Oxidative Intramolecular [4+2]Cycloaddition of *o*-[(ω-Phenylthioethynyl)acyl]phenols Followed by the Aromatic Pummerer-type Reaction: A Novel Preparation of the *peri*-Hydroxy Dihydroquinone Structure

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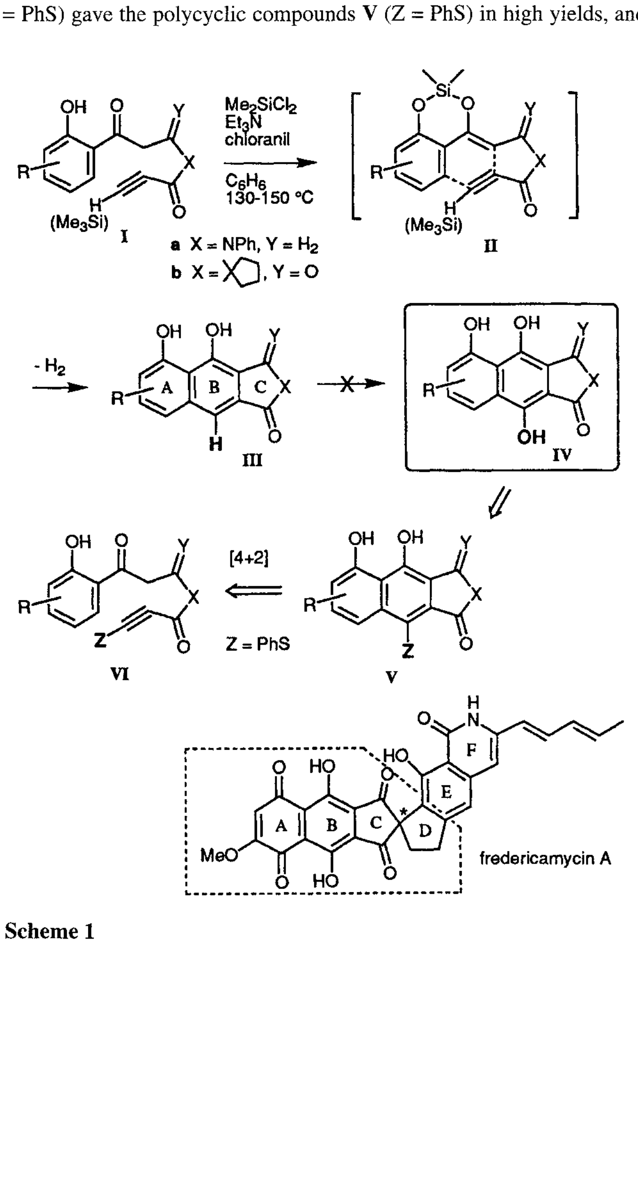
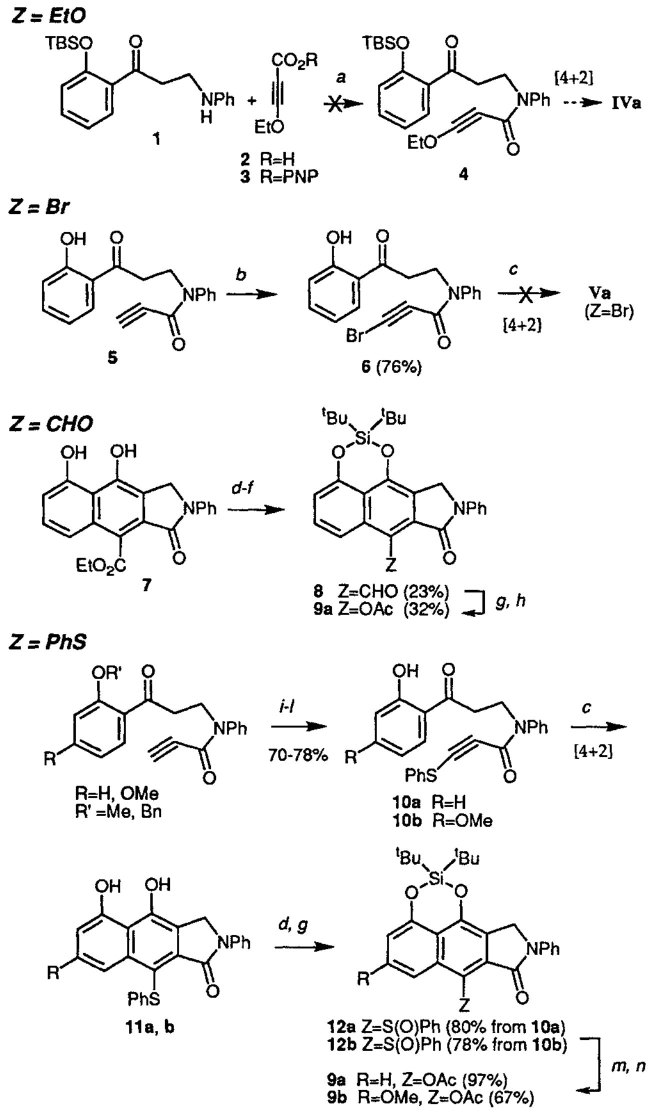
Abstract: The combination of the oxidative intramolecular [4+2]cycloaddition of *o*-acylphenol derivatives **10a,b** and **16** having the ω-phenylthioethynyl group in the acyl chain and the Pummerer-type reaction of the cyclization products afforded the *peri*-hydroxy dihydroquinones **9a,b** and **18** in good overall yields.

We have recently disclosed the novel oxidative intramolecular [4+2]cycloaddition of the silylene-protected dihydroxystyrene derivative **IIa**, *in situ* derived from the *o*-acylphenol **Ia**, leading to the one-step and high yield preparation of the *peri*-hydroxy polycyclic aromatic compound **IIIa**.[1a] This method was applied to an efficient synthesis of the deoxy ABCD-ring system **IIIb** of fredericamycin A, and presented a promising approach toward the asymmetric construction of the chiral spiro junction of the CD-ring if the reaction started from a substrate having a chiral quaternary carbon.[1b,2] However, intensive attempts to introduce the *para*-hydroxy group into the B-rings of **IIIa,b** using known oxidizing reagents such as $NH_4NO_3/(CF_3CO)_2O$, $Pb(OAc)_4$, $PhI(OCOCF_3)_2$, $K_2S_2O_5$, and $K_2S_2O_8$, were completely unsuccessful resulting in the oxidation of the A-ring, formation of complex mixtures or no reaction. We postulated that the cycloaddition of *o*-acylphenols **VI** having the oxy- or its equivalent functional group (Z) at the ω-carbon of the dienophile moiety would resolve this problem (Scheme 1). Here, we report that phenylthioacetylene (Z = PhS) is a suitable dienophile for this purpose. Thus, the cycloaddition of the *o*-acylphenol derivatives **VI** (Z = PhS) gave the polycyclic compounds **V** (Z = PhS) in high yields, and the following conversion of their phenylthio groups into the oxygen functional groups was achieved through the aromatic Pummerer-type reaction[3] to afford the dihydroquinone compounds **IV** in good overall yields.

Although the intramolecular [4+2]cycloaddition of the *o*-acylphenol having an ethoxyethynyl (Z = EtO, such as **4**) or its related alkoxyacetylene moiety as a dienophile part seemed to be the straightforward route to the desired compound **IVa**, our preliminary study to prepare the substrate **4** by the condensation of **1** with **2** or **3** was extremely difficult due to instability of the reagent **2**[4,5] and the product **4**.[6,7] We then examined the substrates having oxygen-convertible functional groups at the ω-car-



Scheme 1

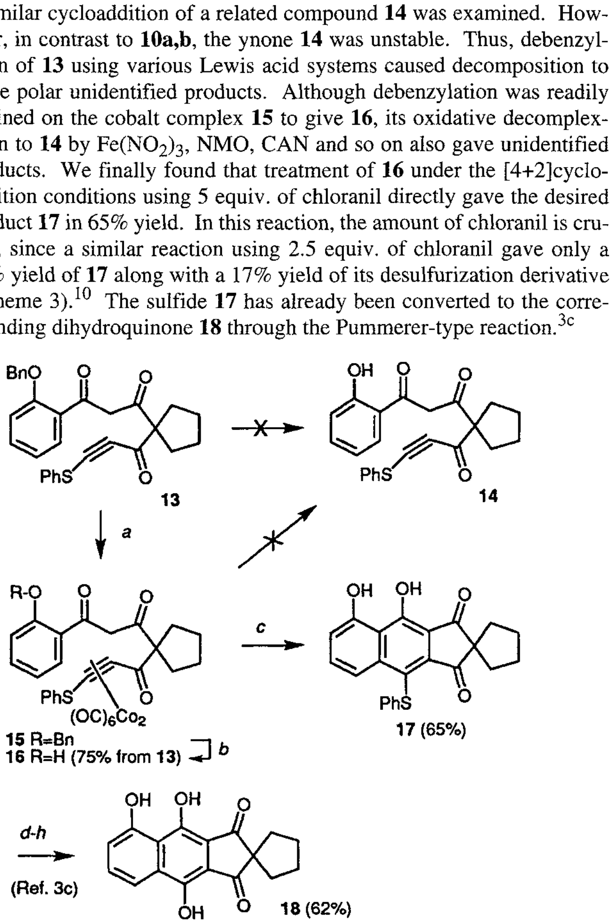


Scheme 2 TBS = Si^{t}BuMe$_2$, PNP = C_6H_4-*p*-NO_2; (*a*) base (for **3**); (*b*) NBS, $AgNO_3$; (*c*) Me_2SiCl_2 (4 eq.), Et_3N (8 eq.), chloranil (2.5 eq.); (*d*) $^tBu_2Si(OTf)_2$, Et_3N; (*e*) DIBAL; (*f*) Swern oxid.; (*g*) *m*-CPBA; (*h*) Ac_2O, pyridine; (*i*) $HC(OMe)_3$, *p*-TsOH; (*j*) LDA, $PhSSO_2Ph$; (*k*) CF_3CO_2H; (*l*) BCl_3; (*m*) $(CF_3CO)_2O$, styrene; (*n*) Ac_2O, AcONa, pyridine.

bon of the dienophile: The bromo compound **6** was prepared from **5**,[8] but its cycloaddition under standard conditions (Me_2SiCl_2, Et_3N, chloranil, C_6H_6, 100-150 °C in a sealed tube) resulted in instantaneous decomposition. The cycloadduct **7**[1] having the ethoxycarbonyl group in the internal ring was converted to the formyl compound **8**. The following Baeyer-Villiger oxidation, however, gave an unsatisfactory yield (Scheme 2).

On the other hand, we found that the [4+2]cycloaddition of the readily prepared and stable ω-phenylthioethynyl compound **10a** proceeded at 100 °C for 5 h to quantitatively give the *peri*-hydroxy polycyclic compound **11a** bearing the phenylthio group. This result was noteworthy, since similar cycloadditions of the corresponding terminal acetylene **Ia** required 130-150 °C for 7 h.[1] The product **11a** was converted to the acetoxylated product **9a** in 78% overall yield *via* the sulfoxide **12a** according to our recently developed aromatic Pummerer-type reaction method.[3] Similarly, **10b** was subjected to the cycloaddition and the Pummerer-type reaction to give the polycyclic dihydroquinone **9b** (Scheme 2).[9,10]

Next, in order to construct the ABCD-ring system of fredericamycin A, a similar cycloaddition of a related compound **14** was examined. However, in contrast to **10a,b**, the ynone **14** was unstable. Thus, debenzylation of **13** using various Lewis acid systems caused decomposition to more polar unidentified products. Although debenzylation was readily attained on the cobalt complex **15** to give **16**, its oxidative decomplexation to **14** by $Fe(NO_2)_3$, NMO, CAN and so on also gave unidentified products. We finally found that treatment of **16** under the [4+2]cycloaddition conditions using 5 equiv. of chloranil directly gave the desired product **17** in 65% yield. In this reaction, the amount of chloranil is crucial, since a similar reaction using 2.5 equiv. of chloranil gave only a 29% yield of **17** along with a 17% yield of its desulfurization derivative (Scheme 3).[10] The sulfide **17** has already been converted to the corresponding dihydroquinone **18** through the Pummerer-type reaction.[3c]



Scheme 3 (*a*) $Co_2(CO)_8$; (*b*) BCl_3; (*c*) Me_2SiCl_2 (10 eq.), Et_3N (20 eq.), chloranil (5 eq.); (*d*) $^tBu_2Si(OTf)_2$, Et_3N; (*e*) *m*-CPBA; (*f*) $(CF_3CO)_2O$, styrene; (*g*) aq. $NaHCO_3$; (*h*) Bu_4NF.

The present results reveal that the combination of the oxidative intramolecular [4+2]cycloaddition of the phenylthioacetylene derivatives and the following aromatic Pummerer-type reaction affords a novel preparation of the *peri*-hydroxy polycyclic dihydroquinone structures. In this methodology, the phenylthioethynyl moiety acts not only as a very reactive dienophile but also as an oxyacetylene (or a ketene) equivalent.[11]

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References and Notes

(1) a) Kita, Y.; Okunaka, R.; Honda, T.; Shindo, M.; Tamura, O. *Tetrahedron Lett.* **1989**, *30*, 3995-3998; b) Kita, Y.; Okunaka, R.; Honda, T.; Kondo, M.; Tamura, O.; Tamura, Y. *Chem. Pharm. Bull.* **1991**, *39*, 2106-2114.

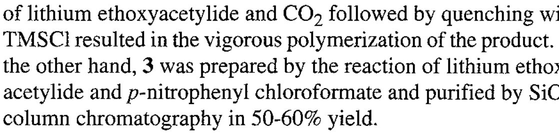
(2) We have also reported the preparation of the DEF-ring of fredericamycin A using a similar cycloaddition methodology. See, Kita, Y.; Ueno, H,; Kitagaki, S.; Kobayashi, K.; Iio, K.; Akai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 701-702.

(3) a) Akai, S.; Takeda, Y.; Iio, K.; Yoshida, Y.; Kita, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 1013-1014; b) Akai, S.; Iio, K.; Takeda, Y.; Ueno, H.; Yokogawa, K.; Kita, Y. *ibid.* **1995**, 2319-2320; c) Kita, Y.; Takeda, Y.; Iio, K.; Yokogawa, K.; Takahashi, K.; Akai, S. *Tetrahedron Lett.* **1996**, *37*, 7545-7548.

(4) Although the preparation of phenoxypropiolic acid was reported,[5] no one succeeded in the preparation of the alkoxy derivatives to the best of our knowledge. Our attempts to prepare **2** by the reaction of lithium ethoxyacetylide and CO_2 followed by quenching with TMSCl resulted in the vigorous polymerization of the product. On the other hand, **3** was prepared by the reaction of lithium ethoxyacetylide and *p*-nitrophenyl chloroformate and purified by SiO_2 column chromatography in 50-60% yield.

(5) Filippova, A. Kh.; Borisowa, A. I.; Shostakovskii, M. F. *Khim. Atsetilena* **1968**, 64-65 (*Chem. Abstr.* **1969**, *70*, 106116c); Laurence, C.; Guillemé, J.; Kirschleger, B. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1341-1343.

(6) Compounds **i-iii** were obtained from the condensation reaction of **1** and **3** under various conditions, which were probably formed through the addition of water or *p*-nitrophenol to initially formed **4** or **3** itself. Further condensation of **1** with **iii** did not proceed.

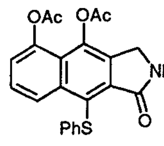


i ii iii

(7) Difficulties in the preparation of the alkoxypropiolates were also reported. See, a) Gupta, I.; Yates, P. *J. Chem. Soc., Chem. Commun.* **1982**, 1227-1228; b) Camps, F.; Coll, J.; Llebaria, A.; Moretó, J. M.; Ricart, S. *Synthesis* **1989**, 123-124; c) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 11323-11334.

(8) Bromination of terminal acetylenes: See, Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727-729.

(9) *Typical procedure*: Under a nitrogen atmosphere, a mixture of **10a** (20 mg, 0.050 mmol), Me_2SiCl_2 (0.025 mL, 0.20 mmol), Et_3N (0.055 mL, 0.40 mmol), and chloranil (31 mg, 0.125 mmol) in dry benzene (3 mL) was heated in a sealed tube at 100 °C for 5 h. The reaction mixture was partitioned between ice-water and CH_2Cl_2. The organic layer was separated, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was washed with hexane to give crude **11a**. Due to its high polarity, this product was identified as the diacetate **11a'** by treatment with Ac_2O (1.2 mL) and pyridine (1 mL) at room temperature for 18 h. Purification of the crude diacetate by SiO_2 column chromatography (hexane-EtOAc) gave **11a'** (25 mg, quant.) as white crystals: mp 210-213 °C (recryst. from hexane-EtOAc), IR (KBr) 1775, 1705, 1617, 1599, 1582 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (3 H, s), 2.51 (3 H, s), 4.78 (2 H, s), 7.07-7.31 (7 H, m), 7.41 (2 H, t, J = 7.5 Hz), 7.60 (1 H, t, J = 7.5 Hz), 7.84 (2 H, d, J = 8 Hz), 8.88 (1 H, d, J = 8 Hz); HRMS calcd for $C_{28}H_{21}NO_5S$, 483.1138; found, 483.1128.



11a'

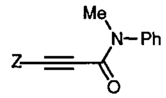
The crude product **11a** was converted to **12a** (80% overall yield from **10a**) and then to **9a** (97% yield), according to the reported method.[3c]

12a: Pale yellow crystals; mp 260-262 °C (decomp.) (recryst. from hexane-C_6H_6); IR (KBr) 1698, 1613, 1599, 1578 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (9 H, s), 1.13 (9 H, s), 4.97 (1 H, d, J = 16 Hz), 5.01 (1 H, d, J = 16 Hz), 7.00 (1 H, d, J = 7.5 Hz), 7.22-7.54 (7 H, m), 7.87 (2 H, d, J = 7 Hz), 7.97 (2 H, d, J = 8 Hz), 8.71 (1 H, d, J = 9 Hz); Anal. Calcd for $C_{32}H_{33}NO_4SSi$: C, 69.16; H, 5.99; N, 2.52; S, 5.77. Found: C, 69.46; H, 6.08; N, 2.52; S, 5.70.

9a: Pale yellow crystals; mp 232-234 °C (recryst. from hexane), IR (KBr) 1771, 1684, 1611 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (18 H, s), 2.57 (3 H, s), 4.92 (2 H, s), 7.04 (1 H, d, J = 7.5 Hz), 7.19 (1 H, t, J = 7.5 Hz), 7.43 (3 H, t, J = 8 Hz), 7.62 (1 H, d, J = 7.5 Hz), 7.87 (1 H, d, J = 8 Hz); Anal. Calcd for $C_{28}H_{31}NO_5Si$: C, 68.68; H, 6.38; N, 2.86. Found: C, 68.47; H, 6.34; N, 2.83.

(10) Satisfactory spectral data (IR, ^1H NMR, HRMS) and/or elemental analyses for the other unknown compounds (**10a**,**b**, **12b**, **9b**, **16**, and the corresponding diacetate of **17**) were obtained.

(11) Comparison of the LUMO energy level for the dienophile model **iv**, corresponding to **10a**, with the unsubstituted **v** and ethoxy derivatives **vi** shows the high reactivity of phenylthioacetylene as the dienophile [The energy levels were calculated by Spartan (ver. 3.1.2) using the AM1 Hamiltonian].



Compound	HOMO/eV	LUMO/eV
iv (Z=PhS)	-8.434	-0.304
v (Z=H)	-8.833	0.138
vi (Z=EtO)	-8.676	0.278