Highly Efficient Synthesis of 2-Substituted *4H*-Chromen-4-ones by Means of F^--Induced 6-*Endo-Digonal* Cyclization of *o*-(Silyloxy)phenyl Ethynyl Ketone Derivatives

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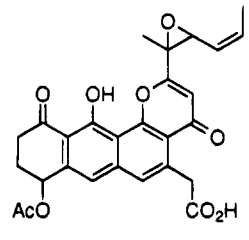
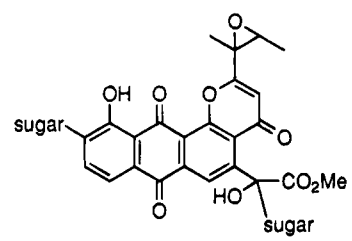
Summary: Efficient synthesis of 2-substituted *4H*-chromen-4-ones, a core structure of the antitumor antibiotic kapurimycin A_3, was achieved through F^--induced cyclization of *o*-(silyloxy)phenyl ethynyl ketone derivatives.

Kapurimycin A_3 (**1**) is an antitumor antibiotic possessing a novel anthra-γ-pyrone ring system bearing a vinyl epoxide side chain.[1] It was shown recently that this epoxide ring is the site of nucleophilic attack by guanine N_7 in duplex DNA resulting in effective DNA alkylation.[2a,b] Recent studies on altromycin[3] (**2**) possessing a closely related ring system have also shown that the epoxide ring is a specific electrophilic site for DNA alkylation.[4] To get



Kapurimycin A_3 (**1**)

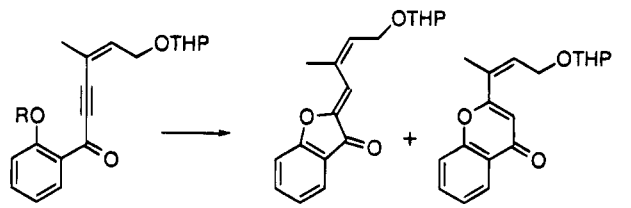


Altromycin (**2**)

an insight into the extraordinarily high reactivity of the epoxide rings of **1** and **2**, we have focused our attention on structure and reactivity relationships of related derivatives possessing an epoxy-substituted γ-pyron ring system. We report herein a facile and efficient synthesis of 2-substituted *4H*-chromen-4-ones, a core structure of both **1** and **2**, through F^--induced cyclization of *o*-(silyloxy)phenyl ethynyl ketone derivatives.

Due to the acid sensitivity of the epoxide functionality of **1**, conventional *4H*-chromen-4-one synthesis using acid-catalyzed cyclization of 1-(*o*-hydroxyaryl) 1,3-diketones is not applicable.[5,6] To achieve an efficient and general synthesis of the 2-substituted *4H*-chromen-4-one ring system we have examined 6-*endo-digonal* cyclization of *o*-hydroxyphenyl ethynyl ketones (*e.g.*, **7**) under basic conditions. Previously, 6-*endo-digonal* cyclizations of *o*-hydroxyphenyl ethynyl ketone derivatives have been reported,[7] but the reactions were always accompanied by simultaneous 5-*exo-digonal* cyclization, giving undesired

Table 1. 5-*Exo-Digonal* vs 6-*Endo-Digonal* Cyclization of 7 and 8



7 : R = H
8 : R = TBDMS

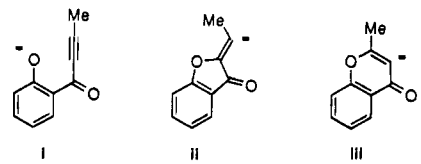
9 **10**

entry	R	condns	yield[a] (%) 9	10
1	H	K_2CO_3/acetone/reflux[b]	70	16
2	H	K_2CO_3/EtOH/rt[b]	57	16
3	TBDMS	KF/18-crown-6/DMF/rt	*c*	97
4	TBDMS	KF/18-crown-6/DMF–MeOH (4:1)	66	13
5	H	KF/18-crown-6/DMF/rt	9	83

[a] Isolated yield. [b] Miranda *et al.*, see ref 7. [c] Not detected.

benzofuranone derivatives. Reaction of the bromomagnesium acetylide derived from **4** with the silyl-protected salicylaldehyde **5** produced alcohol **6** (Scheme 1). Deprotection and subsequent oxidation of benzylic alcohol afforded ketone **7**. According to the report,[7] two products were obtained upon heating an acetone solution of **7** in the presence of K_2CO_3 (Table 1, entry 1). The major product was, however, the undesired benzofuranone derivative **9**,[8] with the major product being chromenone **10**.[9] Reaction of **7** with K_2CO_3 in ethanol did not change the product ratio signifiicantly (Table 1, entry 2). These results indicate the limitation of existing methods for a general synthesis of 2-substituted *4H*-chromen-4-ones.

We carried out theoretical calculations using *o*-hydroxyphenyl 1-propynyl ketone as a model compound. *Ab initio* calculations of the transition states in 5-*exo*- and 6-*endo-digonal* cyclization (TS-5 and TS-6) of phenoxide ion **i** giving vinylanions **ii** and **iii**, respectively, at the 3-21G(*) level indicated that activation energies for the two cyclization processes are very close.[10] Therefore, in the presence of sufficient proton source (phenolic hydro-



i **ii** **iii**

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(1) (a) Hara, M.; Mokudai, T.; Kobayashi, E.; Gomi, K.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1513–1518. (b) Yoshida, M.; Hara, M.; Saitoh, Y.; Sano, H. *J. Antibiot.* **1990**, *43*, 1519–1523.

(2) (a) Hara, M.; Yoshida, M.; Nakano, H. *Biochemistry* **1990**, *29*, 10449–10455. (b) Chan, K. L.; Sugiyama, H.; Saito, I. *Tetrahedron Lett.* **1991**, *52*, 7719–7722.

(3) Brill, G. M.; McAlpine, J. B.; Whittern, D. N.; Buko, A. M. *J. Antibiot.* **1990**, *43*, 229–237.

(4) Sun, D.; Hansen, M.; Clement, J. J.; Hurley, L. H. *Biochemistry* **1993**, *32*, 8068–8074.

(5) For example, see: Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076–1078.

(6) For a general synthesis of *4H*-chromen-4-ones, see: Hepworth, J. D. Pyrans and Fused Pyrans: (iii) Synthesis and Application. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds. Pergamon Press: Oxford, 1984; Vol. 3, pp 737–883.

(7) Garcia, H.; Iborra, S.; Primo, J.; Miranda, M. A. *J. Org. Chem.* **1986**, *51*, 4432–4436.

(8) Stereochemistry of **9** was tentatively assigned as *Z*.

(9) The chromenone structure for **10** was confirmed by 2D NMR (HMQC and HMBC). For further support of the structural assignment, see ref 13.

(10) Spartan molecular modeling software (ver. 3.0) was used for all theoretical calculations. Calculated energies for TS-5, TS-6, **i**, **ii**, and **iii** were −529.430 299 4, −529.431 285 6, −529.461 334 6, −529.438 706 8, and −529.447 764 0 hartrees, respectively. These optimized structures can be found in the supplementary material.

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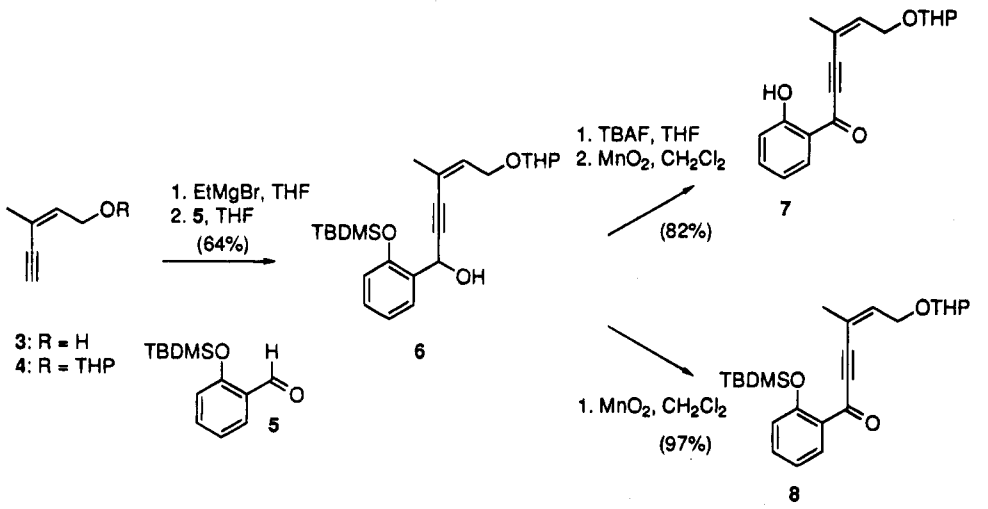
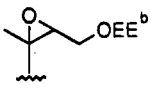
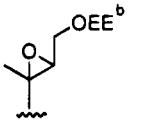
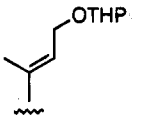
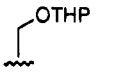
Scheme 1



gen and/or protic solvents), it is difficult to achieve complete selectivity for 6-*endo-digonal* cyclization, and both benzofuranone and chromenone derivatives are always produced, with the product ratio being highly dependent upon the reaction conditions. The calculations also indicated that **ii** is much less stable than **iii**, and therefore the activation energy for **ii** → **i** (5.3 kcal/mol) is much lower than that for **iii** → **i** (10.3 kcal/mol). Accordingly, it is predicted that in the absence of proton donor, unstable vinylanion **ii** rapidly reverts to **i**, whereas anion **iii** has sufficient lifetime to undergo further reaction. Thus, selective chromenone formation would occur under conditions where phenolate anion **i** is generated under completely aprotic conditions. We have found that such reaction conditions are attainable by *in situ* generation of the phenoxide ion from silyl-protected phenol by F^-.

Reaction of ketone **8** with spray-dried KF and 18-crown-6 in anhydrous DMF proceeded smoothly at room temperature to give chromenone **10** in 97% isolated yield (Table 1, entry 3).[11,12] None of benzofuranone **9** was detected in ^1H NMR of the crude mixture.[13] In contrast, addition of a small amount of methanol as a proton source to the same reaction system dramatically changed the product ratio (entry 4), with the major product now being benzofuranone **9**. The presence of a phenolic hydrogen also resulted in a substantial loss of selectivity (entry 5). When the cyclization of **8** was carried out at −20 °C, the formation of both phenol **7** and benzofuranone **9** along with chromenone **10** was observed by ^1H NMR after aqueous workup. Thus, 30 min after addition of KF at −20 °C, the ratio of **10**, **9**, and **7** was 54:37:9, whereas upon prolonged reation (1 h) the formation of **10** was predominant (**10**:**9** = 81:19) with a concomitant decrease of **7**. These results are consistent with our working hypothesis and strongly suggest that the 5-*exo-digonal* process is reversible.

Table 2. 6-*Endo-Digonal* Cyclization of Various Ketones

entry	ketone	R	chromen-4-one (%)[a]	
1	11		15	73
2	12		16	72
3	13		17	83
4	14		18	73

[a] Isolated yield. [b] EE = 1-ethoxyethyl.

Applicability of our method to various substituted ketones, including those possessing epoxide functionality (**11**, **12**), was demonstrated as shown in Table 2. In all these cases, 2-substituted *4H*-chromen-4-ones were obtained in good yields without loss of any stereochemical integrity of the starting material. Again, none of the corresponding benzofuranones were detected.[14] The methods reported here provide a general synthesis for 2-substituted *4H*-chromen-4-ones. This chemistry should be useful for the construction of the ring system of **1** and its congeners.

Supplementary Material Available: Experimental procedures and spectral data for compounds **4**−**18** and optimized structures and coordinates of TS-5, TS-6, **i**, **ii**, and **iii** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(11) Typical experimental procedure: To a solution of **8** (20.3 mg, 49.0 μmol) and 18-crown-6 (26.2 mg, 99.1 μmol) in DMF (1 mL) was added spray dried potassium fluoride (5.7 mg, 98.1 μmol) at 0 °C. The solution immediately turned dark violet, and the reaction mixture was stirred at ambient temperature for 2 h. The mixture was diluted with saturated NH_4Cl and extracted with ethyl acetate. The crude product was purified by column chromatography on silica gel; elution with 15% ethyl acetate in hexane gave **10** (14.2 mg, 97%) as a yellow oil.

(12) Two equivalents of KF and 18-crown-6 were necessary for completion of the reaction, and DMF was essential as a solvent.

(13) For a related approach involving Pd-catalyzed carbonylation of *o*-iodophenol with terminal alkynes giving chromenoes, see: Torii, S.; Okumoto, H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *31*, 6773−6784.

(14) Further support for chromenone formation in the reaction was obtained by transformation of **18** into 2-(hydroxymethyl)-*4H*-chromen-4-one, whose NMR data (^1H NMR and ^{13}C NMR) were identical with those reported (Couquelet, M. P. J. *Synthesis* **1979**, 889).