Synthesis of 2,2′-Dihydroxybisphenols and Antiviral Activity of Some Bisphenol Derivatives

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New diphenylmethane-type 2,2′-dihydroxybisphenols (5a—d) were prepared regioselectively in good yields. We evaluated the antiviral activity of some bisphenol derivatives synthesized by the plaque reduction assay. Most of the compounds showed significant antiviral activity and the 4,4′-dihydroxybisphenol derivative (10) showed higher activity than 2,2′-bisphenol derivatives. This compound had EC_{50} value of 1.8 μg/m1.

Key words bisphenol; bisarylation; sonication; antiviral activity; anti-HSV-1; plaque reduction assay

Triphenylmethane-type bisphenols have antioxidant activity,[1,2] and some of the derivatives show anticancer activity.[3] Recently, we reported a conventional procedure for the preparation of triphenylmethane-type 2,2′-dihydroxybisphenols.[4] For the synthetic application of the procedure and biological evaluation of the related compounds, we attempted to synthesize diphenylmethane-type 2,2′-dihydroxybisphenol derivatives with some aliphatic aldehydes as starting material. In this paper, we wish to report the syntheses of some 2,2′-dihydroxybisphenols for lead compounds and also to communicate significant antiviral activities of some of the related compounds by the plaque reduction assay.[5]

Results and Discussion

Regioselective syntheses of 2,2′-dihydroxybisphenols (**5a**—**d**) with aliphatic aldehydes (**2**—**4**) were achieved in good yields according to the procedure described previously.[4] The results are summarized in Table l. The structures of the products were easily established by spectroscopic methods (^{1}H- and ^{13}C-NMR). The ^{13}C- and ^{1}H-NMR data are listed in Tables 3 and 4. Full assignments of these signals were confirmed by their ^{1}H–^{1}H shift correlation spectroscopy (^{1}H–^{1}H COSY), ^{1}H-detected heteronuclear multiple quantum coherence (HMQC), and heteronuclear multiple-bond correlation (HMBC) spectra.

Antiviral activities of some 2,2′-dihydroxybisphenols (**5b** and **6**—**9**[4]) and 4,4′-dihydroxybisphenol (**10**)[4] (see Fig. 1) were examined by plaque reduction assay as described by Schinazi *et al.*[5] The results (EC_{50}: 50% effective concentration) of six compounds by this assay are summarized in Table 5. Compound **5b** having an isobutyl group instead of the substituted aromatic ring had high cytotoxicity. Antiviral activity of the 2,2′-bisphenol series (**6**—**9**) increased in the order, **6**<**7**<**8**<**9** (see EC_{50} values in Table 5). Higher antiviral activity was observed in the 4,4′-bisphenol derivative (**10**) than the 2,2′-bisphenol series (**6**—**9**). This most active compound (**10**) was estimated to have a 50% cytotoxic concentration (CC_{50}) of 25—30 μg/ml by additional experiments. The selectivity index (CC_{50}/EC_{50}) of **10** was *ca.* 15.

During the past five years, more than a few thousand reports with bisphenol as a key word have appeared, however, to the best of our knowledge, no report has dealt with the an-

Table 1. Reactions between Phenolates **1** and Aldehydes (**2**—**4**)

Entry	Phenol	Aldehyde	Conditions	Product (Yield %)
1	**1a**	**2**	Reflux, CH_2Cl_2, 1 h	**5a** (75)
2	**1a**	**3**	Reflux, CH_2Cl_2, 1 d, sonication	**5b** (60)
3	**1a**	**4**	Reflux, CH_2Cl_2, 20 h, sonication	**5c** (Quant.)
4	**1b**	**4**	Reflux, CH_2Cl_2, 1 d	**5d** (63)*a)*

a) The aldol condensation compound (**11**; $PhCH_2CH_2CH{=}C(CHO)CH_2Ph'$) was also isolated in 10% yield.

Table 2. Analytical and MS Spectroscopic Data for 2,2′-Dihydroxybisphenols (**5a**—**d**)

Compound	mp (°C)	Formula	Analysis (%) Calcd (Found)			Formula, HR-MS *m/z* Calcd (Found)
			C	H	N	
5a	162—164	$C_{16}H_{14}O_6$	63.57 (63.50	4.67 4.60	0 0)	$C_{16}H_{14}O_6$ (M^+) 302.0790 (302.0791)
5b	162—163	$C_{19}H_{20}O_6$	66.27 (66.27	5.85 5.82	0 0)	$C_{19}H_{20}O_6$ (M^+) 344.1260 (344.1257)
5c	41—45	$C_{23}H_{20}O_6 \cdot 0.5H_2O$	68.82 (68.72	5.27 5.43	0 0)	$C_{23}H_{20}O_6$ (M^+) 392.1260 (392.1257)
5d	107—111	$C_{21}H_{20}O_2$	82.86 (82.76	6.62 6.76	0 0)	$C_{21}H_{20}O_2$ (M^+) 304.1463 (304.1466)

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Table 3. ^{13}C-NMR Data for 2,2′-Dihydroxybisphenols (**5a**—**d**)

C No.	**5a**[a]	**5b**[b,c]	**5c**[b,c]	**5d**[b]
1,1′	124.34	122.99	122.58	130.32
2,2′	148.67	146.84	147.04	152.65
3,3′	97.42	98.32	98.48	115.97
4,4′	144.92	146.06	146.23	127.42
5,5′	139.44	142.22	142.30	121.71
6,6′	107.14	106.17	105.95	127.15
–CH<	30.53	32.16	34.42	34.73
OCH_2O	100.21	101.02	101.06	
$–CH_3$	19.78			
$–\underline{C}H_2CH(CH_3)_2$		42.94		
$–CH_2\underline{C}H(CH_3)_2$		25.61		
$–CH_2CH(\underline{C}H_3)_2$		22.64		
$–\underline{C}H_2CH_2Ph''$			35.77	35.66
$–CH_2\underline{C}H_2Ph''$			33.83	33.97
$–CH_2CH_2\underline{Ph}''$			141.83 (1″)	141.97 (1″)
			128.41 (2″)	128.44 (2″)
			128.34 (3″)	128.35 (3″)
			125.88 (4″)	125.86 (4″)

a) Measured in DMSO-d_6. *b*) Measured in $CDCl_3$. *c*) Measured by GX-400.

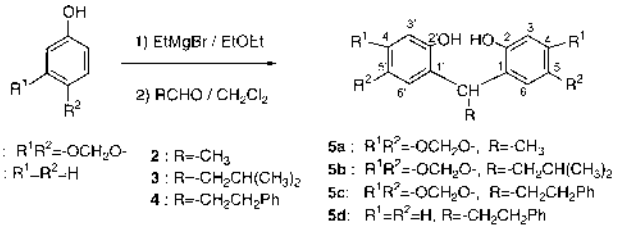

Chart 1

Table 5. Antiviral Activity of Bisphenols (**5b** and **6**—**10**)

	5b	**6**	**7**	**8**	**9**	**10**
EC_{50} (μg/ml)	ND	44.0	14.5	8.6	7.2	1.8

ND=not determined because of cytotoxicity.

Table 4. ^{1}H-NMR Data (*J* in Hz) for 2,2′-Dihydroxybisphenols (**5a**—**d**)

H No.	**5a**[a]	**5b**[b,c]	**5c**[b,c]	**5d**[b]
3,3′	6.38 s	6.35 s	6.36 s	6.77—6.79 m
4,4′				7.03—7.06 m
5,5′				6.90—6.93 m
6,6′	6.58 s	6.73 s	6.75 s	7.32—7.34 m
OCH_2O	5.83 dd (3.7, 0.9)	5.83 dd (21.5, 1.5)	5.83 dd (23.4, 1.5)	
OH	8.88 br s	6.67 br s	6.66 br s	6.68 br s
–CH<	4.53 q (7.3)	4.44 t (7.8)	4.34 t (7.8)	4.50 t (7.5)
$–CH_3$	1.35 d (7.3)			
$–C\underline{H}_2CH(CH_3)_2$		1.85 dd (7.8, 6.8)		
$–CH_2C\underline{H}(CH_3)_2$		1.41—1.48 m		
$–CH_2CH(C\underline{H}_3)_2$		0.91 d (6.4)		
$–\underline{C}H_2CH_2Ph''$			2.25—2.31 m	2.42—2.48 m
$–CH_2\underline{C}H_2Ph''$			2.54—2.58 m	2.55—2.60 m
$–CH_2CH_2\underline{Ph}''$			7.12—7.14 m (2″)	7.12—7.14 m (2″)
			7.22—7.27 m (3″)	7.23—7.27 m (3″)
			7.16—7.18 m (4″)	7.16—7.18 m (4″)

a) Measured in DMSO-d_6. *b*) Measured in $CDCl_3$. *c*) Measured by GX-400.

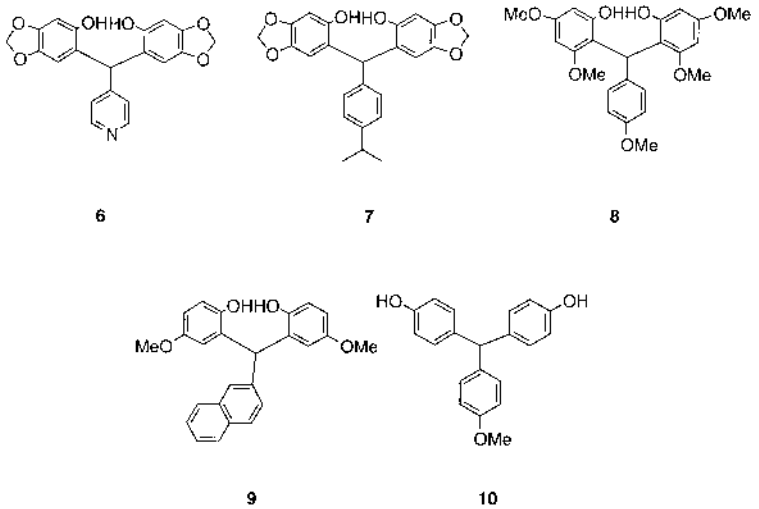

Fig. 1

tiviral activity of such a class of compounds. Quite recently, cosalane, which possesses a dichlorinated disalicylmethane fragment in the molecule, has been reported as an anti-HIV agent. In this fragment, one can also find 4,4′-dihydroxybisphenol moiety.[6] It is noteworthy that these simple bisphenol derivatives showed considerably high antiviral activity. On the basis of our observation, synthetic trials are being made on triphenylmethane-type 4,4′-dihydroxybisphenols. Regarding the molecular modification, there are many combinations of starting aromatic aldehydes and phenols. The synthetic methodologies have already been reported.[4] The results of molecular modification of the prototype **10** and biological screening will be described elsewhere.

Experimental

Melting points were determined by a micro melting point apparatus (Yanagimoto MP-S3) without correction. IR spectra were measured with a Shimadzu FTIR-8100 IR spectrophotometer. The absorption bands attributable to OH, CH, aromatic C=C, and C–O bonds were observed at 3300—3430, 2860—2990, 1580—1640, and 1150—1220 cm^{-1}, respectively. Low- and high-resolution mass spectra (LR-MS and HR-MS) were taken with a JEOL JMS HX-110 double-focusing model equipped with a FAB ion source interfaced with a JEOL JMA-DA 7000 data system. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM A-500 or GX-400. Chemical shifts were expressed in δ ppm downfield from an internal tetramethylsilane (TMS) signal for ^{1}H-NMR and the carbon signal of the corresponding solvent [$CDC1_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm)] for ^{13}C-NMR. Microanalyses were performed with a Yanaco MT-6 CHN corder. Routine monitoring of reactions was carried out using precoated Kieselgel $60F_{254}$ plates (E. Merck). Flash column chromatography was performed using a silicagel (Fuji Silysia FL-60D) with a UV detector. Commercially available starting materials were used without further purification.

General Procedure for the Preparation of 2,2′-Dihydroxybisphenols (5a—d) Under a nitrogen stream a solution of the selected phenol (**1**) (20 mmol) in Et_2O (50 ml) was added dropwise to a solution of 3 M EtMgBr (6.7 ml, 20 mmol) in Et_2O (40 ml) with stirring at room temperature, and the mixture was allowed to stand for 20 min, then Et_2O was removed under vacuum. After addition of CH_2Cl_2 (300 ml) to the residue, a solution of the selected aldehyde (**2**—**4**) (5 mmol) in CH_2Cl_2 (100 ml) was added with stirring. The resulting mixture was refluxed with or without sonication (see Table 1). The reaction was quenched with saturated aqueous NH_4Cl (100 ml), and the mixture was extracted with EtOAc (3×100 ml). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The desired compounds (**5a**—**d**) and by-products (**11**) were purified by flash chromatography (CH_2Cl_2–EtOAc or *n*-hexane–EtOAc as solvent) of the residue.

In the case of **5a**, the product was purified by recrystallization from diisopropylether. The structures of the products were determined by elemental analysis and spectroscopic methods. The yields and physical data are summarized in Tables 1—4.

Compound **11**: Pale yellow oil. HR positive ion FAB-MS: Calcd for $C_{18}H_{19}O$ $(M+H)^+$: 251.1436. Found: 251.1436. ^{1}H-NMR ($CDCl_3$) δ: 2.70—2.76 (4H, m, $PhCH_2CH_2$–), 3.57 (2H, s, Ph′CH_2–), 6.57—6.60 (1H, m, –CH=C<), 7.09—7.16 (5H, m, *ortho*-Ar′H and ArH, *para*-Ar′H), 7.19—7.23 (3H, m, *para*-ArH, *meta*-Ar′H), 7.26—7.29 (2H, m, *meta*-ArH), 9.43 (1H, s, CHO). ^{13}C-NMR ($CDCl_3$) δ_C: 29.61 (Ph′$\underline{C}H_2$–), 30.95 ($PhCH_2\underline{C}H_2$–), 34.38 ($Ph\underline{C}H_2CH_2$–), 126.04 (*para*-C of Ph′), 126.33 (*para*-C of Ph), 128.27, 128.30, 128.40, 128.55 (*ortho*- and *meta*-C of Ph and Ph′), 139.01 (C1′ of Ph′), 140.40 (C1 of Ph), 142.81 (–CH=$\underline{C}$<), 154.55 (–$\underline{C}$H=C<), 194.41 (CHO).

Antiviral Activity Assay The antiviral activities of the compounds were measured by the plaque reduction assays[5] as described below. Confluent monolayers of Vero cells (5×10^5 cells) in 6-well plastic plates were infected with 100 PFU of HSV-l (KOS). After 1 h adsorption period at 37 °C, the cultures were overlaid with 2 ml of DULBECCO's modified Eagle minimum essential medium (DMEM) containing 2% heat-inactivated fetal calf serum and various concentrations of the target compounds. The cultures infected with HSV-1 were incubated in a CO_2 incubator, fixed with formalin and stained with crystal violet in methanol at 3 d after infection. After washing with water and drying, the plaque numbers were counted. Calculated EC_{50} values for the tested compounds are summarized in Table 5.

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