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STUDIES ON THE TOTAL SYNTHESIS OF FREDERICAMYCIN A: DEVELOPMENT OF AN INTERMOLECULAR ALKYNE-CHROMIUM CARBENE COMPLEX CYCLIZATION APPROACH TO THE ABCDE RING SYSTEM

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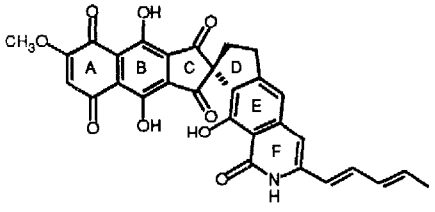
Abstract: *The development of a synthetic approach to the fredericamycin A ABCDE ring system based on a regiospecific intermolecular alkyne-chromium carbene complex cyclization is detailed.*

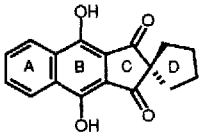
Fredericamycin A (**1**, NSC-305263), a quinone antitumor antibiotic[2] isolated from *Streptomyces griseus*[3] bearing a unique spiro[4.4]nonene central to its structure, has been shown to possess potent *in vitro* cytotoxic activity and confirmed *in vivo* antitumor activity that is derived from its inhibition of RNA and protein synthesis through nondiscriminant oxidative damage to DNA and/or discriminant inhibition of DNA processing enzymes.[2,5] Consequently, since the unambiguous establishment of its structure through a single crystal X-ray structure determination[4] after extensive spectroscopic studies[5] failed to resolve tautomeric structures, fredericamycin A continues to be the subject of biological[2] and extensive synthetic efforts[6] including one recently completed total synthesis.[7] Herein we detail preliminary studies on the development of a general approach to the construction of the fredericamycin A ABCDE ring system applicable to the total synthesis of fredericamycin A and structurally related agents based on the implementation of a regiospecific intermolecular alkyne-chromium carbene complex cyclization.[8]

Key to the development of this convergent assemblage of the fredericamycin A skeleton rests on the facility with which a simple aldol closure might provide for introduction of the spiro[4.4]nonene CD ring system; Scheme I, **5** → **4**;[9] and the feasibility for implementation of a regiospecific inter- or intramolecular alkyne-chromium carbene complex cyclization for introduction of the fully substituted B ring hydroquinone; Scheme I, **7** → **5/6**. Herein we detail preliminary studies resulting in the preparation of **2-3** that establish this as a viable approach to fredericamycin A.

In contrast to initial expectations in which the electronic nature of the alkyne was anticipated to provide a useful and predominate element for control of the regioselectivity of an intermolecular alkyne-chromium carbene complex cyclization, a study of electronic and steric features of the alkyne that control



1 fredericamycin A



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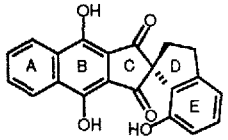

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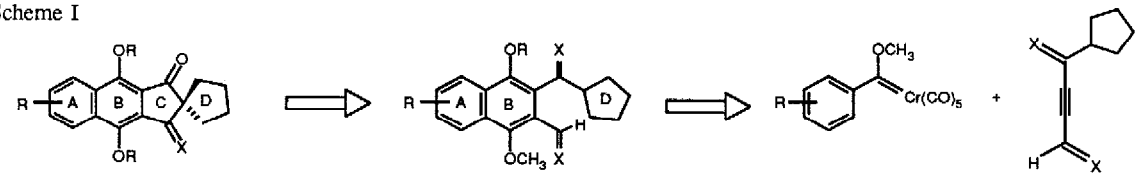
Scheme I



2 X = O, R = H
4 X = OH, H

5 X = O
6 X = OR, H

7

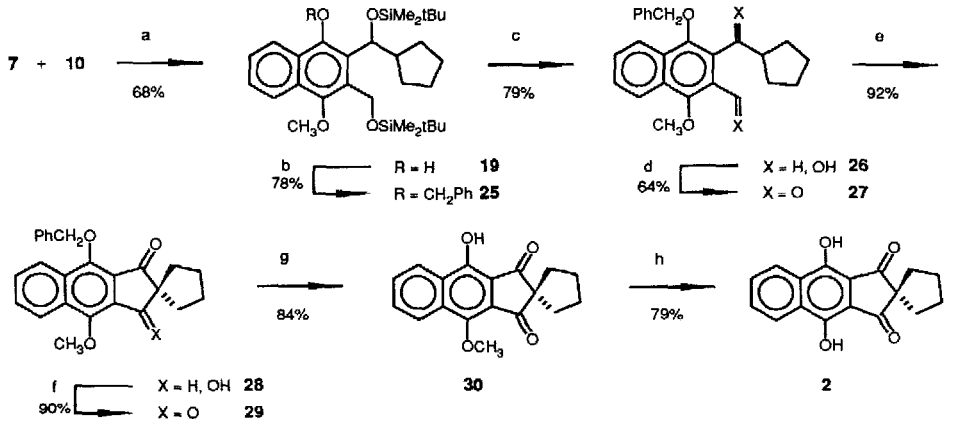
the cyclization mode[8] and regioselectivity[8,10-11] of the reactions of Fischer chromium carbene complexes with acetylenes revealed that the benzannulation chemical conversions were optimal with neutral alkynes (neutral alkynes > electron-deficient alkynes). In addition, modest steric differences in the substitution pattern at the alkyne adjacent carbons proved sufficient to permit complete regiocontrol in the intermolecular cyclization reactions.[8,10-11] Representative results of this study are detailed in Scheme II. As detailed in the recent efforts of Wulff,[8a] the benzannulation reactions proved optimally conducted in heptane versus ether solvents (Et_2O, THF) at concentrations of 0.3 M in the presence of 1.0-1.5 equivalents of alkyne. In addition, under the standard reaction conditions the product derived from the reaction of alkyne **10** with the chromium carbene complex **7** proved to be **20** (entry 9) presumably derived through in situ elimination of *t*-butyldimethylsilanol from the primary reaction product **19** with generation of an unstable orthoquinomethane that suffers a subsequent 1,5-hydrogen shift to provide **20**. Under the Yamashita reaction conditions which generally acylate phenols (entry 6)[11] the elimination was supressed and, contrary to expectations, was attributed experimentally to the inclusion of acetic anhydride in the reaction mixture under conditions that do *not* acylate the phenol (entries 6-8) *and* that accelerate the rate of reaction. Thus, **19** *or* **20** may be obtained cleanly from the reaction of **10** with **7** depending on the reaction conditions selected.

Scheme II

7

Entry		X	R¹	eq.	Conditions	Yield	R		Yield	R
1	**8a**	$OSiMe_2tBu$, H	H	1.4	Ac_2O:Et_3N (1.5 eq:1.5 eq), 80°C, heptane, 1 h, 0.3 M	47%	Ac	**13**	-	
2	**8b**	$OSiPh_2tBu$, H	H	1.5	Ac_2O:Et_3N (1.5 eq:1.5 eq), 80°C, heptane, 3 h, 0.1 M	32%	Ac	**14**	-	
3	**9a**	$OSiMe_2tBu$, H	CO_2CH_3	1.5	65°C, THF, 24 h, 0.03 M	22%	H	**15 16**	-	
4	**9a**			1.5	Ac_2O:Et_3N (1.5 eq:1.5 eq), 80°C, heptane, 19 h, 0.1 M	10%	H	**15 16**	8%	
5	**9b**	$OSiPh_2tBu$, H	CO_2CH_3	1.5	Ac_2O:Et_3N (1.5 eq:1.5 eq), 80°C, heptane, 19 h, 0.1 M	7%	H	**17 18**	6%	Ac
6	**10**	$OSiMe_2tBu$, H	CH_2OSiMe_2tBu	1.1	Ac_2O:Et_3N (1.0 eq:1.0 eq) 80°C, heptane, 4 h, 0.3 M	68%	H	**19 20**	-	H
7	**10**			0.8	Et_3N (1.0 eq), 80°C, heptane, 16 h, 0.3 M	30%	H	**19 20**	17%	H
8	**10**			1.0	Ac_2O (1.0 eq), 80°C heptane, 3 h, 0.3 M	66%	H	**19 20**	-	H
9	**10**			1.0	80°C, heptane, 17 h, 0.3 M	-		**19 20**	74%	H
10	**11**	O	CH_2OSiMe_2tBu	1.5	65°C, THF, 9 h, 0.03 M	0%		**21**		
11	**12**	O	CO_2CH_3	1.5	65°C, THF, 9 h, 0.2 M	0%		**22**		

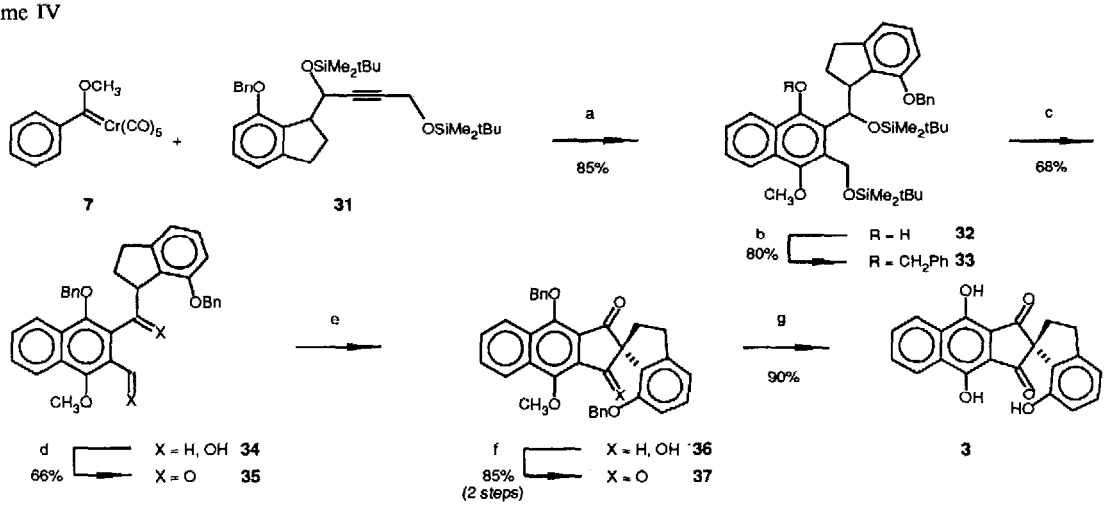
Scheme III



(a) 80°C, heptane, Ac_2O:Et_3N (1.5 eq:1.5 eq), 3 h. (b) $PhCH_2Br$ (1.2 eq), K_2CO_3 (10 eq), $(Bu)_4NI$ (0.1 eq), DMF, 25°C, 15 h. (c) HOAc:THF:H_2O (3:1:1), 40°C, 48 h. (d) $(COCl)_2$ (2.2 eq), DMSO (4.8 eq), Et_3N (10 eq), CH_2Cl_2, -60°C, 1 h. (e) $NaOCH_3$ (0.1 eq), CH_3OH, 40°C, 6 h. (f) PCC (1.5 eq), CH_2Cl_2, 25°C, 5 h. (g) 10% Pd-C (1 eq), HCO_2NH_4 (5 eq), CH_3OH, 25°C, 2 h. (h) EtSH (2.5 eq), NaI (5.0 eq), DMF, 150°C, 3 h.

The application of the regiospecific benzannulation reaction of **7** with **10** to the assemblage of the fredericamycin ABCD carbon framework is detailed in Scheme III. Protection of the free phenol of the benzannulation product **19** as its benzyl ether **25** was accomplished cleanly under mild basic conditions that proceeded without competitive elimination of *t*-butyldimethylsilanol followed by deprotection of the primary and secondary benzylic alcohols afforded **26**. Direct oxidation of diol **26** to keto aldehyde **27** was accomplished cleanly only under the conditions of Swern oxidation[12] and required carefully controlled reaction conditions that ensure activation of both alcohols through formation of the bisalkoxysulfonium salt prior to base-catalyzed elimination of dimethyl sulfide with formal oxidation of the primary and secondary benzylic alcohols. Keto aldehyde **27** cleanly closed to the spirocyclic keto alcohol **28** upon exposure to sodium methoxide thus providing the functionalized spiro[4.4]nonene and establishing the viability of this approach to the fredericamycin A ABCD ring system. Oxidation of the secondary alcohol afforded **29** without detection of a competitive retro aldol reaction and subsequent sequential deprotection of **29** provided **2**.

Scheme IV



(a) 80°C, heptane, Ac_2O (1 eq), 3 h. (b) $PhCH_2Br$ (1.5 eq), K_2CO_3 (10 eq), $(Bu)_4NI$ (0.1 eq), DMF, 25°C, 48 h. (c) $(Bu)_4NF$ (5 eq), THF, 25°C, 72 h. (d) $(COCl)_2$ (2.2 eq), DMSO (4.8 eq), Et_3N (10 eq), CH_2Cl_2, -67°C, 1 h. (e) $NaOCH_3$ (0.1 eq), CH_3OH, 60°C, 3 h. (f) PCC (3 eq), CH_2Cl_2, 25°, 14 h. (g) BBr_3 (3.6 eq), CH_2Cl_2, -78 to 25°C, 19 h.

The extension of these observations to the assemblage of the fredericamycin A ABCDE ring system is detailed in Scheme IV. Regiospecific cyclization of **31**[13] with **7** under the conditions previously developed (0.3 M **7**, 1.0 equiv **31**, 80°C, heptane, 1.0 equiv Ac_2O, 3 h) cleanly provided **32** (85%) as the predominant or exclusive benzannulation product (≥ 95%) without the detection of subsequent products derived from elimination of *t*-butyldimethylsilanol. Conversion of **32** to the keto aldehyde **35**, base-catalyzed aldol closure of **35** to the spirocyclic keto alcohol **36**, and subsequent oxidation provided **37**. Deprotection of **37** provided **3** constituting the partially functionalized fredericamycin A ABCDE ring system.

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