Palladium(0)-Catalyzed Synthesis of 2-Vinyl-2,3-dihydro-benzo[1,4]dioxins

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The reaction of 1,4-bis(methoxycarbonyloxy)but-2-ene (**2a–3a**) or 3,4-bis(methoxycarbonyloxy)but-1-ene (**4a**) with various substituted benzene-1,2-diols was catalyzed by a palladium(0) complex to give substituted 2-vinyl-2,3-dihydro-benzo[1,4]dioxins in good yields via a tandem allylic substitution reaction. In the case of 4-substituted benzene-1,2-diols, the ratio of regioisomers is determined by the relative acidity of the two phenolic protons. For 3-substituted benzene-1,2-diols, this ratio is determined only by steric effects in the case of alkyl substituents, although it is determined mainly by the relative stabilities of the corresponding phenates for other substituents; however, for 3-nitrobenzene-1,2-diol, this ratio is determined by the relative leaving-group ability of 2-nitro- or 3-nitrophenate. When the cyclisation was performed in the presence of an optically active phosphane, chiral 2-vinyl-2,3-dihydro-benzo[1,4]dioxin (**5**) was obtained with enantio-selectivity of up to 45% using BINAP as the chiral phosphane.

Introduction

The 1,4-benzodioxane ring system is present in a large number of structures of therapeutic agents possessing important biological activities. Some of them are antagonists of α-adrenergic receptors giving them antihypertensive properties;[1][2][3][4][5][6] others have affinities with serotonine receptors which are involved in nervous breakdown, schizophrenia and headache,[7][8] or exhibit antihyperglycemic properties.[3] It has been shown that these biological activities are considerably influenced by the chirality of the 1,4-benzodioxane ring.[2,7,9-15] Enantiopure 2-hydroxymethyl-2,5-dihydro-benzo[1,4]-dioxin is the usual starting material for the synthesis of optically pure 2-substituted 2,3-dihydro-benzo[1,4]dioxins. This enantiopure starting material has been obtained from D-mannitol,[16] by condensation of catechol with chiral glycidol[17] or epichlorhydrine,[10a] by Sharpless epoxidation of 1-aryloxy-4-hydroxy-2-butene substrate[18] or recently by an enzymatic or chemical resolution of the racemic compound.[19][20][21]

Although palladium-catalyzed alkylation is now a well-used method in organic synthesis,[22] the use of alcohols or phenols as nucleophiles in this reaction has been described only recently.[23][24] We previously published a preliminary communication on the one-pot preparation of chiral 2-vinyl-2,3-dihydro-benzo[1,4]-dioxin by the palladium-catalyzed condensation of benzene-1,2-diol and *(Z)*-1,4-bis(methoxycarbonyloxy)but-2-ene in the presence of chiral ligands.[25] In this paper, we report a full account of this reaction with respect to regio- and enantioselectivity.

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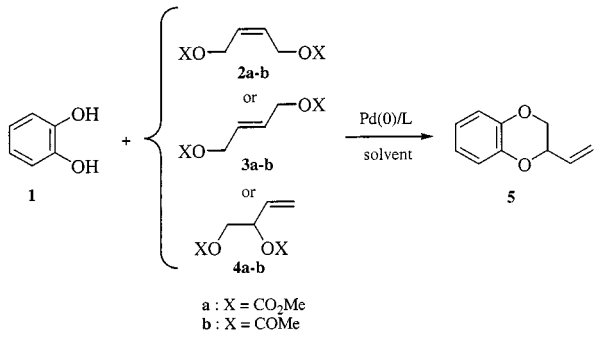
Results and Discussion

Reaction of benzene-1,2-diol (**1**) with *(Z)*-1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**), *(E)*-1,4-bis(methoxycarbonyloxy)but-2-ene (**3a**), or 3,4-bis(methoxycarbonyloxy)but-1-ene (**4a**), at room temperature in THF in the presence of a palladium complex generated in situ by mixing $Pd_2(dba)_3$ [tris(benzylideneacetone)dipalladium] with dppb [1,4-bis(diphenylphosphanyl)butane] gave 2-vinyl-2,3-dihydro-benzo[1,4]dioxin (**5**) (Scheme 1) in 60% yield (Table 1, entries 1, 4 and 5). The cyclized product **5** could also be obtained using allylic acetates **2b** or **4b** as the π-allyl precursor (Table 1, entries 2, 3 and 6); however, in these cases, the reaction has to be performed at 50°C in the presence of two equivalents of Et_3N, in order to generate the corresponding phenate, or in the presence of KF on alumina.[26]



Scheme 1. Preparation of 2-vinyl-2,5-dihydro-benzo[1,4]dioxin

We then turned our attention to the use of 4-substituted benzene-1,2-diols **6a–d** and 3-substituted benzene-1,2-diols **9a–e** in this cyclisation reaction in the

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Table 1. Palladium-catalyzed synthesis of 2-vinyl-2,3-dihydro-benzo[1,4]dioxins **5**, **7−8** and **10−11**[a]

Entry	Benzene-1,2-diol	Allylic Substrate	Benzo [1,4]dioxine	Yield [%][b]	R_f[c] [eluent]	Ratio[d] [%]	Microanalysis Calcd. % C	H	Found % C	H
1	**1**	**2a**	**5**	60[e]	0.7 [PE/EA 4.5:1]	–				
2[f]	**1**	**2b**	**5**	65		–				
3[g]	**1**	**2b**	**5**	40		–				
4	**1**	**3a**	**5**	60		–				
5	**1**	**4a**	**5**	60		–				
6[f]	**1**	**4b**	**5**	68		–				
7	**6a**	**2a**	**7a/8a**	55	0.80 [PE/EA 3:1]	50:50	74.98	6.86	75.60	6.45
8	**6b**	**2a**	**7b/8b**	25	0.40 [PE/EA 1:1]	65:35	65.74	5.98	66.08	6.21
9	**6c**	**2a**	**7c/8c**	97	0.76 [PE/CH_2Cl_2 1:2]	20:80	57.97	4.38	57.99	4.46
10	**6d**	**2a**	**7d/8d**	75	0.63 [PE/CH_2Cl_2/Et_2O 4:6:1]	20:80	69.46	5.30	69.28	5.40
11	**9a**	**2a**	**10a/11a**	50	0.70 [PE/EA 6:1]	40:60	74.98	6.86	74.57	7.05
12	**9b**	**2a**	**10b/11b**	81	0.78 [PE/EA 4.5:1]	5:95	77.03	8.31	77.59	8.14
13	**9c**	**2a**	**10c/11c**	48	0.60 [PE/CH_2Cl_2 1:2]	70:30	68.74	6.29	68.63	6.26
14	**9d**	**2a**	**10d/11d**	45	0.65 [PE/EA 2:1]	25:75	57.97	4.38	57.92	4.32
15	**9e**	**2a**	**10e/11e**	65	0.68 [PE/CH_2Cl_2/Et_2O 4:6:1]	75:25	69.46	5.30	69.73	5.45

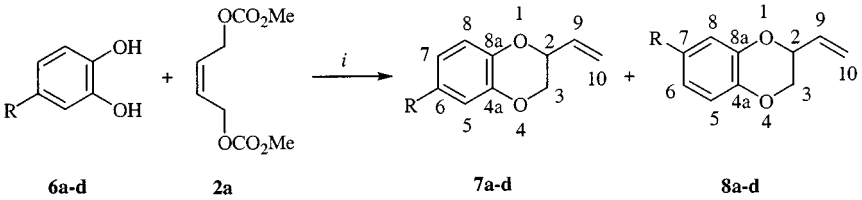
[a] All entries carried out at 25°C for 12 h in the presence of palladium catalyst prepared in situ by mixing $Pd_2(dba)_3$ (5 mol-% Pd) and ligand dppb ([Pd]/[P] = 1:4). – [b] Isolated yield after silica gel column chromatography and not optimized. – [c] PE: petroleum ether, EA: ethyl acetate. – [d] Determined by ^{1}H- and ^{13}C-NMR spectroscopies. – [e] ref.[22g]. – [f] The cyclisation was performed in the presence of Et_3N at 50°C with a ratio benzene-1,2-diol/[Et_3N] = 1:2. – [g] The reaction was performed in the presence of KF/Al_2O_3 at 50°C.

presence of *(Z)*-1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**); in these cases we obtained two regioisomers **7−8** (Scheme 2) and **10−11** (Scheme 3), respectively.

Structure Determination of the Regioisomers

The ^{1}H- and ^{13}C-NMR data of compounds **7−8** and **10−11** are summarized in Tables 2 and 3. The assignments of the structures to the different regioisomers were mainly based on the HMQC and HMBC sequence,[27] and also on the program Selective Distortionless Enhancement by Polarization Transfer (SDEPT-1D) developed by Sanchez-Ferrando and co-workers.[28] The attribution of the signals corresponding to the carbons was made on the basis of the HMBC spectra and are in very good agreement with the chemical shifts predicted from the values of the increments due to the presence of a substituent on the aromatic ring.[29]

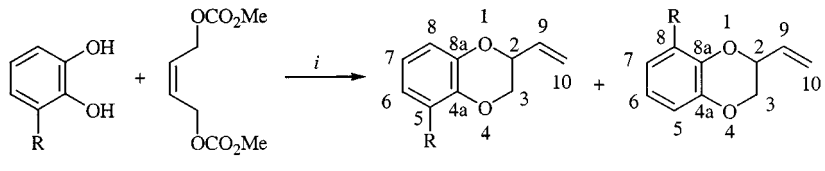
A first example of this structure determination of the two regioisomers in the case of compounds **10c** and **11c** is shown in Figures 1 and 2. From the HMBC spectrum (Figure 1) a correlation between H-3_{eq} at δ = 4.34 of the major isomer and C-4a at δ = 132.65 is obvious, and also a correlation between H-3_{eq} at δ = 4.25 of the minor isomer and C-4a at δ = 143.66. By selective pulsing of the equatorial proton H-3 of the major isomer (Figure 2b) only C-4a at δ = 132.65 showed a signal



6a-d **2a** **7a-d** **8a-d**

a : R = CH_3; **b** : R = NHAc; **c** : R = NO_2; **d** : R = CHO

Scheme 2. *i*: catalyst $Pd_2(dba)_3$/dppb, THF, 25°C, 24 h



9a-e **2a** **10a-e** **11a-e**

a : R = CH_3; **b** : R = *t*-Bu; **c** : R = OCH_3; **d** : R = NO_2; **e** : R = CHO

Scheme 3. *i*: catalyst $Pd_2(dba)_3$/dppb, THF, 25°C, 24 h

Table 2. ^{1}H-NMR data of compounds **5**, **7−8** and **10−11**[a]

Compound	δ H-2 (*J*)	δ H-3$_{ax}$ (*J*)	δ H-3$_{eq}$ (*J*)	δ H-9 (*J*)	δ H-10 (*J*)	δ H-10 (*J*)	δ Ar	δ Other
5[b]	4.57	3.85	4.20	5.87	5.32	5.47	6.60−7.20	2.25 (Me)
7a[c]	4.57−4.63	3.89 (11.3, 7.8)	4.23 (11.3, 1.3)	5.90 (17.3, 10.5, 5.8)	5.37 (10.5, 1.3, 1.3)	5.50 (17.3, 1.3, 1.2)	6.60−7.20	2.25 (Me)
8a[c]	4.57−4.63	3.88 (11.3, 7.8)	4.22 (11.3, 1.3)	5.90 (17.3, 10.5, 5.8)	5.37 (10.5, 1.3, 1.3)	5.50 (17.3, 1.3, 1.2)	6.60−7.20	2.25 (Me)
7b	4.56−4.62	3.89 (11.3, 7.9)	4.24 (11.3, 2.4)	5.89 (17.3, 10.5, 5.8)	5.37 (10.5, 1.3, 1.3)	5.50 (17.3, 1.3, 1.2)	6.75−7.15	2.13 (Me) 7.34 (NH)
8b	4.56−4.62	3.87 (11.3, 7.9)	4.22 (11.3, 2.4)	5.89 (17.3, 10.5, 5.8)	5.37 (10.5, 1.3, 1.3)	5.50 (17.3, 1.3, 1.2)	6.75−7.15	2.13 (Me) 7.34 (NH)
7c	4.63−4.77	3.96 (11.6, 7.8)	4.34 (11.6, 2.6)	5.91 (17.3, 10.6, 5.6)	5.44 (10.5, 1.1, 1.0)	5.55 (17.2, 1.2, 1.1)	6.95−7.85	
8c	4.63−4.77	4.00 (11.6, 7.8)	4.37 (11.6, 2.5)	5.90 (17.3, 10.5, 5.5)	5.44 (10.5, 1.1, 1.0)	5.55 (17.2, 1.2, 1.1)	6.95−7.85	
7d	4.63−4.67	3.95 (11.4, 7.9)	4.32 (11.4, 2.5)	5.91 (17.2, 10.6, 5.6)	5.42 (10.6, 1.2, 1.2)	5.54 (17.2, 1.3, 1.2)	6.98−7.46	9.84 (CHO)
8d	4.63−4.67	3.99 (11.5, 8.7)	4.35 (11.5, 2.5)	5.91 (17.2, 10.6, 5.6)	5.42 (10.6, 1.2, 1.2)	5.54 (17.2, 1.3, 1.2)	6.98−7.46	9.84 (CHO)
10a	4.55−4.71	3.88 (11.3, 7.8)	4.29 (11.3, 2.4)	5.91 (17.3, 10.6, 5.5)	5.36 (10.6, 1.4, 1.4)	5.51 (17.3, 1.4, 1.4)	6.60−6.80	2.23 (Me)
11a	4.55−4.71	3.91 (11.3, 7.8)	4.24 (11.3, 2.4)	5.93 (17.3, 10.6, 5.5)	5.36 (10.6, 1.4, 1.4)	5.51 (17.3, 1.4, 1.4)	6.60−6.80	2.20 (Me)
10b/11b	4.58−4.65	3.89 (11.1, 8.1)	4.26 (11.1, 2.5)	5.90 (17.3, 10.6, 5.6)	5.37 (10.6, 1.4, 1.4)	5.55 (17.3, 1.4, 1.4)	6.76−6.89	1.37 (*t*Bu) **10b** 1.39 (*t*Bu) **11b**
10c	4.58−4.68	3.94 (11.3, 7.9)	4.34 (11.3, 2.4)	5.92 (17.3, 10.5, 5.8)	5.38 (10.5, 1.3, 1.2)	5.52 (17.3, 1.4, 1.3)	6.48−6.84	3.88 (OMe)
11c	4.58−4.68	3.95 (11.3, 7.9)	4.25 (11.3, 2.4)	5.95 (17.3, 10.5, 6.1)	5.38 (10.5, 1.3, 1.2)	5.51 (17.3, 1.4, 1.3)	6.48−6.84	3.87 (OMe)
10d	4.72−4.81	4.00 (11.5, 8.1)	4.45 (11.5, 2.5)	5.91 (17.3, 10.6, 5.6)	5.45 (10.6, 1.2, 1.2)	5.55 (17.3, 1.3, 1.2)	6.86−7.53	
11d	4.72−4.81	4.02 (11.6, 7.5)	4.36 (11.6, 2.5)	5.92 (17.3, 10.5, 5.2)	5.44 (10.6, 1.3, 1.2)	5.60 (17.3, 1.3, 1.2)	6.86−7.53	
10e	4.61−4.83	4.02 (11.5, 7.9)	4.41 (11.5, 2.4)	5.92 (17.3, 10.6, 5.7)	5.43 (10.6)	5.55 (17.3)	6.92−7.41	10.37 (CHO)
11e	4.61−4.83	3.98 (11.5, 7.9)	4.32 (11.5, 2.4)	5.92 (17.3, 10.6, 5.7)	5.43 (10.6)	5.55 (17.3)	6.92−7.41	10.46 (CHO)

[a] In $CDCl_3$. − [b] Ref.[22g] − [c] The signals of **7a** and **8a** could be inverted.

Table 3. $^{13}C\{^1H\}$-NMR data of compounds **5**, **7−8** and **10−11**[a]

Compound	C-2	C-3	C-4a	C-5	C-6	C-7	C-8	C-8a	C-9	C-10	Other
5[b]	73.60	67.50	143.10	117.00	121.50	121.40	117.40	143.10	132.50	119.10	
7a[c]	73.53	67.63	142.63	116.65	131.01	121.90	117.37	140.83	132.58	118.97	20.64 (Me)
8a[b]	73.64	67.56	140.75	116.98	122.12	131.21	117.70	142.73	132.58	119.02	20.65 (Me)
7b	73.55	67.62	142.83	109.75	131.65	113.91	117.18	139.93	132.28	119.28	24.31 (Me)
8b	73.68	67.51	139.84	116.87	113.74	131.82	110.05	142.97	132.22	119.20	168.46 (CO)
7c	74.25	67.30	142.70	113.19	141.71	117.73	117.34	148.98	131.20	120.12	
8c	73.53	67.80	148.86	117.04	117.56	141.84	113.49	142.81	131.20	112.07	
7d	73.27	67.23	148.70	118.44	124.00	130.71	118.01	143.229	131.55	119.60	190.78 (CHO)
8d	74.07	67.76	143.39	117.75	130.55	124.28	117.46	148.57	131.49	119.70	190.66 (CHO)
10a	73.48	67.64	141.28	126.56	120.66	120.76	114.98	142.88	132.62	119.02	15.48 (Me)
11a	73.44	67.45	141.28	114.64	120.42	122.94	126.85	142.78	132.72	118.53	15.46 (Me)
10b/11b	72.93	67.38	143.32	115.24	120.37	118.77	138.87	141.96	132.64	118.34	29.48 (*t*Bu) **10b** 29.70 (*t*Bu) **11b**
10c	73.41	67.63	132.65	148.84	104.00	120.35	110.06	143.72	132.22	119.15	55.98 (OMe)
11c	73.75	67.26	143.66	109.72	120.09	104.30	149.05	132.65	132.35	119.42	55.98 (OMe)
10d	73.44	67.98	139.40	138.40	118.04	120.35	122.27	144.62	131.29	120.30	
11d	74.22	67.18	144.62	121.77	120.17	118.04	138.40	139.40	130.88	120.12	
10e	73.24	67.68	145.88	124.92	123.23	120.88	121.11	143.66	131.70	119.76	188.95 (CHO)
11e	73.96	67.19	146.14	120.91	120.58	122.88	125.07	143.30	131.55	119.62	188.79 (CHO)

[a] In $CDCl_3$. − [b] Ref.[22g] − [c] The signals of **7a** and **8a** could be inverted.

enhancement by polarization transfer (SDEPT effect), and by pulsing of the same proton of the minor isomer (Figure 2c) only the coupled carbon at C-4a at δ = 143.66 showed a positive SDEPT effect.

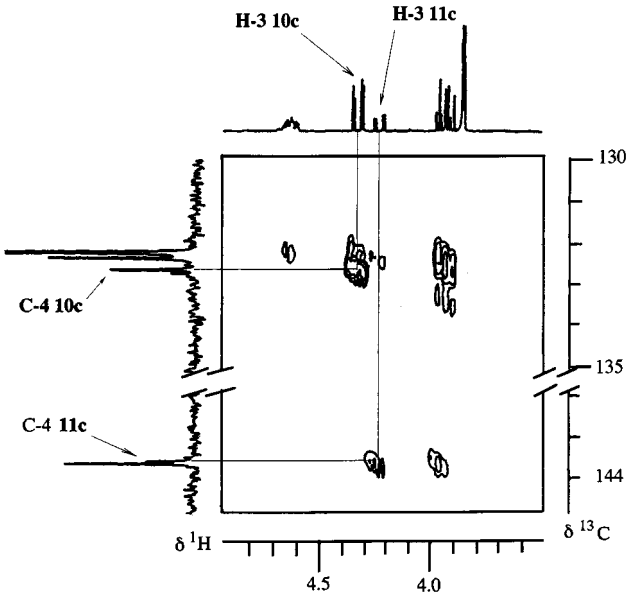


Figure 1. HMBC spectrum of the mixture **10c**−**11c**

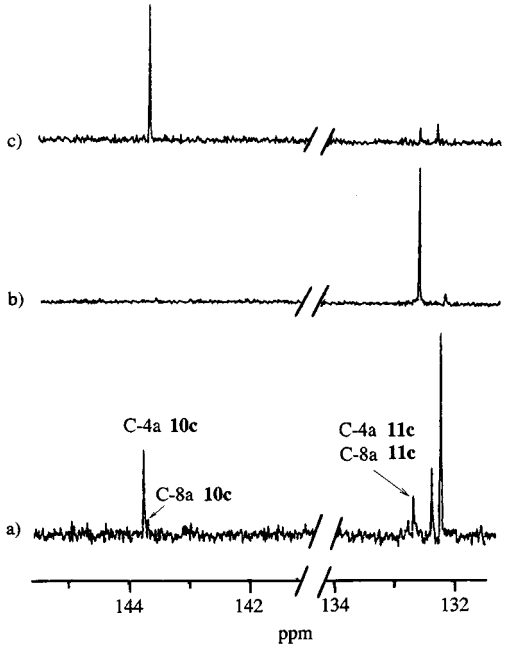


Figure 2. SDEPT spectra of the mixture **10c**−**11c**; a) ^{13}C-NMR spectrum; b) SDEPT-1D on H-3 at δ = 4.34; c) SDEPT-1D on H-3 at δ = 4.25

A second example involving compounds **7b** and **8b** is shown in Figure 3. By selective pulsing of the equatorial proton H-3 of the major isomer at δ = 4.24, only the coupled C-4a carbon atom at δ = 142.83 showed a signal enhancement by polarization transfer (SDEPT effect).

4-Substituted Benzene-1,2-diols

4-Methylbenzene-1,2-diol (**6a**), 4-*N*-acetylaminobenzene-1,2-diol (**6b**), 4-nitrobenzene-1,2-diol (**6c**), and 4-

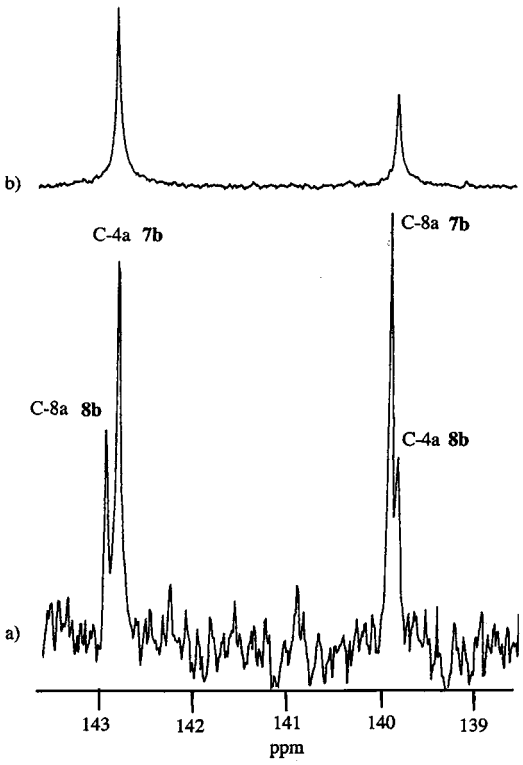


Figure 3. SDEPT spectra of the mixture **7b**−**8b**; a) ^{13}C-NMR spectrum; b) SDEPT-1D on H-3 at δ = 4.24

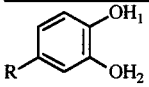
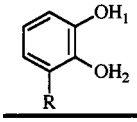
formylbenzene-1,2-diol (**6d**), reacted with *(Z)*-1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**) to give the corresponding regioisomeric 2,3-dihydrobenzo[1,4]dioxines **7**−**8** in 55, 25, 97, and 75% yields, respectively (Table 1, entries 7−10), and in ratios of 50:50, 65:35, 20:80, and 20:80, respectively. Formation of **8** as the major regioisomer was observed in the case of benzene-1,2-diols **6c**−**d** bearing electron-withdrawing groups. This arises from the attack of the phenate generated at position 1 on the π-allyl complex, followed by the attack of the phenate generated at position 2 on the next π-allyl system.

Conversely **7** was the major regioisomer formed in the case of 4-*N*-acetylaminobenzene-1,2-diol (**6b**) bearing an electron-donating group. This is formed primarily from the attack of the phenate firstly generated at position 2, and secondly by the phenate generated at position 1. 4-Methylbenzene-1,2-diol (**6a**) gave a 50:50 mixture of the two regioisomers.

These results could be correlated to the relative acidities of the phenolic function. The calculated values of pK_a using the MOPAC program are summarized in Table 4. For benzene-1,2-diols **6c** and **6d**, the first abstraction of the more acidic phenolic proton H_1 gave predominantly the regioisomer **8**, although for benzene-1,2-diol **6b** the abstraction of the more acidic proton H_2 led to the preferential formation of the regioisomer **7**. Benzene-1,2-diol **6a** having two phenolic functions with the same acidity gave an equal mixture of the two regioisomers. It is also noteworthy that benzene-1,2-diol

6b having an electron-donating group gave the lowest yield of the cyclized product.

Table 4. pK_a values of substituted 1,2-benzenediols[a]

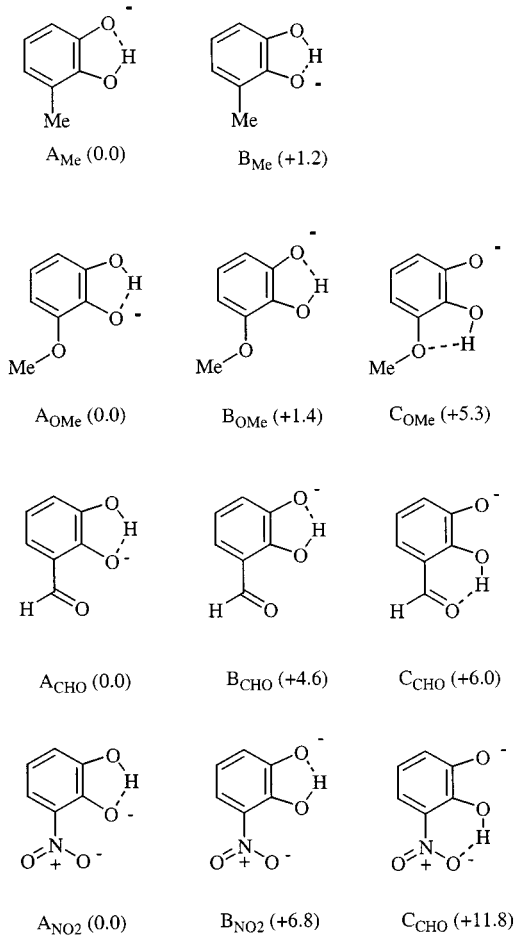
Catechol	Compound	R	pK_a(H_1)	pK_a(H_2)
	**6a**	CH_3	16	16
	6b	NHAc	18	17
	6c	NO_2	9	12
	6d	CHO	13	14
	**9a**	CH_3	16	16
	9b	*t*-Bu	16	16
	9c	OCH_3	16	16
	9d	NO_2	12	8
	9e	CHO	14	12

[a] Values calculated using the MOPAC programm, in DMSO.

3-Substituted Benzene-1,2-diols

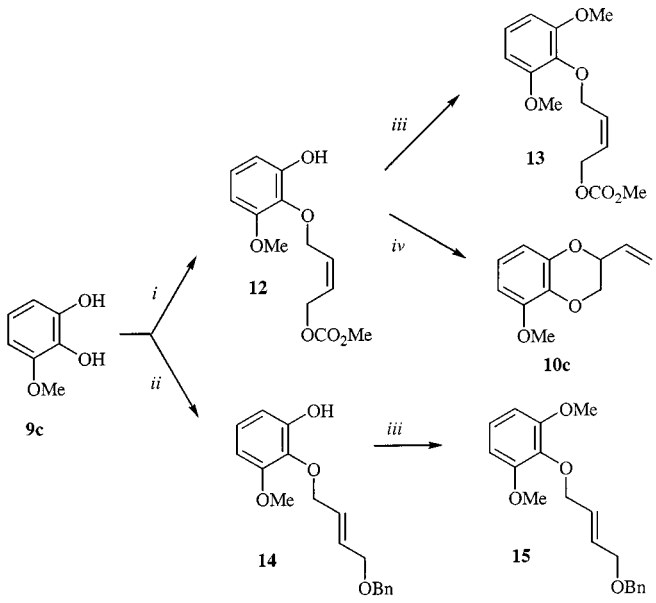
Condensation of 3-methylbenzene-1,2-diol (**9a**), 3-*tert*-butylbenzene-1,2-diol (**9b**), 3-methoxybenzene-1,2-diol (**9c**), 3-nitrobenzene-1,2-diol (**9d**), and 3-formylbenzene-1,2-diol (**9e**), with biscarbonate **2a** gave the cyclized products **10**−**11** in 50, 81, 48, 45, and 65% yields, respectively (Table 1, entries 11−15), and in regioisomeric ratios of 40:60, 5:95, 70:30, 25:75, and 75:25, respectively. It should be noted that regioisomer **11b** was only detected by the presence of the signal of the *tert*-butyl group in ^{1}H- and ^{13}C-NMR spectroscopy.

A survey of these results shows that there is no correlation between the acidity of the phenolic protons (Table 4) and the observed regioselectivity. It is also obvious that the different behaviour observed between **9a** and **9b** is mainly due to a steric effect, the larger *tert*-butyl group preventing the approach of the phenate, generated by the abstraction of the hydrogen H_2 α to the alkyl substituent, from the π-allyl system. In order to gain a deeper insight into the factors controlling the regioselectivity, we carried out some calculations concerning the relative stabilities of the phenates generated by abstraction of a phenolic hydrogen (Scheme 4). These results show clearly that the more stable anionic forms obtained from **9a**, **9c**, and **9e**, led effectively to the formation of the major regioisomer. In order to be sure that no interconversion occurred between the two regioisomers **10** and **11**, the intermediate **12** resulting from the *O*-alkylation of allylic biscarbonate **2a** at the α-phenolic function was prepared in 14% yield via a Mitsunobu reaction between 3-methoxybenzene-1,2-diol (**9c**) and *(Z)*-4-(methoxycarbonyloxy)but-2-en-1-ol (Scheme 5). The regioselectivity of the coupling reaction was ascertained by the transformation of **12** into compound **13** using dimethylsulfate in the presence of potassium carbonate in acetone; the NMR data of **13** are in agreement with the proposed structure. Cyclization of this intermediate **12** in the presence of a catalytic amount of palladium(0) at 20°C gave **10c** as the unique regioisomer in 85% yield. Moreover, reaction of 3-methoxybenzene-1,2-diol (**9c**) with *(Z)*-1-benzyloxy-4-(methoxycarbonyloxy)but-2-ene in the presence of palladium(0) also gave the coupling product **14** as the unique regioisomer, although in low yield (14%). The regioselectivity of the reaction was again ascertained by the transformation of compound **14** into the symmetric compound **15**. This regioselectivity is in quite good agreement with the highest stability of the anionic form A.



Scheme 4. Calculated relative stabilities (in kcal·mol^{-1}) of the anionic structures

For 3-nitrobenzene-1,2-diol (**9d**) the result was quite different. The energy difference between the two anionic structures A and B is very high. We have previously noted that 2-nitro and 4-nitrophenol are allylated in very low yields using allyl methyl carbonate as the allylating reagent in the presence of a palladium catalyst, although 3-nitrophenol gave a higher yield.[24g] This peculiar behaviour is probably due to the high leaving-group ability of 2-nitrophenate, giving back the π-allyl complex very easily. This could also be the case for 3-nitrobenzene-1,2-diol (**9d**) (Scheme 6). *O*-alkylation of **9d** occurred kinetically at the position α to the nitro group to give the intermediate D; however this nitro aromatic group, being a good leaving group in palladium chemistry, gave back the π-allyl intermediate. *O*-alkylation also occurred



Scheme 5. *i: (Z)* $HOCH_2CH{=}CHCH_2OCO_2Me$, PPh_3, DEAD. – *ii*: $Pd_2(dba)_3$/dppb, *(Z)* $BnOCH_2CH{=}CHCH_2OCO_2Me$, THF. – *iii*: Me_2SO_4, K_2CO_3. – *iv*: $Pd_2(dba)_3$/dppb, THF, 24 h.

at the position β to the nitro group to give the *O*-allylated intermediate E; in this case the nitro aromatic is a poorer leaving group and the reverse reaction is more difficult. Thus, in the case of 3-nitrobenzene-1,2-diol (**9d**) we can postulate that the cyclisation reaction occurs mainly under thermodynamic control.

Asymmetric Synthesis of 2-Vinyl-2,3-dihydro-benzo[1,4]dioxin

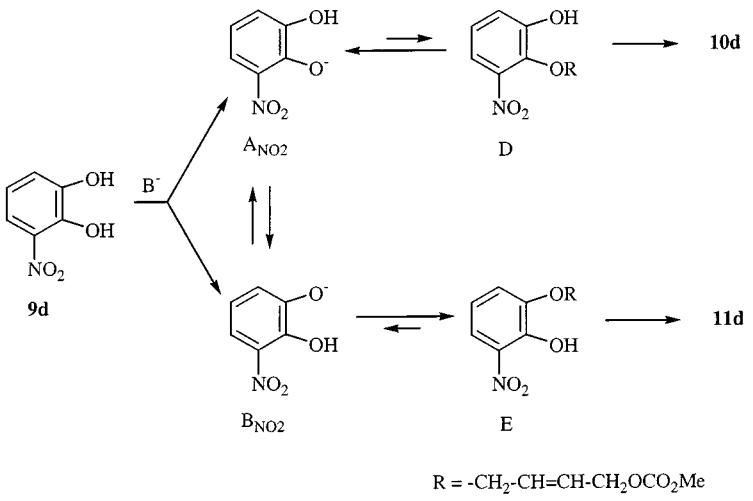
We next turned our attention to the chiral version of this cyclization reaction using benzene-1,2-diol (**1**) and the different allylic compounds **2a**–**b**, **3a** and **4a**–**b** (Table 5).

We first explored the condensation of benzene-1,2-diol (**1**) with *(Z)* 1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**) in tetrahydrofuran as the solvent at room temperature in the presence of a palladium(0) catalyst generated from $Pd_2(dba)_3$ and a chiral ligand. The use of ligands *(S,S)*-BDPP, *(S,S)*-DIOP or *(S,S)*-BPPM gave compound **5** in high chemical yields, but with low enantioselectivities (Table 5, entries 1–3). Surprisingly Trost′s ligand also gave rather disappointing results (Table 5, entry 4). The highest selectivities were obtained using *(R)*-BIPHEMP or *(R)*-BINAP as the chiral ligands, with *ee* values of up to 38% (Table 5, entries 5–6).

The nature of the solvent has an important influence both on the chemical yield and the enantioselectivity of the reaction. The highest yields and enantioselectivities were obtained using oxygenated solvents such as dioxane (40% *ee*), tetrahydropyran (THP) (33% *ee*) and dimethoxyethane (DME) (45% *ee*) (Table 5, entries 7–9). Dimethylformamide also gave quite good yield (78%) and *ee* (44%) (Table 5, entry 10), while chloroform gave a lower yield, but the same enantioselectivity (43%) (Table 5, entry 11).

The substitution of *(Z)*-**2a** by the allylic carbonates *(E)*-**3a** or **4a** in this cyclization reaction gave the 2-vinyl-2,3-dihydro-benzo[1,4]dioxin (**5**) with the same yields and enantioselectivities (Table 5, entries 14–15). These results preclude that the determining enantioselective step, namely the second alkylation reaction, is the same for the thr*ee* allylic biscarbonates with probably a rapid equilibrium between the different π-allyl complexes via $\eta^3 \rightleftharpoons \sigma \rightleftharpoons \eta^3$ and *syn* ⇌ *anti* isomerizations. The same behaviour was noticed by Hayashi and collaborators in the palladium-catalyzed cyclization of various amino alcohols with biscarbonates **2a** and **3a**.[30]

When the diacetates *(Z)*-**2b** and **4b** were used as the π-allyl precursors, in the presence of Et_3N as the base,



Scheme 6. Mechanism of formation of **10d** and **11d**

Table 5. Palladium-catalyzed asymmetric synthesis of 2-vinyl-2,3-dihydro-benzo[1,4]dioxin (**5**)[a]

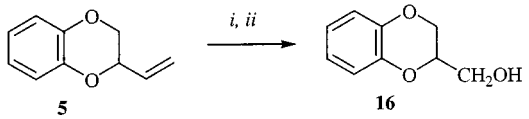
Entry	Allylic substrate	Amine[b]	Phosphane	Solvent	*T* [°C]	Yield [%][c]	*ee* [%][d] (config.)
1	**2a**	no	(*S*,*S*)-BDPP[e]	THF	25	63	14 (*R*)
2	**2a**	no	(*S*,*S*)-DIOP[f]	THF	25	72	0
3	**2a**	no	(*S*,*S*)-BPPM[g]	THF	25	75	5 (*R*)
4	**2a**	no	(*R*,*R*)-Trost ligand[h]	THF	25	7	20 (*R*)
5	**2a**	no	(*R*)-BIPHEMP[i]	THF	25	60	38 (*R*)
6	**2a**	no	(*R*)-BINAP[j]	THF	25	70	37 (*R*)
7	**2a**	no	(*R*)-BINAP	dioxane	25	62	40 (*R*)
8	**2a**	no	(*R*)-BINAP	THP	25	73	33 (*R*)
9	**2a**	no	(*R*)-BINAP	DME	25	45	45 (*R*)
10	**2a**	no	(*R*)-BINAP	DMF	25	78	44 (*R*)
11	**2a**	no	(*R*)-BINAP	$CHCl_3$	25	45	43 (*R*)
12	**2b**	Et_3N	(*R*)-BINAP	THF	50	92	37 (*R*)
13	**2b**	Et_3N	(*R*)-BINAP[k]	THF	50	60	35 (*R*)
14	**3a**	no	(*R*)-BINAP	THF	25	60	37 (*R*)
15	**4a**	no	(*R*)-BINAP	THF	25	60	37 (*R*)
16	**4b**	Et_3N	(*R*)-BINAP	THF	50	50	30 (*R*)
17	**4b**	Et_3N	(*R*)-BINAP[k]	THF	50	54	25 (*R*)

[a] All entries carried out under N_2 for 24 h in the presence of palladium catalyst prepared in situ by mixing $Pd_2(dba)_3$ (5 mol-% Pd) and ligand ([Pd]/[P] = 1:2). The ratio of **1**/allylic substrate = 1:1.5. – [b] Amine/**1** = 2:1. – [c] Isolated yield after silica gel column chromatography and not optimized. – [d] Determined by GPC analysis with a chiral stationary phase column (Chiraldex™ GC Column, type B-PH, 30 m × 0.32 mm). Absolute configuration in brackets. – [e] (2*S*,4*S*)-2,4-Bis(diphenylphosphanyl)pentane. – [f] (2*R*,3*R*)-2,3-*O*-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphanyl)butane. – [g] (2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-(diphenylphosphanyl)-2-[(diphenylphosphanyl)methyl]-pyrrolidine. – [h] (1*R*,2*R*)-1,2-bis-*N*-[2′-(diphenylphosphanyl)benzoyl]-1,2-diaminocyclohexane. [i] (*R*)-6,6′-Dimethyl-2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl. – [j] (*S*)-2,2′-Bis(diphenylphosphanyl)-1,1′-binaphtyl. – [k] $[PdCl(\eta-C_3H_5)]_2$ was used in place of $Pd_2(dba)_3$.

enantioselectivity of up to 37 and 30% was obtained, respectively. This is quite similar to the values obtained using the corresponding biscarbonates (Table 5, entries 12 and 16). Replacement of $Pd_2(dba)_3$ by $[Pd(C_3H_5)Cl]_2$ gave almost the same results (Table 5, entries 13 and 17).

Finally this cyclization was extended to naphtalene-3,4-diol and (*Z*)-1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**) in the presence of (*R*)-BINAP as the chiral ligand, giving the cyclized product in 51% yield but only 11% enantioselectivity.

The absolute configuration of compound **5** was determined by correlation with the known 2-hydroxymethyl-2,3-dihydro-benzo[1,4]dioxin (**16**) (Scheme 6).[17] Ozonolysis of (+)-**5** having $[\alpha]_D^{25} = +4.5$ (c = 1, $CHCl_3$), followed by reduction with sodium tetrahydroborate, gave compound **16**, which turned out to be the (*R*) isomer by measurement of the optical rotation{from (+)-**16**: $[\alpha]_D^{25} = +7.5$ (c = 0.5, C_2H_5OH); ref.[17] for (*R*)-**16**: $[\alpha]_D^{25} = +34.1$ (c = 0.5, C_2H_5OH)}.



5 $[\alpha]_D^{20}$ +4.5 **16** $[\alpha]_D^{20}$ +7.5

Scheme 7. *i*: O_3. – *ii*: $NaBH_4$

Conclusion

In conclusion, substituted 2-vinyl-2,3-dihydro-benzo[-1,4]dioxins could be obtained in good yields through a tandem allylic substitution reaction between 1,4-bis(methoxycarbonyloxy)but-2-ene or 3,4-bis(methoxycarbonyloxy)but-1-ene and various substituted benzene-1,2-diols catalyzed by a palladium(0) complex. In the case of 4-substituted benzene-1,2-diols, the regioisomer ratio is determined by the relative acidity of the two phenolic protons. For the 3-substituted benzene-1,2-diols, the situation is more complex. The regioisomer ratio is determined only by steric effects in the case of alkyl substituents, although it is determined mainly by the relative stabilities of the corresponding phenates in the other cases. However for 3-nitrobenzene-1,2-diol, this ratio is determined by the relative leaving group ability of 2-nitro- or 3-nitrophenate.

When the cyclization was performed in the presence of an optically active phosphane, chiral 2-vinyl-2,3-dihydro-benzo[1,4]dioxin was obtained with enantioselectivity of up to 45%, whatever the π-allyl precursor used.

Experimental Section

General Remarks: ^{1}H-NMR (200 and 400 MHz) and ^{13}C-NMR (50 MHz) spectra were obtained using a Bruker AM 200 and ARX400 spectrometer. Chemical shifts are reported on the δ scale with reference to tetramethylsilane as an internal standard. Gradient-enhanced 2D HQMC and 2D HMBC spectra resulted from a 80 × 1024 and a 128 × 1024 data matrix size, respectively, with 2–4 and 4–16 scans per *t*1 value; the interpulse delay was set to 3.5 ms and 60 ms, respectively, and the recycle time was 1 s; a 2:2:1 gradient ratio was used. Broad-band ^{13}C decoupling with GARP1 was applied during acquisition, a sine bell filter function was used prior to Fourier transformation in both dimensions, and linear prediction was sometimes applied in the indirect dimension.[27] For selective 1D DEPT spectra (SDEPT), soft proton pulses with an amplitude field of 25 Hz were applied from the decoupler; the interpulse delay was optimized to 5–7 Hz and as a function of the

nature of the selected proton.[28] − Optical rotations were determined using a Perkin−Elmer 241 polarimeter. − GC analyses were recorded with a Shimadzu capillary gas chromatography equipped with a Chiraldex™, type B-PH (30 m × 0.32 mm) capillary column. − pK_a values were calculated using the MOPAC program Computer Assisted Mechanistic Evaluation of Organic Reactions developed by W. L. Jorgensen′s research group at Yale University, New Haven, CT 06520−8107, USA. − Reactions involving organometallic catalysis were carried out in Schlenk tubes under an inert atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone. The following compounds were prepared according to literature procedures: but-3-en-1,2-diol,[31] *(Z)*-1,4-bis(methoxycarbonyloxy)but-2-ene (**2a**),[32] 4-*N*-acetylaminobenzene-1,2-diol (**6b**),[33] 3-*tert*-butylbenzene-1,2-diol (**9b**),[34] 3-nitrobenzene-1,2-diol (**9c**),[34] *(Z)*-4-(methoxycarbonyloxy)but-2-en-1-ol,[35] *(Z)*-4-methoxycarbonyloxy)-1-benzyloxybut-2-ene[36] and (*1R,2R*)-1,2-bis-*N*-[2′-(diphenylphosphanyl)benzoyl]-1,2-diaminocyclohexane.[37] *(R)*-6,6′-Dimethyl-2,2′-bis(diphenylphosphanyl)-1,1′-biphenyl (BIPHEMP) was a gift from Dr. Schmid (Hofmann La Roche, Bale, Switzerland).

3,4-Bis(methoxycarbonyloxy)but-1-ene (4a): To a solution of but-3-en-1,2-diol (1 g, 11 mmol) and pyridine (3.2 mL, 40 mmol) in CH_2Cl_2 (30 mL) was slowly added a solution of methyl chloroformate (2.9 mL, 38 mmol) in 10 mL of THF at 0°C. After disappearance of the starting material visualized by TLC, the solution was filtered, and then washed with water saturated with $CuSO_4$. Evaporation of the solvent gave a residue which was separated by chromatography on silica to give 670 mg of compound **4a** as an oil (30%); R_f 0.47 (eluent: petroleum ether/ethyl acetate, 4:1). − ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 6 H, CH_3), 4.19 (dd, *J* = 11.9, 7.3 Hz, 1 H, CH_2), 4.33 (dd, *J* = 11.9, 7.6 Hz, 1 H, CH_2), 5.36 (d, *J* = 10.3 Hz, 1 H, =CH_2), 5.31−5.50 (m, 1 H, CH), 5.46 (d, *J* = 17.1 Hz, 1 H, =CH_2), 5.83 (ddd, *J* = 17.1, 10.3, 6.3 Hz, 1 H, -CH=). − ^{13}C NMR ($CDCl_3$): δ = 55.00 (2 × CH_3), 67.90 (CH_2), 75.87 (CH), 119.86 (=CH_2), 131.44 (−CH=), 154.98 (CO), 155.20 (CO). − $C_8H_{12}O_6$ (204.18): calcd. C 47.06, H 5.92; found C 47.08, H 5.90.

***(Z)*-4-(Methoxycarbonyloxy)-1-(2-methoxy-6-hydroxy)phenoxybut-2-ene (12):** To a solution of 3-methoxybenzene-1,2-diol (**9c**) (479 mg, 3.4 mmol), *(Z)*-4-(methoxycarbonyloxy)but-2-en-1-ol (500 mg, 3.4 mmol), and DEAD (596 mg, 3.4 mmol), in THF (16 mL) was slowly added PPh_3 (897 mg, 3.4 mmol) at 0°C. After being stirred for 12 h at 25°C, the solvent was evaporated and the residue was separated by chromatography on silica to give 128 mg of compound **12** as an oil (14%); R_f 0.58 (eluent: petroleum ether/ethyl acetate, 3:1). − ^{1}H NMR ($CDCl_3$): δ = 3.80 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 4.71 (d, *J* = 6.4 Hz, 2 H, CH_2), 4.73 (d, *J* = 6.4 Hz, 2 H, CH_2), 5.75−5.87 (m, 1 H, −CH=), 5.93−6.05 (m, 1 H, −CH=), 6.13 (s, 1 H, OH), 6.47 (dd, *J* = 8.3, 1.2 Hz, 1 H, H_{arom}), 6.61 (dd, *J* = 8.3, 1.2 Hz, 1 H, H_{arom}), 6.94 (dd, *J* = 8.3, 8.3 Hz, 1 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 55.29 (CH_3), 56.19 (CH_3), 63.51 (CH_2), 68.13 (CH_2), 127.95 and 130.44 (−CH=), 104.27, 108.69, 124.74, 134.22, 144.46 and 153.00 (C_{arom}), 156.03 (CO). − $C_{13}H_{16}O_6$ (268.27): calcd. C 58.20, H 6.01; found C 58.23, H 6.26.

***(Z)*-4-(Methoxycarbonyloxy)-1-(2,6-bismethoxy)phenoxybut-2-ene (13):** To a solution of **12** (88 mg, 0.33 mmol) in acetone (4 mL) was added K_2CO_3 (70 mg, 0.5 mmol) and dimethylsulfate (50 mg, 0.4 mmol). After disappearance of the starting material, visualized by TLC, the solution was filtered and the solvent was evaporated to give an oil which was separated by chromatography on silica to give 60 mg of compound **13** (65%); R_f 0.58 (eluent: petroleum ether/ethyl acetate, 3:1). − ^{1}H NMR ($CDCl_3$): δ = 3.77 (s, 6 H, CH_3), 3.85 (s, 6 H, CH_3), 4.63 (d, *J* = 6.6 Hz, 2 H, CH_2), 4.72 (d, *J* = 6.9 Hz, 2 H, CH_2), 5.68−5.77 (m, 1 H, −CH=), 5.80−6.09 (m, 1 H, −CH=), 6.57 (d, *J* = 8.3 Hz, 2 H, H_{arom}), 6.99 (dd, *J* = 8.3, 8.3 Hz, 1 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 54.90 (CH_3), 56.17 (2 × CH_3), 63.81 (CH_2), 68.11 (CH_2), 1267.87 and 136.52 (−CH=), 105.30, 124.09, 126.87, 136.52 and 153.88 (C_{arom}), 155.77 (CO). − $C_{14}H_{18}O_6$ (282.29): calcd. C 59.57, H 6.43; found C 59.01, H 6.53.

***(Z)*-4-Benzyloxy-1-(2-methoxy-6-hydroxy)phenoxybut-2-ene (14):** A solution of $Pd_2(dba)_3$ (19.6 mg, 0.02 mmol) and dppb (34.5 mg, 0.08 mmol) in THF (5 mL) was added to a degassed mixture of 3-methoxybenzene-1,2-diol (**9c**) (150 mg, 1.07 mmol) and *(Z)*-1-benzyloxy-4-(methoxycarbonyloxy)but-2-ene (253 mg, 1.07 mmol), in THF (2 mL). After being stirred for 12 h at 25°C, the solvent was evaporated and the residue was separated by chromatography on silica to give 51 mg of compound **14** as an oil (16%); R_f 0.54 (eluent: petroleum ether/diethyl ether, 1:1.5). − ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 3 H, CH_3), 4.03−4.05 (m, 2 H, CH_2), 4.48 (s, 2 H, CH_2), 4.58−4.61 (m, 2 H, CH_2), 5.78 (s, 1 H, OH), 5.91−5.99 (m, 2 H, −CH=), 6.46 (dd, *J* = 8.3, 1.3 Hz, 1 H, H_{arom}), 6.59 (dd, *J* = 8.3, 1.3 Hz, 1 H, H_{arom}), 6.92 (dd, *J* = 8.3, 8.3, 1 H, H_{arom}), 7.23−7.33 (m, 5 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 55.87 (CH_3), 69.79 (CH_2), 72.21 (CH_2), 73.03 (CH_2), 128.44 (2 × −CH=), 104.07, 108.08, 124.21, 127.69, 127.95, 128.12, 131.74, 138.17, 149.58 and 152.59 (C_{arom}). − $C_{18}H_{20}O_4$ (300.34): calcd. C 71.98, H 6.71; found C 71.39, H 6.73.

***(Z)*-4-Benzyloxy-1-(2,6-bismethoxy)phenoxybut-2-ene (15):** This compound was prepared from **14** using the procedure described for compound **13**. Yield 51%; R_f 0.54 (eluent: petroleum ether/diethyl ether, 1:1.5). − ^{1}H NMR ($CDCl_3$): δ = 3.84 (s, 6 H, CH_3), 4.03 (dd, *J* = 5.5, 1.0 Hz, 2 H, CH_2), 4.45 (s, 2 H, CH_2), 4.54 (dd, *J* = 6.1, 0.8 Hz, 2 H, CH_2), 5.82−5.93 (m, 1 H, −CH=), 5.99−6.09 (m, 1 H, −CH=), 6.57 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 6.98 (dd, *J* = 8.4, 8.4 Hz, 1 H, H_{arom}), 7.23−7.33 (m, 5 H, H_{arom}). − ^{13}C NMR ($CDCl_3$): δ = 56.43 (2 × CH_3), 70.41 (CH_2), 72.22 (CH_2), 73.39 (CH_2), 129.82 and 130.68 (−CH=), 105.59, 124.06, 127.90, 128.09, 128.70, 137.03, 138.70 and 154.11 (C_{arom}). − MS (70 eV); *m/z* (%): 154 (100), 139 (36), 111 (16), 96 (27), 93 (22), 68 (12), 65 (19).

General Procedure for the Cyclization Reaction: A solution of tris-(dibenzylideneacetone)dipalladium (6.5 mg, 0.0063 mmol) and the ligand (0.025 mmol for dppb and 0.0125 mmol for a chiral ligand) in 3 mL of THF was stirred at room temperature for 30 min. To the solution were added the catechol (0.25 mmol) and the biscarbonate or the diacetate (0.35 mmol) dissolved in 3 mL of THF; in the case of the diacetate, 0.25 mmol of NEt_3 was added. The mixture was stirred at the desired temperature for 24 h. The solution was concentrated under reduced pressure and the residue was separated by chromatography on silica gel to give the cyclized product. In the asymmetric cyclization, the enantioselectivity was determined by GPC analysis using a chiral stationary-phase column Chiraldex™ type B-PH, 30 m × 0.32 at 85°C.

Determination of the Configuration of Compound 5: A solution of **5** (162 mg, 1 mmol), exhibiting $[\alpha]_D^{20}$ = +4.5 (*c* = 1, $CHCl_3$), in CH_2Cl_2 (8 mL) and CH_3OH (2 mL) was treated with gaseous ozone at −78°C. After addition of $NaBH_4$ (75.7 mg, 2 mmol) at −78°C, the solution was stirred for 1.5 h at 25°C. The organic phase was extracted with diethyl ether. Evaporation of the solvent gave 130 mg of 2-hydroxymethyl-2,5-dihydrobenzo[1,4]dioxine (**16**) as a solid (80%) having $[\alpha]_D^{20}$ = +7.5 (*c* = 0.5, C_2H_5OH); m.p. 73°C. − ^{1}H NMR ($CDCl_3$): δ = 2.19 (br. s, 1 H, OH), 3.78−3.91 (m, 2 H, CH_2), 4.01−4.12 (m, 1 H, CH_2), 4.19−4.29 (m, 2 H, CH,

CH_2), 6.77−6.89 (m, 4 H, H_{arom}). − These data are in agreement with those reported in the literature.[17]

Acknowledgments

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