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An Efficient Preparation of *peri*-Hydroxy Dihydroquinone Derivatives through a Pummerer-type Rearrangement of Silylene-protected *peri*-Hydroxy Aromatic Sulfoxides

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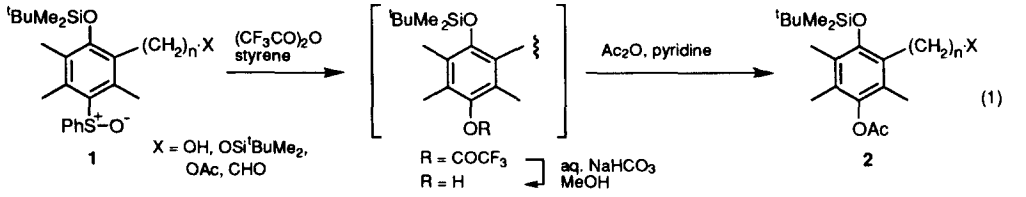
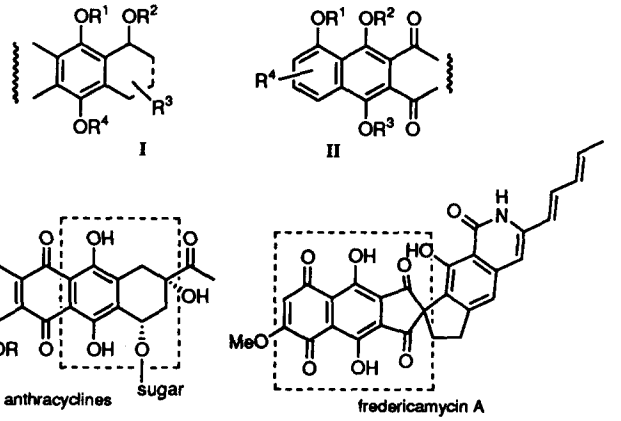
Abstract: Silylene protection of two dihydroxy groups of the *peri*-hydroxy aromatic sulfides **6a-f** was essential for the subsequent Pummerer-type reaction. The overall process provided a novel and efficient approach to the *peri*-hydroxy dihydroquinone derivatives **9a-f**.

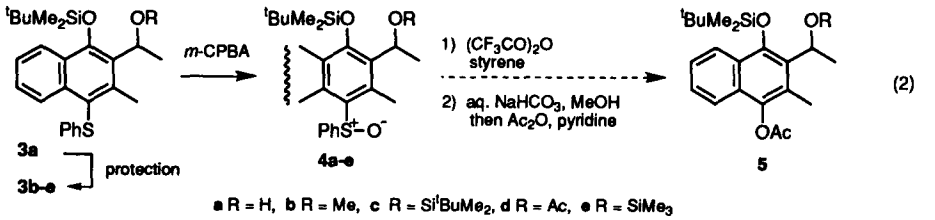
Silylene formation from two *H*-acidic functional groups is one of the useful methods in synthetic organic chemistry due to its stability under various kinds of reaction conditions and easy deprotection under selected conditions.[1,2] In addition to the efficient nature of the silylene group as a protective group, silylene formation was successfully employed in the Diels-Alder reaction of *in situ* generated dihydroxystyrene derivatives in which it effected the fixing of the conformation of the molecules and prevented the elimination of the hydroxy groups.[3] It has also been applied to control the stereochemistry in the Diels-Alder reactions, glycosylations, and aldol reactions.[4] Here we describe another useful application of silylene formation in which silylene-protection of two neighboring hydroxy groups of aromatic sulfides **6** was essential for a Pummerer-type rearrangement of the derived sulfoxides **8**. The overall process provided a novel and efficient preparation of the *peri*-hydroxy dihydroquinone derivatives **9**.

Very recently, we have developed a novel *ipso*-substitution of the sulfinyl group of *p*-sulfinylphenyl silyl ethers **1** into acyloxy groups (eq. 1).[5] In this reaction, the silyloxy group worked as an efficient electron donating group to produce a Pummerer-type rearrangement under mild conditions in high yields. Because this method is compatible with several functional groups such as hydroxy, silyloxy, acyloxy, and formyl groups at the ω-position of the side chain, we have next planned to extend this method to construct suitably protected dihydroquinones having neighboring hydroxy groups (for example, **I** and **II**) which are included in biologically important *peri*-hydroxy polycyclic aromatic quinones such as anthracyclines or fredericamycin A. However, the application of this method to the sulfoxide **4a** having a 1-hydroxyalkyl side-chain was unsuccessful due to easy migration of the silyl group to the benzylic hydroxy group during the oxidation of **3a**, the difficult purification of the obtained **4a** by SiO_2 chromatography, and unfavorable behavior under Pummerer conditions.



The use of the *O*-protected derivatives **4b-e** was not attainable, which resulted in the ready migration of the silyl group of **3a** (for the preparation of **3b** and **3c**) and complications during the Pummerer-type reaction (for **4d** and **4e**) (eq. 2). These difficulties were attributable to steric congestion needed for separate protection of the two neighboring hydroxy groups and/or easy decomposition and elimination of the benzylic functional groups.[6]





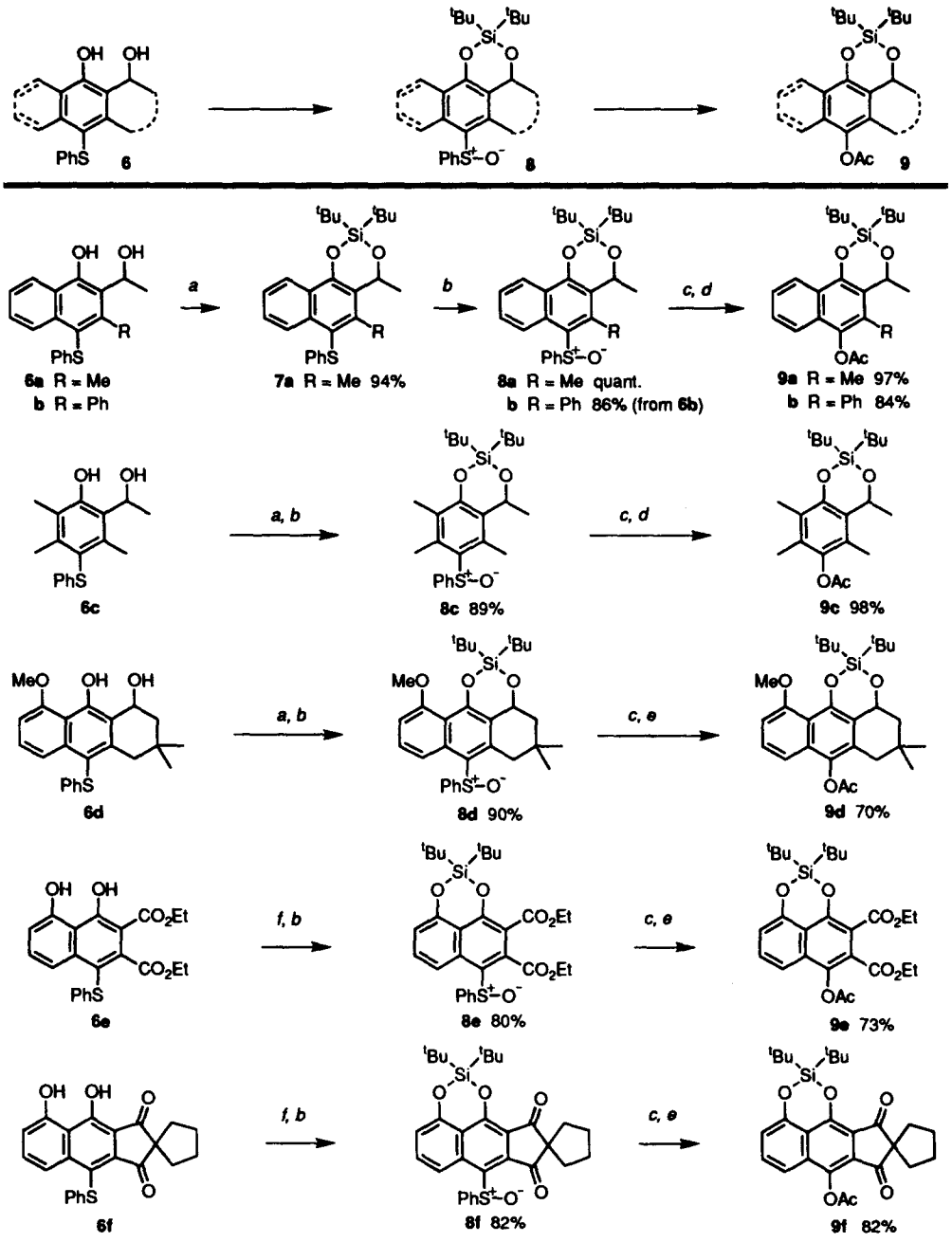
a R = H, b R = Me, c R = Si^{t}BuMe$_2$, d R = Ac, e R = SiMe$_3$

These problems were clearly resolved by silylene protection of both hydroxy groups. Thus, the treatment of the dihydroxy sulfide **6a** with ^{t}Bu$_2$Si(OTf)$_2$ gave the silylene-protected sulfide **7a** in 94% yield. The silylene group was found to be sufficiently stable to SiO_2 chromatography and to the following transformations. The oxidation of **7a** with *m*-CPBA below -30°C quantitatively gave the sulfoxide **8a**, which was subjected to the Pummerer-type reaction producing the *p*-acetoxy product **9a** (isolated in 97% yield after acetylation). On the other hand, a similar Pummerer-type reaction of the corresponding isopropylidene derivative, prepared from **6a** in 61%, gave a complex mixture.[7] This methodology is generally applied to several types of dihydroxy sulfides **6b-d** to give 63-87% overall yields of the silylene-protected dihydroquinones **9b-d**. In a similar manner, the sequential silylene-protection and the Pummerer-type reaction of the 1,8-dihydroxynaphthalenes **6e, f** provided the *peri*-hydroxy dihydroquinone derivatives **9e, f**, corresponding to structure **II**, in good overall yields. The results are listed in Table 1.[8,9] Desilylation of the crude product **9g** gave the dihydroquinone **10**,[10] which was readily oxidized to the quinone **11** in good yields (eq. 3).

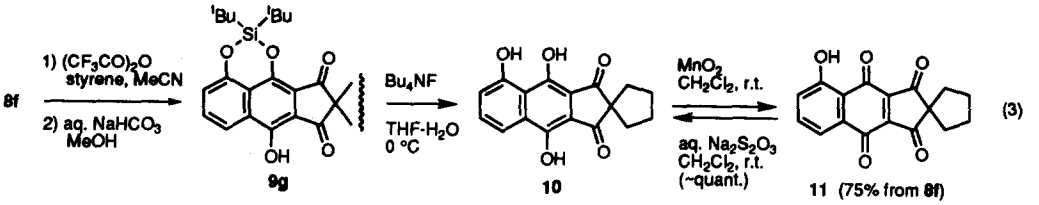
Thus, the present procedure features a ready silylene protection, mild reaction conditions, a high yield of Pummerer-type rearrangement and ready deprotection of the silylene group, which would afford a novel and promising methodology for the total synthesis of naturally occurring *peri*-hydroxy polyaromatic quinones. Application of this strategy to the total synthesis of such natural products is now under investigation.

Acknowledgment: This study was performed using Special Coordination Funds of the Science and Technology Agency of the Japanese Government.

Table 1. Preparation of *peri*-Hydroxy Dihydroquinone Derivatives **9** through Silylene protection and a Pummerer-type Reaction.



a, $^tBu_2Si(OTf)_2$, pyridine, CH_2Cl_2, r.t.; *b*, *m*-CPBA, CH_2Cl_2, -30 °C; *c*, $(CF_3CO)_2O$, styrene, $CHCl_3$ (for **8a-d**) or MeCN (for **8e, f**), 0 °C→r.t.; *d*, aq. $NaHCO_3$, MeOH, r.t. then Ac_2O, pyridine, r.t.; *e*, Ac_2O, AcONa, pyridine, r.t.; *f*, $^tBu_2Si(OTf)_2$, Et_3N, DMF, r.t.



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6. Similar easy migration of the silyl group from the phenolic hydroxy group into its neighboring benzylic hydroxy group and easy elimination of the benzylic hydroxy group were often observed during anthracycline syntheses. For an example, see; Tamura, Y.; Akai, S.; Kishimoto, H.; Sasho, M.; Kirihara, M.; Kita, Y. *Chem. Pharm. Bull.*, **1988**, *36*, 3897-3914.
7. This is probably due to insufficient electron-donation and instability of the isopropylidene group compared to the silylene group. A comparison between these two bifunctional protective groups on a Lewis acid-catalyzed Diels-Alder reaction was reported. See, Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.*, **1983**, *48*, 3252-3265.
8. **Typical procedures**: *Preparation of the sulfoxide 8a*; Under a nitrogen atmosphere, pyridine (0.04 mL, 0.50 mmol) and $^tBu_2Si(OTf)_2$ (0.050 mL, 0.14 mmol) were added to an ice-cooled solution of **6a** (36 mg, 0.115 mmol) in dry CH_2Cl_2 (3 mL), and the reaction mixture was stirred at room temperature for 2 h. The mixture was worked-up as usual and purified by SiO_2 column chromatography to give **7a** (49 mg, 94%). A solution of **7a** (49 mg) was dissolved in CH_2Cl_2 (4 mL) and cooled to -65 °C, to which was added m-CPBA (80% purity, 23 mg, 0.108 mmol). The reaction mixture was gradually warmed to -30 °C and stirred for 2 h. The mixture was poured into sat. aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was washed with sat. aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated. Purification of the residue by SiO_2 column chromatography gave **8a** (51 mg, quant.).
Pummerer-type reaction of 8a; Under a nitrogen atmosphere, $(CF_3CO)_2O$ (0.055 mL, 0.40 mmol) was added to a solution of **8a** (18.7 mg, 0.040 mmol) and styrene (14 mg, 0.13 mmol) in dry $CHCl_3$ (2 mL) at 0 °C. The reaction mixture was stirred for 30 min and concentrated. The residue was dissolved in MeOH (5 mL) and sat. aqueous $NaHCO_3$ (4 drops) was added. After being stirred for 1 h, CH_2Cl_2 (4 mL) and sat. aqueous NH_4Cl (4 drops) were added, dried (Na_2SO_4), and concentrated. To the residue were added pyridine (0.20 mL) and Ac_2O (0.20 mL), and the reaction mixture was stirred at room temperature for 5 h. The usual work-up and SiO_2 chromatography purification of the crude product gave **9a** (15.5 mg, 97%). White crystals, mp 149-150 °C (hexane-benzene); IR ($CHCl_3$) 1767, 1364, 1208 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (9 H, s), 1.21 (9 H, s), 1.60 (3 H, d, J = 6.5 Hz), 2.16 (3 H, s), 2.46 (3 H, s), 5.45 (1 H, q, J = 6.5 Hz), 7.42-7.51 (2 H, m), 7.59-7.65 (1 H, m), 8.22-8.27 (1 H, m). *Anal.* Calcd. for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68,59; H, 8.07.
All other new compounds, **8a-f**, **9b-f**, **10**, and **11**, were fully characterized by spectroscopic means and elemental analysis and/or high resolution mass spectroscopy.
9. The dihydroxy sulfides **6** were readily prepared by the site selective introduction of the phenylthio group into the corresponding *p*-unsubstituted phenol derivatives and/or by the cycloaddition of the 4-(phenylthio)homophthalic anhydride to the dienophiles. Details will be presented in a forthcoming paper.
10. The dihydroquinone **10** was partially oxidized to **11** during purification, while acetylation of crude **10** by Ac_2O-pyridine gave the corresponding triacetate in 86% yield from **8f**. Two quinone compounds **10** and **11** are interconvertible nearly quantitatively.

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