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Formation of Benzo[*b*]fluorenes and the Benzo[*a*]fluorene Core of the Fluostatins by Cyclization of Diaryldiynones

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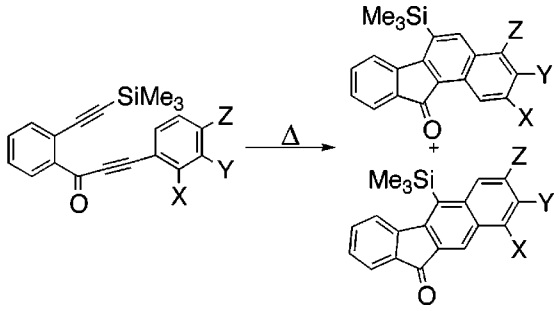
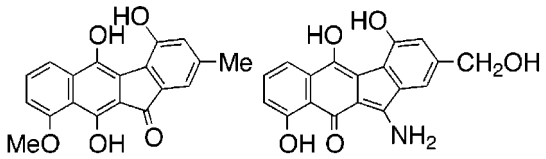
ABSTRACT



Thermal cyclization of 1-[2-(trimethylsilylethynyl)phenyl]-3-arylpropinones was expected to give benzo[*b*]fluorenones. However, benzo[*a*]-fluorenones were also formed as a result of a new rearrangement. These tetracycles possess the core structure of the fluostatins and isoprekinamycin.

Kinafluorenone (**1**)[1] and stealthin A (**2**)[2] are representative benzo[*b*]fluorene natural products structurally related to the kinamycins,[3] a group of naturally occurring quinones that display a variety of interesting antibiotic activities.[4]



1 2

Recently, we reported a concise approach for construction of the tetracyclic nucleus of the benzo[*b*]fluorene antibiotics[5] based on application of the [4 + 2] cycloaddition of arylalkyne-allenes developed by Schmittel.[6,7] Since the thermal reaction of enynes with alkynes also leads to

(1) (a) Cone, M. C.; Melville, C. R.; Gore, M. P.; Gould, S. J. *J. Org. Chem.* **1993**, *58*, 1058. (b) Carney, J. R.; Hong, S.-T.; Gould, S. J. *Tetrahedron Lett.* **1997**, *38*, 3139.

(2) Shin-ya, K.; Furihata, K.; Teshima, Y.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1992**, *33*, 7025.

(3) Gould, S. J. *Chem. Rev.* **1997**, *97*, 2499.

(4) For recent synthetic work, see: (a) Koyama, H.; Kamikawa, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 203. (b) Mohri, S.; Stefinovic, M.; Scieckus, V. *J. Org. Chem.* **1996**, *61*, 5722. (c) Koyama, H.; Kamikawa, T. *Tetrahedron Lett.* **1997**, *38*, 3973 and references therein. (d) Kumamoto, T.; Tabe; Yamaguchi, K.; Ishikawa, T. *Tetrahedron Lett.* **2000**, *41*, 5693. (e) Frutos, O.; Atienza, C.; Echavarren, A. M. *Eur. J. Org. Chem.* **2000**, in press, and references therein.

(5) de Frutos, Ó.; Echavarren, A. M. *Tetrahedron Lett.* **1997**, *38*, 7941.

(6) (a) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975. (b) Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999. (c) Schmittel, M.; Kiau, S.; Siebert, M.; Strittmatter, M. *Tetrahedron Lett.* **1996**, *37*, 7691. (d) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1843. (e) Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3*, 807. (f) Schmittel, M.; Maywald, M.; Strittmatter, M. *Synlett* **1997**, 165. (g) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *35*, 1843. (h) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Strittmatter, M. *Angew. Chem., Int. Ed.* **1998**, *110*, 2067. (i) Schmittel, M.; Strittmatter, M. *Tetrahedron* **1998**, *54*, 13751. (j) Schmittel, M.; Rodríguez, D.; Steffen, J.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2152.

(7) (a) Dopico, P. G.; Finn, M. G., *Tetrahedron* **1999**, *55*, 29. (b) Alajarín, M.; Molina, P.; Vidal, A. *J. Nat. Prod.* **1997**, *60*, 747. (c) Wang, K. K.; Zhang, H.-R.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 1650. (d) Zhang, H.-R.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 7996.

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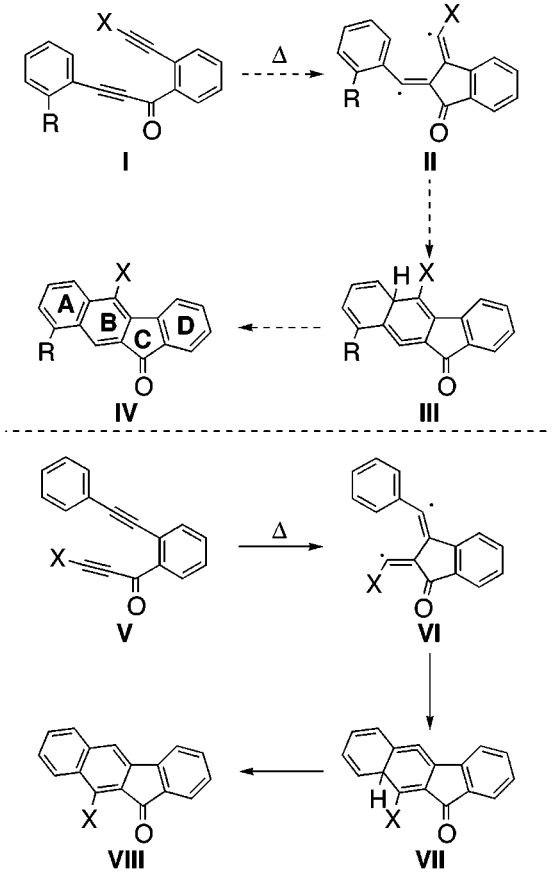
annulation,[8] we decided to explore the cyclization of 1-[2-(trimethylsilylethynyl)phenyl]-3-arylpropinones (**I**) (Scheme 1).

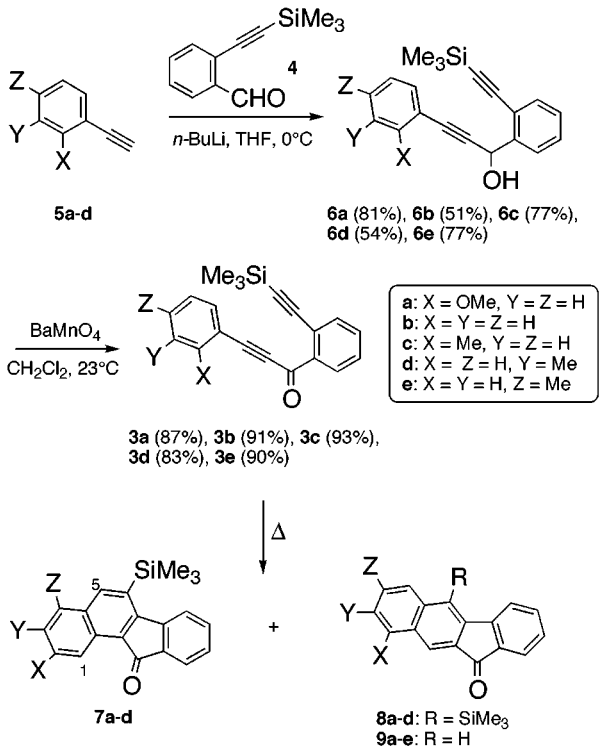
Scheme 1



The reaction was expected to proceed through diradical **II** and strained cyclic allene **III** as intermediates to give benzo[*b*]fluorenones **IV**.[7−10] The alternative thermal cyclization of 1-[(2-phenylethynyl)phenyl]propynones (**V**) has been recently shown to proceed through diradical **VI** and allene **VII** to give benzo[*b*]fluorenes **VIII** (X = H, Ph, $SiMe_3$).[9a,11]

Ynones **3a**−**d** were readily synthesized in two steps by reaction of benzaldehyde **4**[12] with the lithium acetylides derived from **5a**−**d**[13] followed by oxidation of the alcohols **6a**−**d** with $BaMnO_4$ (Scheme 2).

Scheme 2



The cyclizations of **3a**−**c** were best carried out by heating 0.06−0.2 M solutions in 1,2-dichlorobenzene under refluxing conditions (180 °C) (method A). Alternatively, the reactions could also be carried out in the solid state as a dispersion in Celite (method B) or in toluene in a sealed tube (method C).[14] We first studied the cyclization of **3a** with an *o*-methoxy substituent, which surprisingly led to the formation of benzo[*a*]fluorenones **7a**−**e** and of benzo[*a*]fluorenone **7a** as the major product under method A (Table 1, entries 1 and 3).[15] Desilylated tetracycle **9a**, with the regiochemistry of naturally occurring benzo[*b*]fluorenones, was obtained in 25% yield under conditions B (entry 2). Mixtures of benzo[*a*]- and benzo[*b*]fluorenones were also obtained from ynones **3b**−**d**, although in these cases the later were the major products (entries 4−9).[16]

(8) (a) Danheiser, R. L.; Gould, A. E.; Fernández de la Pradilla, R.; Helgason, A. L. *J. Org. Chem.* **1994**, *59*, 5514. (b) Burrell, R. C.; Daoust, K. J.; Bradley, A. Z.; DiRico, K. J.; Johnson, R. P. *J. Am. Chem. Soc.* **1996**, *118*, 4218. (c) Wills, M. S. B.; Danheiser, R. L: *J. Am. Chem. Soc.* **1998**, *120*, 9378. (d) González, J. J.; Francesch, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Org. Chem.* **1998**, *63*, 2854.

(9) (a) Rodríguez, D.; Navarro, A.; Castedo, L.; Domínguez, D.; Saá, C. *Org. Lett.* **2000**, *2*, 1497. See also: (b) Rodríguez, D.; Castedo, L.; Domínguez, D.; Saá, C. *Tetrahedron Lett.* **1999**, *40*, 7701. (c) Schmittel, M.; Strittmatter, M.; Schenk, W. A.; Hagel, M. *Z. Naturforsch.* **1998**, *53b*, 1015.

(10) For related cyclization of diynes, see: (a) Bradley, A. Z.; Johnson, R. P. *J. Am. Chem. Soc.* **1997**, *119*, 9917. (b) Miyawaki, K.; Suzuki, R.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1997**, *38*, 3943. (c) Miyawaki, K.; Kawano, T.; Ueda, I. *Tetrahedron Lett.* **1998**, *39*, 6923. (d) Ueda, I.; Sakurai, Y.; Kawano, T.; Wada, Y.; Futai, M. *Tetrahedron Lett.* **1999**, *40*, 319.

(11) However, extension of this approach for the synthesis of benzo[*b*]-fluorenones with the required OR substituent on the A ring based on this approach would presumably give rise to mixtures of regioisomers.

(12) Suufert, J.; Abraham, E.; Raeppel, S.; Brückner, R. *Liebigs Ann.* **1996**, 447.

(13) Arylacetylenes **5a**−**e** were prepared by the palladium-catalyzed Sonogashira coupling of the corresponding aryl iodides or bromides with trimethylsilylacetylene followed by desilylation.

(14) (a) γ-Terpinene was added, as a high boiling 1,4-cyclohexadiene, to facilitate hydrogen migration (step **III** → **IV**, Scheme 1). (b) Benzylated derivatives were obtained as byproducts under these conditions as a result hydrogen abstraction from toluene followed by radical coupling.

(15) Benzo[*a*]fluorenones **7** show downfield signals in the ^{1}H NMR spectra at 9.06−8.84 and 8.39−7.95 (s) corresponding to H-1 and H-5, respectively. The carbonyl signal of **7** appears at δ 196.1−196.7 in the ^{13}C NMR spectra, while benzo[*b*]fluorenones **8** and **9** show this resonance at δ 193.8−193.1. The structures of **7a**, **7e**, **8e**, and **9e** were confirmed by ^{1}H−^{1}H (COSY or NOESY) and ^{1}H−^{13}C (HMBC and HMQC) correlations. **9b** showed ^{1}H and ^{13}C NMR data identical with those described.[9a]

Table 1. Thermal Cyclization of Arylynones **3**

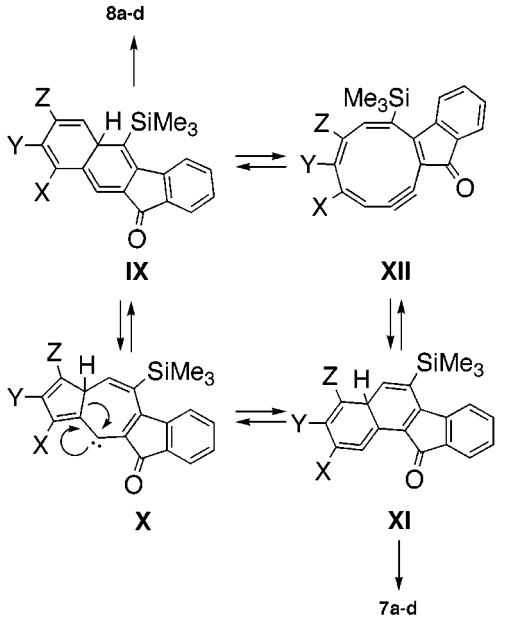
entry	ynone	method[a]	time (h)	products (%)[b]	ratio **7**:(**8** + **9**)
1	**3a**	A	48	**7a** (63), **8a** (17)[c]	3.7:1
2	**3a**	B	24	**7a** (25), **9a** (25)	1:1
3	**3a**	C	16	**7a** (30), **8a** (9)[d]	3.3:1
4	**3b**	A	96	**7b** (8), **8b** (25), **9b** (18)	1:5.3
5	**3b**	B	14	**7b** (24), **8b** (20), **9b** (32)	1:2.2
6	**3b**	C	79	**7b** (18), **8b** (11), **9b** (37)	1:2.7
7	**3c**	A	216	**7c** (38), **8c** (13), **9c** (45)	1:1.5
8	**3d**	A	48	**7d** (8), **8d** (30), **9d** (9)	1:4.9
9	**3e**	A	48	**7e** (14), **8e** (41), **9e** (7)	1:3.4

[a] A = 1,2-dichlorobenzene under reflux (180 °C); B = Celite, 180 °C; C = toluene, γ-terpinene, 180 °C, sealed tube. [b] Isolated yields. [c] Based on 71% conversion. [d] Based on 79% conversion.

Addition of an alcohol was expected to trap intermediates of type **III**, leading to benzo[*b*]fluorenones **IV** (Scheme 1).[9a] However, no effect on the product selectivity was observed upon addition of ethylenglycol, a high boiling proton donor, to the reaction mixtures. On the other hand, treatment of ynones **3** with Lewis acids such as $ZnCl_2$ or $Y(OTf)_3$ led only to unchanged starting materials.

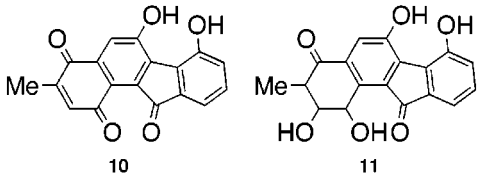
The remarkable formation of benzo[*a*]fluorenones in the cyclization of ynones **3** unveils a new rearrangement. A rationale for this transformation is presented in Scheme 3.

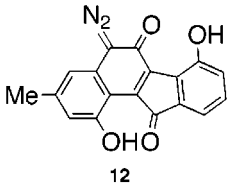
Scheme 3



Ring closure of a diradical of type **II** (Scheme 1) would give intermediate **IX**,[17] which would yield benzo[*b*]fluorenones **8a**−**d** by a formal [1,5]-hydrogen migration.[5,6,9] Strained allene **IX** could also rearrange to a carbene **X**, which may evolve to give allene **XI**. The transformation of **X** to **XI** is somewhat reminiscent of that proposed in the benzene ring contraction rearrangement, which occurs in skeletal reorganizations of polycyclic aromatic hydrocarbons under pyrolysis.[18] Alternatively, **IX** might suffer ring opening to form cyclodeca-1,3,5,7-tetraen-9-yne intermediate **XII**, which could electrocyclize to give **XI**.[19]

The unexpected formation of benzo[*a*]fluorenones **7** in the thermal cyclizations of ynones **3** suggests a simple approach for the synthesis of fluostatins A (**10**) and B (**11**).[20] In particular, **10**, a selective inhibitor of the enzyme dipeptidyl peptidase III,[19a] shows a core structure that is related to that of **7d**. Interestingly, isoprekinamycin, a metabolite isolated from *Streptomyces murayaensis* several years ago, which was originally named prekinamycin,[3] has been very recently demonstrated to be diazobenzo[*a*]fluorenone **12**.[21]





The approach described in this paper allows for the synthesis of benzo[*a*]- and benzo[*b*]fluorenones[22] from readily available starting materials. Efforts at controlling the selectivity in the thermal closure of more substituted ynones of type **3** for the synthesis of kinafluorenone (**1**), fluostatin A (**10**), and isoprekinamycin (**12**) are in progress.

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

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(16) Chromatography (gravity column, 30:1 hexane/EtOAc) allowed for the separation of the benzo[*a*]- and benzo[*b*]fluorenones.

(17) The most stable structure for these intermediates has been shown to be the singlet rather than the triplet (biradical).[9a]

(18) (a) Preda, D. V.; Scott, L. T. *Org. Lett.* **2000**, *2*, 1489. (b) Scott, L. T. *Pure Appl. Chem.* **1996**, *68*, 291. (c) Scott, L. T.; Hashemi, M. M.; Schultz, T. H.; Wallace, M. B. *J. Am. Chem. Soc.* **1991**, *113*, 9692. (d) See also ref 8c.

(19) We thank a reviewer for suggesting this fascinating pathway.

(20) (a) Akiyama, T.; Harada, S.; Kojima, F.; Takahashi, Y.; Imada, C.; Okami, Y.; Muraoka, Y.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 553. (b) Akiyama, T.; Nakamura, K. T.; Takahashi, Y.; Naganawa, H.; Muraoka, Y.; Aoyagi, T.; Takeuchi, T. *J. Antibiot.* **1998**, *51*, 586.

(21) 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.

(22) The synthesis of substituted benzo[*a*]- and benzo[*b*]fluorenones could be of interest in the analysis of organic pollutants. For the occurrence of these derivatives in urban aerosols, see, e.g.: Allen, J. O.; Dookeran, N. M.; Taghizadeh, K.; Lafleur, A. L.; Smith, K. A.; Sarofim, A. F. *Environ. Sci. Technol.* **1997**, *31*, 2064.