipitation and recrystallization (Table 1, entry 1).

Table 1. Optimization of Indanone Dianion Annulation[a]

entry	base, solvent	equiv of **9**	total solvent volume, mL	yield, %
1	LDA, THF	1.0	4.4	46
2	LDA, THF	1.0	3.4	65
3	LDA, THF	0.8	3.4	77
4	LDA, THF	1.2	3.4	60
5	LDA, THF	0.8	1.8	71
6	LDA, THF	0.8	1.5	60
7	LDA, Et_2O	0.8	3.4	65
8	LHMDS, THF	0.8	2.6	26
9	KHMDS, THF	0.8	4.8	0
10	LTMP, THF	0.8	3.4	80

[a] Conditions: 1.0 mmol of **7**, 2.25 mmol of base, −78 to 0 °C; 0.8−1.2 mmol of **9** added at −78 °C.

Optimization of the reaction conditions was undertaken next. Concentrations of the reactants had a marked effect on the yields (Table 1, entries 1 and 2; 3, 5, and 6). Higher yields were obtained when dimethyl phthalate was used as the limiting reagent (entries 2−4). Changing the solvent to diethyl ether was not beneficial (cf. entries 3 and 7). Commercially available bases, such as LHMDS or KHMDS (entries 8 and 9) or commercial LDA, were considerably inferior to freshly prepared LDA. Lithium tetramethylpiperidide (LTMP), on the other hand, produced a slightly improved yield (entry 10).

With a substantial quantity of the model tetracycle **11** in hand, we examined the installation of the diazo group at C11. Previously, this transformation was accomplished in moderate yields via hydrazone formation followed by oxidation with Fetizon's reagent.[5,8b] The following alternative procedure appears to be more convenient (Scheme 2). Crude tosylhydrazone **12a** easily prepared by refluxing **11** in ethanol with tosylhydrazide was directly oxidized with CAN to yield

(6) Synthesis of stealthins: (a) Gould, S. J.; Melville, C. R.; Cone, M. C.; Chen, J.; Carney, J. R. *J. Org. Chem.* **1997**, *62*, 320. (b) Koyama, H.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 203.

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(9) For a review of existing approaches, see refs 1b and c.

(10) Enantioselective total synthesis of kinamycin C: Lei, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 14790.

(11) For synthetic studies towards kinamycins, see: (a) Kumamoto, T.; Tabe, N.; Yamaguchi, K.; Ishikawa, T. *Tetrahedron Lett.* **2000**, *41*, 5693. (b) Kumamoto, T.; Tabe, N.; Yamaguchi, K.; Yagishita, H.; Iwasa, H.; Ishikawa, T. *Tetrahedron* **2001**, *57*, 2717. (c) Kitani, Y.; Morita, A.; Kumamoto, T.; Ishikawa, T. *Helv. Chim. Acta* **2002**, *85*, 1186. (d) Zhao, Z.; Guo, L.; Birman, V. B. *Abstracts of Papers*, 231st ACS National Meeting, Atlanta, GA, March 26−30, 2006; American Chemical Society: Washington, DC, 2006; ORGN 473.

(12) For synthetic studies toward lomaiviticins, see: (a) Nicolaou, K. C.; Denton, R. M.; Lenzen, A.; Edmonds, D. J.; Li, A.; Milburn, R. R.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 2076. (b) Freed, J. D. Ph.D. Thesis, Harvard University, 2005. (c) Pongdee, R. Ph.D. Thesis, Texas A&M University, 2003.

(13) (a) Isolation of the "original prekinamycin": Seaton, P. J.; Gould, S. J. *J. Antibiot.* **1989**, *42*, 189. (b) Reassignment of the name "prekinamycin" to the compound prepared by Hauser and Zhou (ref 5): Gould, S. J.; Chen, J.; Cone, M. C.; Gore, M. P.; Melville, C. R.; Tamayo, N. *J. Org. Chem.* **1996**, *61*, 5720. (c) Structure revision of the original prekinamycin: Proteau, P. J.; Li, Y.; Chen, J.; Williamson, R. T.; Gould, S. J.; Laufer, R. S.; Dmitrienko, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 8325.

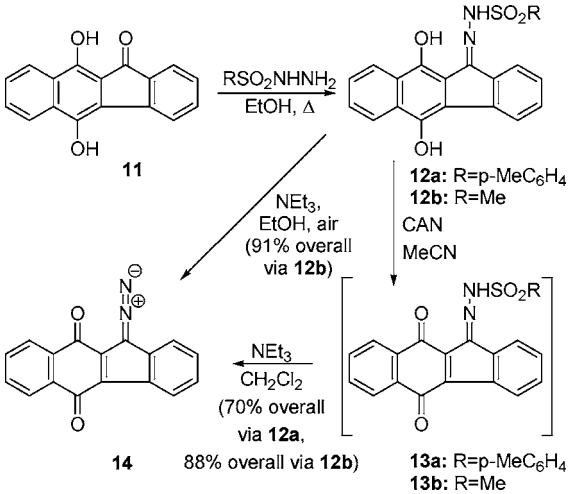
(14) Feldman, K. S.; Eastman, K. J. *J. Am. Chem. Soc.* **2005**, *127*, 15344.

(15) Compound **11** was first prepared long before the discovery of benzo[b]fluorenones in nature: (a) Koelsch, C. F. *J. Am. Chem. Soc.* **1945**, *67*, 159. (b) Bader, A. R.; Ettlinger, M. G. *J. Am. Chem. Soc.* **1953**, *75*, 730.

(16) Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1977**, *42*, 3212.

(17) Condensation of 1-indanone with phthaldialdehyde leading to benzo[*b*]fluorenone has been reported, although the mechanism is not likely to involve the dianion formation: (a) Thiele, J.; Schneider, J. *Liebigs Ann.* **1909**, *369*, 287. (b) Streitwieser, A., Jr.; Brown, S. M. *J. Org. Chem.* **1988**, *53*, 904.

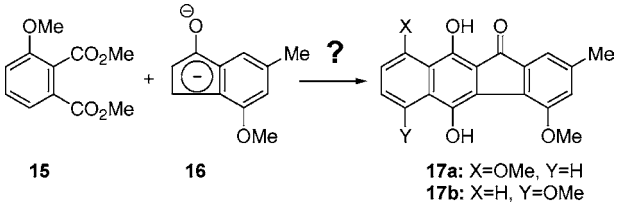
Scheme 2. Installation of the Diazo Group



the unstable quinone derivative **13a**, which underwent transformation into the desired diazoquinone **14**[8b] rapidly upon treatment with triethylamine or slowly on storage. Chromatographic separation of **14** from the *p*-toluenesulfinic acid byproduct, however, proved to be somewhat inconvenient. Therefore, the analogous procedure was developed employing mesylhydrazide instead of tosylhydrazide, which eliminated the purification problems and led to an improved yield of **14**. Even more conveniently, **12b** could be subjected to triethylamine under an air atmosphere, directly producing **14** in 91% overall yield.

Having thus optimized the preparation of the model diazoquinone **14**, we turned our attention to the synthesis of prekinamycin. Application of our newly developed annulation methodology to this target necessitated the use of an unsymmetrical phthalate diester (cf. **15**[18]), which might conceivably lead to regioselectivity problems (Scheme 3).

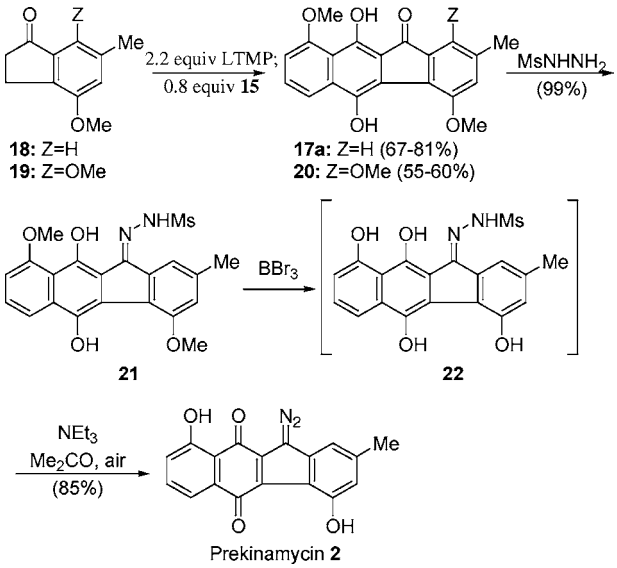
Scheme 3. Regioselectivity Issue



However, we predicted that the desired regioisomer would predominate because the reaction was presumed to commence with the nucleophilic attack of the more reactive *β*-position of the indanone dianion on the more reactive ester moiety of **15**. Indeed, the reaction of **15** with indanone **18**[5] led to the desired product **17a** in 67−81% yields (based on **15**) using LTMP as the base. At most trace amounts of the minor regioisomer, **17b** could be detected in the supernatant solution. Previously, compound **17a** was utilized in the synthesis of prekinamycin[5] and stealthin C.[6a] Benzofluorenone **20**, which serves as an intermediate in our ongoing synthetic studies toward kinamycins,[10e] was produced in an analogous fashion from indanone **19**[19] in 55−60% yield.

Refluxing **17a** with $MsNHNH_2$ in ethanol produced crude mesylhydrazone **21**. Its global demethylation with excess BBr_3[20] in dichloromethane, followed by treatment of the crude reaction mixture with triethylamine under an air atmosphere, gave rise to prekinamycin **2** in 85% overall yield (Scheme 4). The NMR spectra of the synthetic prekinamycin matched exactly those found in the literature.[5]

Scheme 4. Synthesis of Prekinamycin



In conclusion, a new, rapid approach to benzo[*b*]fluorene derivatives has been developed, which provides a convenient synthetic access to prekinamycin and its unnatural analogues and thus should facilitate their biological study. Studies aimed at the total synthesis of kinamycins via the biogenetically patterned dearomatization strategy are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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