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A NOVEL INTRAMOLECULAR [4+2]CYCLOADDITION OF SILYLENE PROTECTING DIHYDROXYSTYRENE DERIVATIVES: A VERSATILE SYNTHESIS OF LINEARLY CONDENSED PERI-HYDROXY AROMATIC COMPOUNDS

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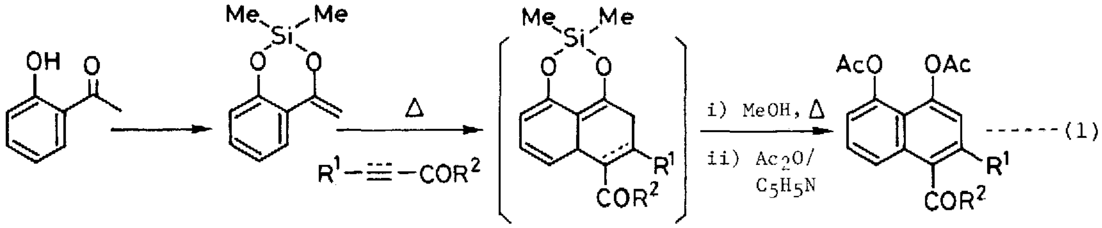
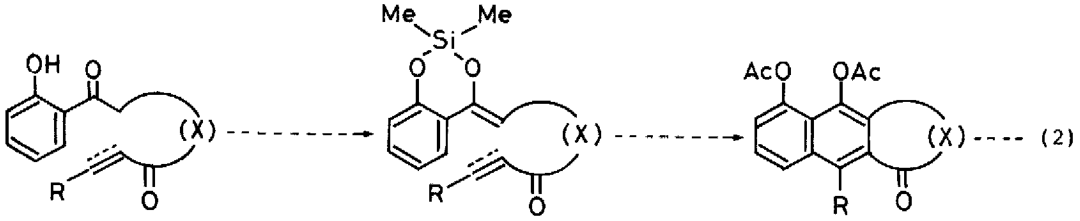
Summary: The first example of an intramolecular [4+2]cycloaddition of the silylene protecting dihydroxystyrene derivatives leading to linearly condensed peri-hydroxy aromatic compounds (6a-c) is described.

In connection with our efforts[1] toward a synthesis of biologically important peri-hydroxy aromatic compounds[2] such as anthracycline, pyranonaphthoquinone, and fredericamycin A, we have reported[3] a novel [4+2]cycloaddition of the silylene-protecting dihydroxystyrene to dienophiles (eq. 1). It is expected to be a short and efficient synthetic method for the peri-hydroxy polycyclic compounds if the cycloaddition reaction could be extended to the intramolecular system (eq. 2) (Scheme 1). Generally, the intermolecular cycloaddition of the silylene-protecting dihydroxystyrene derivatives was performed by heating of the dihydroxystyrene derivatives with 0.5-1.0 equivalents of dienophiles in absolute benzene at 130°C for 2 days in a sealed tube followed by oxidative desilylation in refluxing methanol to give the aromatized compounds, which were isolated as the acetylated peri-hydroxy naphthalene derivatives. The conditions, however, were not suitable for the intramolecular systems and gave a miserable yield of the cycloaddition products. We have now developed an excellent method which converts the silylene-protecting dihydroxystyrenes having dienophiles in the molecules into the linearly condensed peri-hydroxy polycyclic compounds in high yields and short steps.

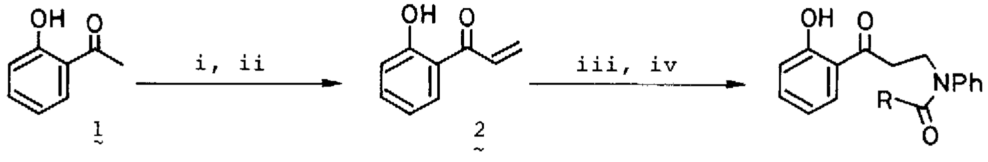




$X=CH_2$, NR, O

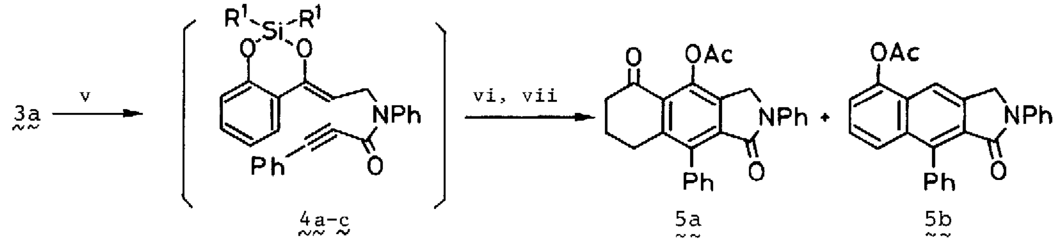
Scheme 1

The starting o-hydroxy carbonyl compounds (3a-c) were prepared from o-hydroxyacetophenone (1) in 4 steps. Hydroxymethylation of the acetyl group of 1 followed by dehydration with c-H_2SO_4 in benzene gave the known vinyl ketone (2).[4] Michael reaction of 2 with aniline gave the terminal amino compound, which was condensed with α,β-unsaturated carboxylic acids by using dehydrating agent, dicyclohexylcarbodiimide (DCC) or (trimethylsilyl)ethoxyacetylene[5] to give 3a-c in considerable yields. Initially, the dimethylsilylene derivative (4a), isolated by the reaction of 3a with dichlorodimethylsilane/Et_3N, was heated under the same conditions as in the case of intermolecular cycloaddition to give a low yield of the cycloaddition products: Heating of a benzene solution of 4a at 130-150°C for 2 days in a sealed tube and the mixture was concentrated. Oxidative desilylation in refluxing methanol followed by acetylation gave the cycloaddition products, 5a and 5b in 15% and 11% yields, respectively. The yield of the products was dramatically improved when the reaction was performed without isolation of of 4a. Thus, a solution of 3a, dichlorodimethylsilane, and Et_3N in absolute benzene was heated and the same work-up as described above gave a 92% yield of 5a and 5b in a 35:57 ratio. Variation of the substituents on silicon atom among dimethyl, diethyl, and diphenyl groups resulted in a slight increase in the ratio of 5a vs 5b from 35:57 to 48:52 (Scheme 2).



i) 2.4 equiv LDA/$(HCHO)_n$; ii) c-H_2SO_4/C_6H_6; iii) $C_6H_5NH_2$/EtOH; iv) RCO_2H, DCC/CH_2Cl_2 or RCO_2H, TMS-C≡C-OEt, cat. HgO/CH_2Cl_2

3a; R= C≡CPh (82%)
b; R= C≡CH (90%)
c; R= (Z) $CH=CHCO_2Me$ (58%)

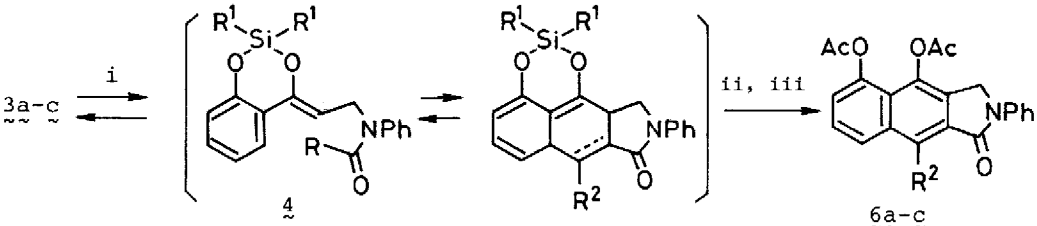


v) $R^1{}_2SiCl_2/Et_3N$, sealed tube, 130-150°C; vi) MeOH, reflux; vii) Ac_2O/C_5H_5N

	R^1	% Yield of 5a	5b
a	Me	35	57
b	Et	37	47
c	Ph	48	52

Scheme 2

Although the yield of cycloadducts (5a and 5b) was improved, the desired fully aromatized *peri*-hydroxy adduct (6a) could not be obtained at all.[6] After many unsuccessful trials,[7] an excellent result arose by addition of chloranil in the reaction of 3a and dichlorosilane, which produced 6a selectively in high yield. Thus, to a suspension of 3a (0.054 mmol) and chloranil (0.136 mmol) in absolute benzene (5 ml), Et_3N (0.217 mmol) and dichlorodimethylsilane or dichlorodiphenylsilane (0.108 mmol) were added dropwise. The mixture was heated in a sealed tube at 130-150°C and worked up as described above to give 6a in an excellent yield. Other *o*-hydroxy carbonyl compounds (3b,c) gave the corresponding *peri*-hydroxy polycyclic compounds (6b,c) in high yields (Scheme 3).



i) $R^1{}_2SiCl_2/Et_3N$, chloranil, sealed tube;
ii) MeOH, reflux; iii) Ac_2O/C_5H_5N

Starting Compounds	R	Reaction Conditions ($R^1{}_2SiCl_2$, time)	Products	R^2	% Yields
3a	C≡CPh	Me_2SiCl_2, 48h	6a	Ph	97
		Ph_2SiCl_2, 48h			92
3b	C≡CH	Me_2SiCl_2, 7h	6b	H	84
		Ph_2SiCl_2, 48h			75
3c	(Z) $CH=CHCO_2Me$	Me_2SiCl_2, 18h	6c	CO_2Me	64
		Ph_2SiCl_2, 48h			65

Scheme 3

It should be noted that the initially-formed unstable *Z*-olefin intermediates (**4**)[10] could be regenerated reversibly under the reaction conditions and caused intramolecular Diels-Alder reaction to give the adducts which were readily oxidized with chloranil to the stable *peri*-hydroxy polycyclic aromatic compounds irreversibly in high yields. All new compounds, **3a-c**, **5a,b** and **6a-c** exhibited spectroscopic[11] and analytical data in accordance with the assigned structures. Application of the present method to the preparation of the biologically important naturally occurring *peri*-hydroxy polycyclic compounds is in progress.

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6 Effort to obtain **6a** from **5a** under the dehydrogenation conditions failed.

7 Heating of the boronate or stannylene derivative, obtained by the reaction of **3a** with $PhB(OH)_2$ in benzene[8] or $(n\text{-}Bu)_2SnO$ in benzene,[9] caused the intramolecular cycloaddition and the subsequent oxidative deprotection could give **6a**, but the yield never exceeded 44%.

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10 Stereospecific generation of *Z*-olefin was ascertained in the reaction of *o*-hydroxypropiophenone with dichlorodimethylsilane/Et_3N.

11 Selected spectroscopic data for **5a**: i.r. ($CHCl_3$) ν 1770, 1705, 1690 cm^{-1}; ^1H n.m.r. (500 MHz, $CDCl_3$) δ 2.49 (s, 3H, OAc), 4.78 (s, 2H, CH_2N). **5b**: i.r. ($CHCl_3$) ν 1760, 1695 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 2.54 (s, 3H, OAc), 5.03 (s, 2H, CH_2N). **6a**; i.r. ($CHCl_3$) ν 1775, 1765, 1700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 2.47 (s, 3H, OAc), 2.53 (s, 3H, OAc), 4.83 (s, 2H, CH_2N). **6b**; i.r. ($CHCl_3$) ν 1775, 1700 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 2.44 (s, 3H, OAc), 2.49 (s, 3H, OAc), 4.84 (s, 2H, CH_2N). **6c**; i.r. ($CHCl_3$) ν 1770, 1740, 1710 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 2.44 (s, 3H, OAc), 2.49 (s, 3H, OAc), 4.15 (s, 3H, CO_2Me), 4.84 (s, 2H, CH_2N).

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