at 28 °C and 180 rpm on a rotary shaker.

Preparation of Labeled Substrates. Samples of sodium [1-^{13}C]acetate (99% ^{13}C) and sodium [2-^{13}C]acetate (99% ^{13}C) were obtained from Aldrich Chemical Co. [3-^{13}C]Alanine (98% ^{13}C) was obtained from Merck and Co. [2-^{13}C]Mevalonic acid was synthesized in four steps from 3-buten-1-ol and [2-^{13}C]ethyl bromoacetate (99% ^{13}C, Aldrich) essentially by the procedure of Tanabe.[22] [3-^{13}C]Leucine was synthesized by the procedure of Overton,[15] and the label was introduced from $Ba^{13}CO_3$ (99% ^{13}C, Aldrich). 3-(2*E*)-[3-^{13}C]Methylcrotonic acid was prepared from [^{13}C]iodomethane (99% ^{13}C, Aldrich) by the method of Aberhart.[23]

Addition of Labeled Substrates. Labeled substrates were administered to 44–48 h liquid cultures (50–100 mL), which were then incubated for an additional 48 h to allow incorporation of labeled compounds. Sodium [1-^{13}C]acetate and sodium [2-^{13}C]acetate were each added at three different final concentrations of 0.25, 0.50, and 1.00 mg/mL. Results from the 1.00 mg/mL experiment are reported in Table I. [2-^{13}C]Mevalonic acid was also added at three final concentrations: 0.05, 0.10, and 0.25 mg/mL. Results from the 0.25 mg/mL experiment are reported in Table I. [3-^{13}C]Leucine was added at a final concentration of 0.32 mg/mL (0.25 mM). [3-^{13}C]Alanine was added at final concentrations of 0.05, 0.10, and 0.25 mg/mL, and the results from the 0.25 mg/mL experiment are shown in Table II. 3-(2*E*)-[3-^{13}C]Methylcrotonic acid was added at 0.05 and 0.25 mg/mL.

^{13}C NMR Spectra. ^{13}C nuclear magnetic resonance spectra were acquired in $CDCl_3$ at 75 MHz on a Bruker WM-300WB instrument. ^{13}C-NMR measurements were made under the following conditions: 30° pulse; acquisition time, 0.54 s; spectral width, 15.15 kHz; 105 000 scans; and continuous broad-band ^{1}H decoupling. Relative ^{13}C abundances were determined by calculating the ratio of peak heights (1-Hz line broadening) of labeled and natural abundance spectra and normalizing on the mean of the positions which appeared to be unlabeled.[13] For each experiment, a standard deviation was calculated for the set of unlabeled signals plus the smallest "labeled" signal. In Tables I and II, the entries in bold are two standard deviations above 1.0.

Trichothecene Analysis. Fermentations were monitored for trichothecene production by GC analysis of TMS-derivatized ethyl acetate extracts. Dried extracts were derivatized with TBT (Pierce) at 80 °C for 1 h. A Spectra-Physics 7100 GC equipped with a DB-1 coated (0.25-μm) capillary column (30 m × 0.25 mm) and FID detector were used for the analysis. The GC temperature program consisted of an initial oven temperature of 120 °C with an immediate 15 deg/min gradient to 210 °C for 1 min and a 5 deg/min gradient to 260 °C for 10 min. The retention time observed for T-2(TMS) in this system was 17.9 min.

General Isolation Procedure. The above fermentations (50–100 mL) were extracted with equal volumes of ethyl acetate (3×), and the solvents were removed in vacuo. The residue was then applied directly to a silica TLC plate (2mm, Merck) and developed with 98% $CHCl_3$ 2% MeOH. The band with an R_f = 0.35–0.45 was then scraped and eluted with ethyl acetate. Final purification was carried out by reverse-phase HPLC in a Spectra-Physics 8100 HPLC equipped with a Zorbax ODS column (25 cm × 0.46 cm i.d.) and was followed by UV detection at 205 nm. The mobile phase employed was an isocratic system of 70% MeOH/H_2O. Under these conditions the retention time for T-2 toxin was 20 min. Yields of T-2 toxin obtained from the 50–100-mL cultures varied from 1.7 to 11.7 mg.

Registry No. 2, 21259-20-1; leucine, 61-90-5; isovaleric acid, 503-74-2.

(22) Lawson, J. A.; Colwell, W. T.; SeGraw, J. I.; Peters, R. H.; Dehn, R. L.; Tanabe, M. *Synthesis* **1975**, 729–730.
(23) Aberhart, D. J. *J. Labeled Comp. Radiopharm.* **1983**, *20*, 605–610.

Reduction of *o*-Hydroxybenzaldehydes by Aqueous Titanium Trichloride. A New Route to 2-(Benzofuran-2-yl)phenols

Angelo Clerici* and Ombretta Porta*

Dipartimento di Chimica del Politecnico, Pza L. da Vinci 32, 20133 Milano, Italy

Alberto Arnone

CNR, Centro di Studio per le Sostanze Organiche Naturali, Dipartimento di Chimica del Politecnico, Pza L. da Vinci 32, 20133 Milano, Italy

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Reduction of *o*-hydroxybenzaldehydes **1a–k** by aqueous titanium trichloride is a new simple way to the synthesis of the title compounds **2a–k**. The temperature at which the reduction occurs (50 or 80 °C) is related to the nature and position of the R group in the benzene ring. When the reduction is performed at 0 °C in the presence of acetaldehyde, stereoselective formation of 1,3-dioxolanes **7** occurs, due to in situ condensation with the intermediate diols. A mechanism is proposed to account for the formation of both **2** and **7**. Two-dimensional NMR methods have been used to completely assign ^{1}H and ^{13}C NMR resonances of the 2-(benzofuran-2-yl)phenols **2a–d,f–h**.

In recent years much attention has been given to the antifungal activities of certain hydroxy- and methoxy-substituted 2-phenylbenzofurans,[1] and different methods have been reported[2] for the synthesis of these compounds, structurally related to the phytoalexins Vignafuran[3] and Moracin.[4] On continuation of our studies on the reducing properties of aqueous titanium trichloride,[5] we report herein a new, one-step synthesis of 2-(benzofuran-2-yl)-

(1) (a) Chamberlain, K.; Carter, G. A. *Pestic. Sci.* **1980**, *11*, 526. (b) Carter, G. A.; Chamberlain, K.; Wain, R. L. *Ann. Appl. Biol.* **1978**, *88*, 57. (c) Martin, M.; Dewick, P. M. *Phytochemistry* **1979**, *18*, 1309.
(2) Pandey, G.; Krishna, A.; Bhalerao, U. T. *Tetrahedron Lett.* **1989**, *30*, 1867, and references therein.
(3) (a) Duffley, R. P.; Stevenson, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 802. (b) Preston, N. W.; Chamberlain, K.; Skip, R. A. *Phytochemistry* **1975**, *14*, 1843.
(4) (a) Burke, J. M.; Stevenson, R. *J. Chem. Res. Synop.* **1985**, *34*. (b) Clough, J. M.; Inderjit, S.; Widdowson, D. A. *Tetrahedron Lett.* **1987**, *28*, 2645.
(5) Clerici, A.; Porta, O. *J. Org. Chem.* **1987**, *52*, 5099, and references therein.

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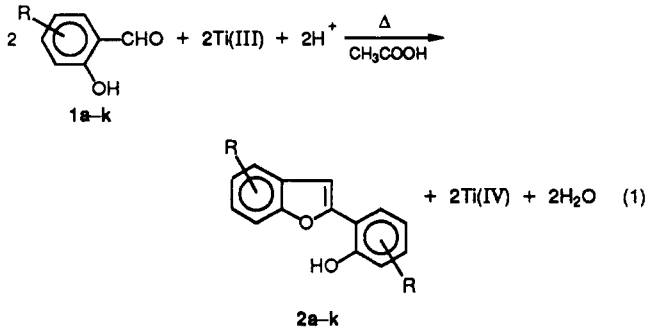
Table I. Product Isolated Yields (percent) in the Reduction of 1a–k in the Absence and Presence of Acetaldehyde

		yield, % (CH_3CHO absent)					yield, % (CH_3CHO present)	
substrate 1	temp, °C	2	3	4	5	unreac 1	7	unreac 1
a	0	10 (18)[a]	*b*	8		60	76	20
a	50	43	40			10		
b	0					100	84	11
b	50	75	16			5		
c	0					100		100
c	50					100		
c	80	20	45			30		
d	0					100	80	15
d	50	54	21			20		
e	80	30			20	*c*		
f	0	tr				75[c]	*c*	19
f	80	78			20			
g	0						65	22
g	80	43 (67)[a]	20	24		6		
h	0						70[d]	16
h	80	46 (65)[a]	14	21		7		
k	0	(95)[a]	tr	98			*e*	
k	50	87	11					

[a] Total yield after transformation of **4a,g,h,k** into **2a,g,h,k**, respectively. [b] 18% of **6a'** (Scheme II) is isolated. [c] A brown powder of undefined composition containing titanium is also formed. [d] 11% of **8h** (Scheme I) is formed. [e] **4k** is obtained in quantitative yield.

phenols **2a–k** (Chart I), which are obtained in moderate-to-good yields (Table I) by reduction of *o*-hydroxybenzaldehydes **1a–k** in acetic acid, according to eq 1.



a, R = H **a**, R = 5-OCH_3 **a**, R = 5-Br
b, R = 3-OCH_3 **b**, R = 3-OH **b**, R = 5-Cl
c, R = 4-OCH_3 **c**, R = 5-OH **c**, R = 2-OH-1-naphthaldehyde

(5a*r*,10bc)-5a,10b-Dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furans **3** or 2-(benzofuran-3-yl)phenols **5** and (4b*r*,9bc)-4b,9b-dihydrobenzo[*b*]benzo[4,5]furo[2,3-*d*]-furans **4** (Chart I) are formed together with **2** in variable amounts depending on the nature of the R substituent. The results obtained are summarized in Table I.

Results and Discussion

Inspection of the data in Table I reveals that the temperature at which reduction of **1a–k** by Ti(III) ion becomes synthetically significant is strongly correlated to the nature and position of the R group in the benzene ring. The lower the electron density on the aldehydic carbonyl carbon, the lower the temperature required for the reduction to occur.

2-Hydroxy-1-naphthaldehyde **1k** is quantitatively reduced to **4k** at 0 °C, salicylaldehyde **1a** is easily reduced to **2a** and **3a** at 50 °C, but only some reduction occurs at 0 °C. While all three methoxysalicylaldehydes considered (**1b–d**) are recovered unchanged at 0 °C, the two bearing the methoxy group in a meta position (**1b** and **1d**) are reduced at lower temperature (50 °C) than the one with the methoxy group in the para position (**1c**) to the aldehydic function (80 °C).

Dihydroxybenzaldehydes **1e** and **1f** behave similarly to methoxysalicylaldehydes, though a higher temperature (80 °C) is required for the reduction to occur. A potential synthetic limitation is, however, observed in the case of **1e**: in fact, only 50% of the starting 2,3-dihydroxybenzaldehyde affords the desired reduction products, the remaining being recovered as a black–brown solid containing titanium. Such a result is consistent with the competitive chelation of titanium ion with the two hydroxyl groups[6] other than with the aldehydic and *o*-hydroxyl groups[7] of **1e**.

Reduction of *o*-hydroxybenzaldehydes bearing an electron-withdrawing substituent (Br and Cl, **1g** and **1h**, respectively) affords a red–brown precipitate of undefined composition containing titanium both at 0 and 50 °C. However, titanium dioxide precipitates and the products are easily extracted with an organic solvent from the reaction mixture by performing the reaction at 80 °C.

It is important to note that, under the present reaction conditions (pH = 1), aromatic aldehydes without an *o*-hydroxyl group are not reduced by aqueous titanium trichloride. Only in basic medium (pH = 10–12), owing to the increased reducing power of Ti(III) ion, does reductive hydrodimerization of benzaldehyde occur.[8]

Notwithstanding that the $E_{1/2}$ of salicylaldehyde is more negative than $E_{1/2}$ of benzaldehyde (–1.02 and –0.98 V vs SCE at pH = 1, respectively),[9] reduction of the former easily occurs at pH = 1. Intramolecular Ti chelation,[7] represented by A in Scheme I,[10] reversing the polar nature of the hydroxyl group, makes reduction of 1 thermody-

(6) Titanium tetrachloride and pyrochatecol have been shown to form the compound $H_2[Ti(C_6H_4O_2)_3]$ in 90% yield when made to react together in benzene solution. Funk, H.; Schlegel, A.; Zimmerman, K. *J. Prakt. Chem.* **1956**, *3*, 320; *Chem. Abstr.* **1957**, *51*, 10409.

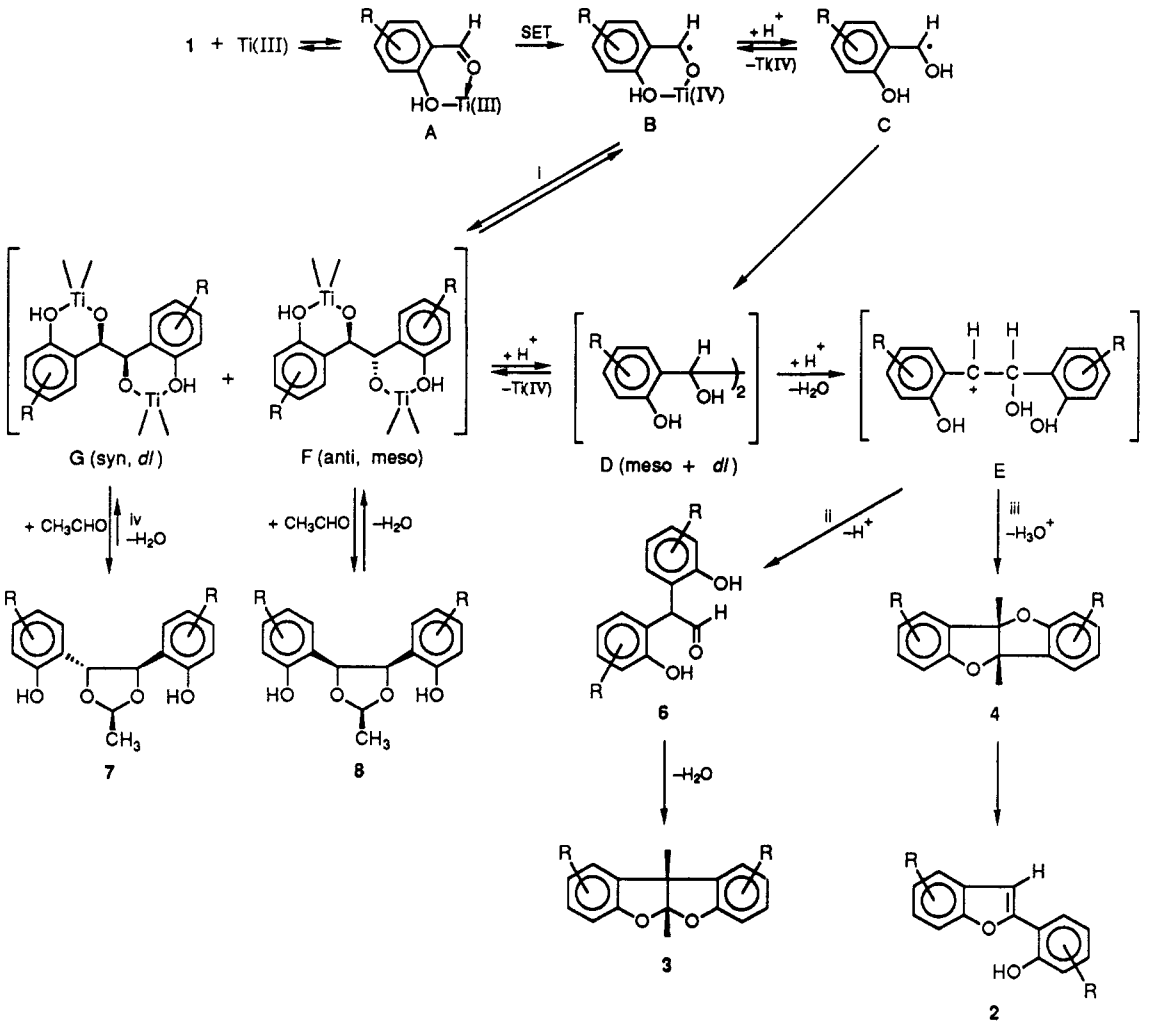
(7) The same type of chelates, as represented by A in Scheme I, are formed between $TiCl_4$ or $Ti(OR)_4$ and salicylaldehyde. Molecular weight determination showed that Ti(IV) ion is pentacoordinate in these compounds: (a) Yamamoto, A.; Kambara, S. *J. Inorg. Nucl. Chem.* **1961**, *21*, 58; *Chem. Abstr.* **1962**, *56*, 11187. (b) Mehrotra, R. C.; Verma, I. D. *J. Less Common Met.* **1961**, *3*, 321; *Chem. Abstr.* **1962**, *56*, 6877.

(8) Clerici, A.; Porta, O. *J. Org. Chem.* **1985**, *50*, 76.

(9) Meites, L. *Polarographic Techniques*, 2nd ed.; Interscience Publishers: New York, 1965; p 680.

(10) A and B must be considered as empirical formulas, since the coordinative valences of Ti(III) and Ti(IV) ions are presumably completed by water, chloride ions, and/or molecules of solvent in which the reaction occurs.

Scheme I

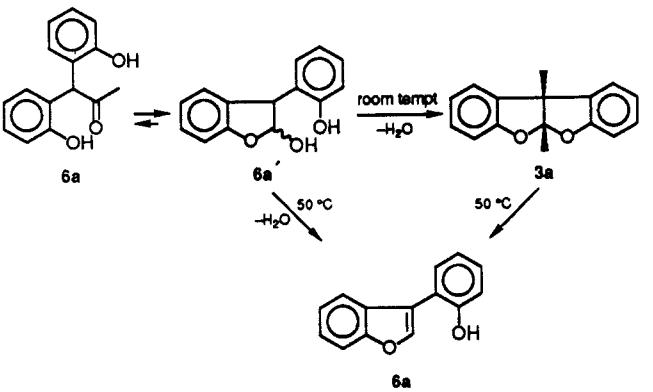


namically possible at a suitable temperature, even at low pH.

Following the activation of the precursor complex A, a single electron transfer (SET) takes place from the metal to the carbonyl group of the ligand to form B,[10] which in acidic medium may well equilibrate with the free ketyl radical C (Scheme I). The next step can be dimerization of either B or C to afford the corresponding chelated G or F or free D diols (meso and *dl*) that, owing to the acidity of the medium, dehydrate to the intermediate benzylic carbocation E. Pinacolone rearrangement of E (path ii, Scheme I) to the benzylic aldehyde **6** is the key step to acetals **3**.

Though we find no trace of dimers in these reactions, evidence that diols are the reaction intermediates is given by (1) the formation of the corresponding 1,3-dioxolanes **7** when reduction of **1a–h** is performed in the presence of acetaldehyde and (2) the isolation of rearranged product **6a** (18% yield) when reduction of **1a** is performed at 0 °C (Scheme II). We will discuss in detail in a separate section both the reaction conditions and the mechanistic and stereochemical aspects involved in the formation of **7**. It should be emphasized that compound **6a** exists in $CDCl_3$ solution as an equilibrium mixture of the two ring-closed hemiacetal forms **6a′** in a 2:1 ratio, as shown by the integral ratio of the H-2′ signals resonating at δ 5.82 and 6.15. Accordingly, the ^{13}C NMR spectrum presents two resonances for C-2′ at δ 106.99 and 102.18, characteristic of carbon atoms of an hemiacetal function. In the liquid state

Scheme II

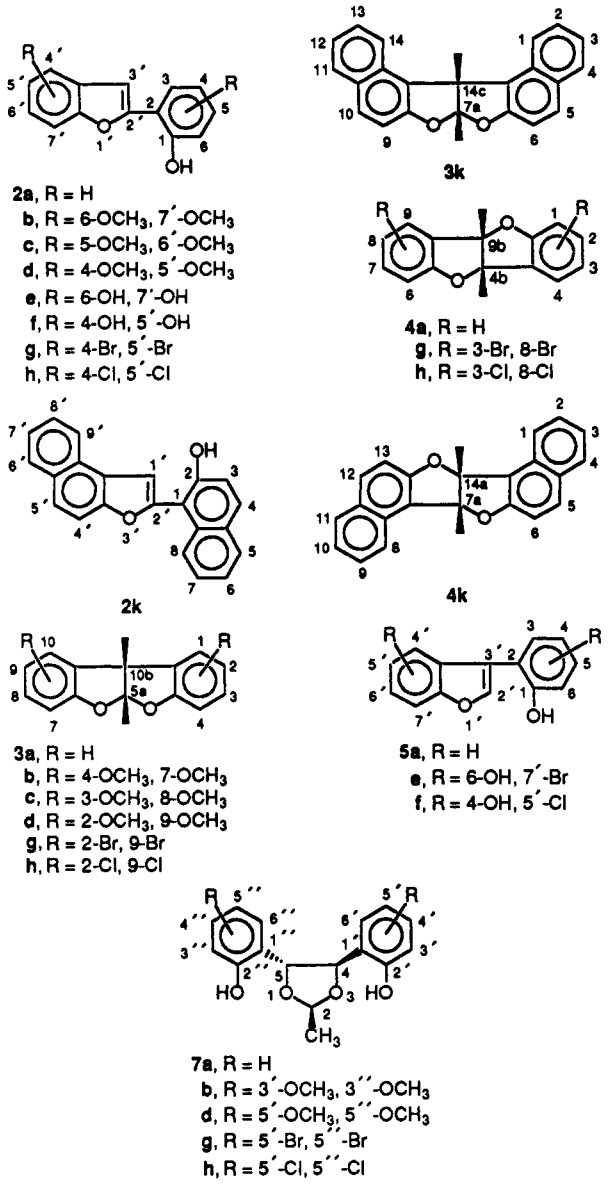


also, the ring-opened form **6a** is absent since the IR spectrum (neat) shows no carbonyl band absorption. This behavior is similar to that encountered for versiconal acetate[11] and, recently, for versiconal analogues.[12]

As depicted in Scheme II, treatment of **6a′** with 1:1 acetic acid/concentrated hydrochloric acid mixture results in dehydrocyclization to acetal **3a** at room temperature. Both **6a′** and **3a** are converted into **5a** by similar treatment

(11) Steyn, P. S.; Vleggaar, R.; Wessels, P. L.; Scott, D. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 460.
(12) Gorst-Allman, C. P.; Steyn, P. S. *J. Chem. Soc., Perkin Trans 1* **1987**, 163.

Chart I



at 50 °C. The intermediacy of **3a** in the transformation **6a'** → **5a** is evidenced by the fact that **3a** itself precipitates at first and then redissolves by prolonging the reaction time. It remains that, under the conditions of Table I, only ring closure to **3** occurs without further ring opening to **5** (Scheme I). Transformation of **3** into **5** requires a higher hydrogen ion concentration than that present in the reaction mixture.[13] An exception is observed when R is a hydroxyl group (**1e** and **1f**):[14] due to the increased basicity of the dihydrobenzofuran oxygen, ring opening to **5e** and **5f** already occurs at the hydrogen ion concentration of the reaction medium.

The ^{1}H NMR spectra of compounds **3a–d,g,h** (Table IV) are entirely in accord with the proposed structures. Moreover, the ^{13}C NMR spectrum of **3a** shows a signal at δ 112.37, characteristic of an acetal carbon atom. The assignment of this resonance to C-5a follows from the observed correlation with the 5a-proton resonating at δ 6.79 in the ^{1}H NMR spectrum. The cis junction between the two dihydrofuran rings is established from the value of the vicinal coupling constants between H-5a, H-10b and H-7a, H-14c (^3J = 6.7–6.9 and 6.1 Hz, respectively) very similar to that found in aflatoxin B_1,[15] the stereochemistry of which has been determined by crystal X-ray analysis.[16] Cyclodehydration to **4** (path iii, Scheme I) is the alternate path the intermediate benzylic carbocation E follows in addition to the already considered pinacolone rearrangement (path ii). The ether type structure **4**, with the exception of **4g** and **4h**, is unstable under the reaction conditions ($t \geq 50$ °C). Ring opening spontaneously occurs during the reaction, thereby resulting in the formation of **2**. Evidence that **4** is the intermediate to **2** is given by the following experimental observations: (1) **4a** and **4k**, isolated only at 0 °C, are quantitatively converted into **2a** and **2k** under the reaction conditions at 50 °C; (2) **4g** and **4h**, which, on the contrary, still survive at 80 °C (Table I), are transformed into **2g** and **2h** by heating them at 50 °C in a 1:1 acetic acid/concentrated hydrochloric acid mixture. The higher hydrogen ion concentration required for the ring opening in these two cases may well be related to the electron-withdrawing nature of the R group (Br and Cl) which decreases the basicity of the dihydrobenzofuran oxygen in **4g** and **4h**.[17] The ^{1}H NMR spectra of compounds **4a,g–k** (Table IV) contain only half of the expected signals, the ethereal protons (H-4b, H-9b and H-7a, H-14a) resonating at δ 6.24–6.91. This is the result of the dimeric nature of these compounds, which have a C_2 symmetry axis perpendicular to the plane of the molecule. The magnitude of the vicinal coupling constants between H-4b, H-9b and H-7a, H-14a (^3J = 7.2–7.4 and 7.5 Hz, respectively), obtained by analysis of the ^{13}C–H satellites,[18] is indicative of a cis junction between the two dihydrofuran rings.[19]

The product distribution shown in Table I indicates that the dihydrocyclization leading to **2**, through **4**, is preferred over the pinacolone rearrangement leading to **3**. The only exception is 4-methoxysalicylaldehyde **1c**, which, upon reduction, affords **3c** in higher yield than **2c**, a result consistent with the high migratory aptitude of the *p*-anisol group.[20] Thus, the sequence of reactions depicted in the right-hand side of Scheme I affords a new simple one-pot synthesis of 2-(benzofuran-2-yl)phenols **2**. The isomeric 2-(benzofuran-3-yl)phenols **5** may be obtained, as a minor product, upon further treatment of **3**.[13]

Since the chromatographic mobilities either of **3** and **4** or of **2** and **5** are comparable, it turns out to be very useful that, under the present conditions, **3** is stable while **4** is not: indeed, owing to the greater mobility of **3** with respect to **2**, their separation is easily achieved by flash column chromatography.

The ^{1}H and ^{13}C NMR resonances of compounds **2a–d,f–h** and **5a,f** have been completely assigned (Tables II and III). These assignments are based on chemical shift criteria, analysis of the ^{1}H–^{1}H and ^{13}C–^{1}H coupling con-

(13) It is already known that acetals **3** are converted into phenols **5** by refluxing them in acetic acid containing hydrochloric or sulfuric acid: (a) Coxworth, E. C. M. *Can. J. Chem.* **1966**, *44*, 1092. (b) Coxworth, E. C. M. *Can. J. Chem.* **1967**, *45*, 1777.

(14) In the reduction of **1e** and **1f**, acetals **3e** and **3f** are not isolated, the corresponding **5e** and **5f** being formed directly instead, both in 20% yield.

(15) Asao, T.; Buchi, G.; Abdel-Kader, M. M.; Chang, S. B.; Wick, E. L.; Wogan, G. N. *J. Am. Chem. Soc.* **1965**, *87*, 882.

(16) Cheung, K. K.; Sim, G. A. *Nature* **1964**, *201*, 1185.

(17) Conversion of **4** into **2** is likely to occur by protonation of the ethereal oxygen, subsequent ring opening, and formation of a carbocation which undergoes facile H^+ loss. The same mechanism would apply to the conversion of **3** into **5**. Accordingly, the hydroxyl group makes the ring opening easier in **3e** and **3f** (see ref 14).

(18) Jackman, L. M.; Sterwhell, S. *Application of NMR Spectroscopy in Organic Chemistry*; Pergamon Press: Oxford, 1969; p 140.

(19) Cardillo, B.; Cornia, M.; Merlini, L. *Gazz. Chim. Ital.* **1975**, *105*, 1151.

(20) (a) Bachmann, W. E.; Ferguson, J. W. *J. Am. Chem. Soc.* **1934**, *56*, 2081. (b) Bachmann, W. E.; Steinberger, H. R. *Ibid.* **1934**, *56*, 170.

Table II. ^{1}H NMR Chemical Shifts (δ)[a] of Compounds 2a–d,f–h and 5a,f

proton[b,c]	2a	2b	2c	2d	2f[d]	2g	2h	5a[e]	5f[e]
3	7.67	7.69	7.53	7.22	7.26	7.94	7.84	7.42	7.00
4	6.94	6.94	6.57					7.00	
5	7.20	6.84		6.83	6.63	7.42	7.31	7.27	6.62
6	6.95		6.54	6.89	6.81	7.00	7.08	6.98	6.83
3′	7.03	7.42	6.84	7.05	7.27	7.46	7.50		
4′	7.53	7.20	7.43	7.03	6.94	7.91	7.76	7.61	7.15
5′	7.22	7.13	6.89					7.26	
6′	7.24	6.79		6.89	6.71	7.46	7.34	7.34	6.80
7′	7.45		7.06	7.39	7.34	7.61	7.65	7.54	7.42
OH-1	7.16	6.42	7.25	6.78	9.64	10.93	10.94	5.35	9.24

[a] Chemical shifts in $CDCl_3$ for **2a–d** and **5a**, in DMSO-d_6 for **2f–h** and **5f**. [b] The OCH_3 signals for **2b–d** resonate at δ 4.04 and 3.91, 3.87 and 3.82, and 3.85 and 3.82, respectively. [c] For **2a,c,d,f–h**, $^5J_{3',7'}$ = 1.0 Hz. [d] OH-4 and OH-5′ resonate at δ 8.89 and 9.10, respectively. [e] For **5a** and **5f** H-2′ resonates at δ 7.79 and 8.12, respectively.

Table III. ^{13}C NMR Chemical Shifts (δ)[a] of Compounds 2a–d,f–h and 5a,f

carbon[b,c]	2a	2b	2c	2d	2f	2g	2h	5a	5f
1	153.20	143.15	154.47	147.42	147.47	154.65	153.73	153.18	150.35
2	116.24	116.74	109.35	116.60	116.95	118.63	117.62	117.80	119.39
3	127.09	118.96	127.80	111.07	111.58	128.51	125.12	130.30	115.77
4	120.74	119.68	107.77	153.36	149.85	110.90	122.95	120.86	147.65
5	130.09	110.21	161.24	116.37	116.36	132.60	129.27	129.33	115.11
6	117.18	146.68	102.07	118.04	116.95	118.81	117.85	115.92	117.03
2′	153.97	152.12	153.80	154.53	152.88	152.51	152.31	142.94	145.17
3′	103.65	106.39	101.16	104.13	105.59	106.43	106.09	116.83	117.70
3′a	128.59	131.48	121.92	129.24	130.12	131.81	130.70	126.68	127.80
4′	120.97	113.60	120.74	103.38	105.45	124.10	120.62	120.60	106.07
5′	123.30	123.33	112.22	156.19	153.28	115.75	127.36	123.15	153.78
6′	124.36	106.64	157.82	113.10	112.83	127.54	124.39	124.95	113.42
7′	110.92	145.15	95.86	111.37	110.79	113.32	112.27	111.78	112.08
7′a	153.58	143.15	154.76	148.95	147.25	152.51	151.64	155.44	149.06

[a] Chemical shifts in $CDCl_3$ for **2a–d** and **5a**, in DMSO-d_6 for **2f–h** and **5f**. [b] The OCH_3 signals for **2b–d** resonate at δ 56.23 and 56.14, 55.79 and 55.41, and 55.83 and 55.83, respectively. [c] For **2a–d,f–h**, $^1J_{C\text{-}3',H\text{-}3'}$ ranges between 175 and 183.5 Hz, while for **5a,f**, $^1J_{C\text{-}2',H\text{-}2'}$ is 202.5 and 204 Hz, respectively; the remaining aromatic $^1J_{C,H}$ ranges between 157 and 169.5 Hz.

Table IV. ^{1}H NMR Chemical Shifts (δ) of Compounds 3a–d,g,h and 4a,g,h in $CDCl_3$

proton[a,b]	3a	3b	3c	3d	3g[c]	3h	4a	4g[c]	4h
1	7.31	6.98	7.21	6.93	7.76	7.33	6.85	6.82	6.82
2	6.88	6.89	6.48				7.25	7.40	7.24
3	7.09	6.75		6.68	7.29	7.15	6.95		
4	6.84		6.48	6.80	6.83	6.84	7.51	7.66	7.48
4b							6.24	6.41	6.28
5a	6.79	6.96	6.90	6.86	6.99	6.91			
10b	4.88	5.05	4.90	4.95	5.18	4.99			

[a] The OCH_3 signals for **3b–d** resonate at δ 3.86, 3.74, and 3.76, respectively. [b] For **4a,g,h**, $^3J_{4b,9b}$, obtained by analysis of the ^{13}C–H satellites, ranges between 7.2 and 7.4 Hz, while for **3a–d,g,h**, $^3J_{5a,10b}$ ranges between 6.7 and 6.9 Hz. [c] Chemical shifts in $CDCl_3$/DMSO, ca. 1:1.

stants, low-power selective heteronuclear ^{13}C–^{1}H decouplings, long-range ^{13}C–^{1}H (COLOC) and one-bond ^{13}C–^{1}H shift-correlated 2D NMR experiments, and comparison with the reported chemical shifts and coupling constants of related compounds.[21] The magnitude of the one-bond (C, H) coupling constant of C-3′ (^1J = 175–183.5 Hz) and of the five-bond (H, H) coupling constant (^5J = 1.0 Hz) between H-3′ and H-7′ in compounds **2** and the magnitude of the one-bond (C, H) coupling constant of C-2′ (^1J = 202.5–205.5 Hz) in compounds **5** support these assignments.

Stereoselective Formation of 1,3-Dioxolanes 7. Irrespective of the nature of the R group, reduction of **1a,b,d,g,h**[22] becomes possible at 0 °C if performed in the presence of acetaldehyde (molar ratio 1:Ti(III):CH_3CHO = 1:1.5:3). Due to in situ condensation of the intermediate diols with acetaldehyde, a clean reaction leading to stereoselective formation of *trans*-4,5-diaryl-2-methyl[1,3]-dioxolanes **7** in good yields (Table I) is observed. The only 1,3-dioxolane isolated with the substituent aryl groups in the cis arrangement (**8h**, 11%) comes from the reduction of **1h**. The ^{1}H NMR spectra of **7** and **8h** are consistent with the structures depicted in Chart I and Scheme I. In particular, the spectra of dioxolanes **7** show the presence of two magnetically nonequivalent methine protons, H-4 and H-5, indicating that the two aryl groups are trans disposed. Instead, the spectrum of **8h** presents coincident signals for H-4 and H-5 and for corresponding aromatic protons, suggesting that the two aryl groups are cis disposed. Conclusive confirmation of the structure and stereochemistry of **7h** and **8h** follows from the results of NOE difference experiments (see Experimental Section). Specifically, the cis relationship among the C-2 methyl group, H-5 (at δ 5.05), and H-6′ (at δ 7.38) and among H-2, H-4 (at δ 5.26), and H-6″ (at δ 7.36) in compound **7h** derives from the NOEs observed for H-5 (1.5%) and H-6′ (2.5%) upon irradiation of the protons of C-2 methyl

(21) (a) Platzer, N.; Basselier, J. J.; Demerseman, P. *Bull. Soc. Chim. Fr.* **1974**, *905*. (b) Arnone, A.; Nasini, G.; Venturini, I. *Gazz. Chim. Ital.* **1988**, *118*, 675. (c) Elvidge, J. A.; Foster, R. G. *J. Chem. Soc.* **1964**, 981.

(22) The exceptions are **1k**, which at 0 °C is quantitatively reduced to **4k** in both the presence and absence of acetaldehyde, **1c**, which is recovered unchanged, and **1e** and **1f**, which both afford a vitreous material containing titanium.

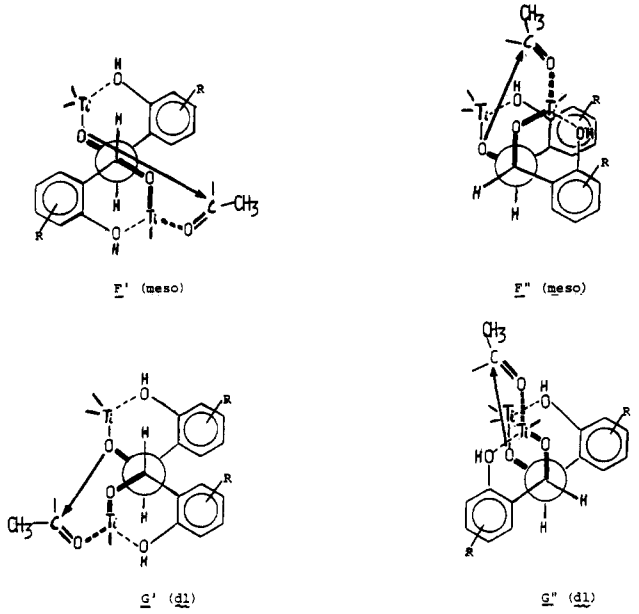


Figure 1.

groups and from those observed for H-4 (6%) and H-6″ (5%) upon irradiation of H-2. Similar NOE experiments permit the establishment of the cis relationship among C-2 methyl group, H-6′ and H-6″, and among H-2, H-4, and H-5 in compound **8h**.

Since the formation of **7** involves condensation of hydroxyl groups having the syn relative configuration, the syn[23] or *dl* diol G must be the precursor of **7**, and the anti[23] or meso diol F is the precursor of **8**. Whereas the absence of **8** may be related to the lower stability[24] of 1,3-dioxolanes having the substituent groups cis and/or to a more crowded transition state (Figure 1) in the acetalization step, the absence of the meso diol F also (or of products deriving from free diol D) must involve either stereoselective or reversible dimerization of the intermediate radicals B (path i, Scheme I). Because it is well-known that sterically crowded radicals predominantly yield meso dimers[25] or, at least, equal amount of both isomers,[8,26] it is to be ruled out that the coupling process would stereoselectively afford the *dl* dimer. Thus, to explain the stereoselective formation of **7**, we suggest that dimerization of B is a reversible process in which the equilibrium evolves to regenerate the *dl* diol selectively trapped by acetaldehyde in the condensation step (path iv).

Concerning path iv, it is well documented[27] that acetalization is a reversible process that may be shifted to the side of acetal only by removing the water formed with various acid-type dehydrating agents. Indeed, under the present conditions, notwithstanding the aqueous medium (H_2O/CH_3COOH, volume ratio 1:1) and the low concentration of acetaldehyde, **7** is formed in good yield.

A mechanism in which acetalization occurs within the coordination sphere of titanium ion, before the free diol D could be formed, would explain the extensive formation of **7**. In other words, we suggest that the Ti(III) ion that reduces the *o*-hydroxybenzaldehydes **1** is already coordinated with the acetaldehyde molecule that is going to form **7**. The Newman projections of the transition state leading to **7** and **8**, according to this interpretation, are depicted in Figure 1. Among the conformations in which the aldehydic and hydroxyl groups are suitably located to react, the two of *dl* diol (G′ and G″) both have less steric interaction than that of meso diol F″; the less hindered conformation is F′, but the two reactive centers are too far away to react.

The assumption that acetaldehyde completes the coordinative valence of Ti(III) ion[28] accounts also for the increased reducing power of the metal ion at 0 °C when acetaldehyde is present.

Any attempt to hydrolize **7** to the corresponding *dl* diol D results in the formation of variable amounts of **2–5** depending on the temperature and hydrogen ion concentration. This proves that the intermediate diols are unstable to acid and supports the working hypothesis that acetalization occurs before the free diol could be formed.

Experimental Section

General Methods. All starting materials were commercially available research grade chemicals and used as received. The aqueous $TiCl_3$ solution (15% w/v) was standardized against 0.1 N Ce(IV) solution. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-250 spectrometer. Chemical shifts are in ppm (δ) from $SiMe_4$ as an internal standard. NOE difference spectra were obtained by alternatively subtracting right off-resonance free-induction decays (FIDs) from right on-resonance induced FIDs. IR spectra were recorded on a Perkin-Elmer Model E 177. Mass spectra were determined on a Hitachi-Perkin-Elmer RMU 6D instrument at 70 eV. Melting points were taken on a Köffler apparatus (uncorrected). Flash column chromatography was carried out by using Merk silica gel (particle size 0.004–0.063 mm).

General Procedure to 2-(Benzofuran-2-yl)phenols 2. To a well-stirred solution of the substrate (**1a–k**, 10 mmol) in acetic acid (15 mL), kept under N_2 at 0, 50, or 80 °C, the $TiCl_3$ solution (15 mmol) is added at once. A rapid color change from blue to red-brown is observed upon mixing the reagents. The reaction mixture is allowed to stir at the given temperature (Table I) for 1 h. The crude mixture is then extracted with ethyl acetate (3 × 150 mL), and the combined extracts are washed with a little water (2 × 25 mL), dried over anhydrous Na_2SO_4, and reduced in vacuo to leave a solid residue, which is "flash" chromatographed on a silica gel column (50 × 2.5 cm) with the appropriate eluant. As a rule, **3** and **4** are eluted first, then **2**. The data of Table I are product isolated yields (percent) based on the starting **1a–k**.

General Procedure to 1,3-Dioxolanes 7. To a well-stirred solution of the substrate (**1a,b,d,f–h**, 10 mmol) and acetaldehyde (30 mmol) in acetic acid (15 mL), kept under N_2 at 0 °C, the $TiCl_3$ solution (15 mmol) is added at once. The reaction mixture is allowed to react under stirring at 0 °C for 1 h. Upon workup as above, the crude residue is purified by flash column chromatography. The more mobile phase is unreacted substrate **1**; the second eluted fraction corresponds to 1,3-dioxolanes **7**.

Spectroscopic Data. All compounds of Table I were isolated. ^1H and ^{13}C NMR resonances of **2a–d,f–h** and **5a,f** are reported in Tables II and III, respectively. ^1H NMR resonances of **3a–d,g,h** and **4a,g,h** are collected in Table IV. All new compounds gave satisfactory elemental analyses and their structural assignments were deduced from Tables II–IV and from the following data.

2-(Benzofuran-2-yl)phenol (2a) and (5a*r*,10b*c*)-5a,10b-Dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furan (3a). Reduction

(23) According to Masamune nomenclature: Masamune, S.; Ali, A. S. K.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, 557.

(24) 1,3-Dioxolane derivatives formed by condensation with hydroxyl groups having syn configuration are thermodynamically more stable than those formed by condensation with hydroxyl groups having anti configuration. This order of stability reflects the destabilization of the 1,3-dioxolane ring on account of nonbonded interactions between *cis*-1,2-substituents: Clode, D. M. *Chem. Rev.* **1979**, *79*, 491.

(25) (a) Waters, W. A. *Mechanisms of Oxidation of Organic Compounds*; Methuen: London, 1964; p 35. (b) Huang, R. L.; Singh, S. *J. Org. Chem.* **1958**, *23*, 81. (c) Erra Balsells, R.; Frasca, A. R. *Tetrahedron* **1982**, *38*, 245. (d) Grimshaw, J.; Ramsey, J. S. *J. Org. Chem. C* **1966**, 653.

(26) (a) Brown, W. G.; McClure, D. E. *J. Org. Chem.* **1970**, *35*, 2036. (b) Goh, S. H.; Ong, S. H.; Sich, I. *Org. Magn. Reson.* **1971**, 713.

(27) Flowers, H. M. *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; London, 1971; p 1029.

(28) The type of the ligand at titanium determines the electronic and steric nature of the reagent: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin 1986; Chapter I.

of **1a** (1.22 g, 10 mmol) was done at 50 °C. After workup, purification of the crude residue (1.1 g) by flash column chromatography (20% ethyl ether–hexane) gave at first **3a** (0.42 g, 40%) as a white solid [mp 116 °C from ethanol (lit. mp 116–7 °C);[16] ^{13}C NMR ($CDCl_3$) δ 50.10 (d, C-10b), 12.37 (d, C-5a), 110.15, 121.86 123.89 and 128.83 (d, Ar C), 127.15 (s, C-10a and C-10c), 157.71 (s, C-4a and C-6a); IR (Nujol) ν_{max} 1600, 1230, 1200, 1150, 1090, 980 cm^{-1}; MS, *m/e* 210 ($M^{\bullet+}$, 100), 181, 152] and then **2a** [0.45 g, 43%; mp 99 °C from aqueous ethanol (lit. mp 98–9 °C);[29] IR (Nujol) ν_{max} 3250 (OH) cm^{-1}; MS *m/e* 210 ($M^{\bullet+}$, 100), 181 (50), 154, 153, 105, 77].

(4b*r*,9b*c*)-4b,9b-Dihydrobenzo[*b*]benzo[4,5]furo[2,3-*d*]furan (4a) and 2-(2′-Hydroxy-2′,3′-dihydrobenzofuran-3′-yl)phenol (6a′). Reduction of **1a** (2.44 g, 20 mmol) was done at 0 °C. After workup, flash column chromatography on the crude residue (2.2 g) with 20% ethyl acetate–hexane afforded in order **4a** [0.17 g, 8%; mp 118–9 °C from ethanol (lit. mp 116–8 °C);[19] ^{13}C NMR ($CDCl_3$) δ 86.42 (d, C-4b and C-9b), 110.78, 121.12, 126.52, 131.3 (d, Ar C), 124.39 (s, C-4a and C-9a), 160.00 (s, C-5a and C-10a); IR (Nujol) ν_{max} 1490, 1470, 1320, 1240 cm^{-1}; MS, *m/e* 210 ($M^{\bullet+}$, 100), 181, 105] unreacted salicylaldehyde **1a** (0.72 g, 60%), **2a** (0.21 g, 10%), and then **6a′** (0.42 g, 18%) as a thick liquid. **6a′** was a mixture of two epimers in the ratio of ca. 2:1 from ^{1}H and ^{13}C NMR spectra. Major epimer: ^{1}H NMR ($CDCl_3$) δ 4.37 (1 H, br s, OH-1), 4.72 (1 H, d, ^3J = 3.1 Hz, H-3′), 5.82 (1 H, dd, ^3J = 3.5 and 3.1 Hz, H-2′), 6.00 (1 H, d, ^3J = 3.5 Hz, OH-2′), 6.7–7.4 (8 H, m, Ar H); ^{13}C NMR ($CDCl_3$) δ 50.49 (d, C-3′), 106.99 (d, C-2′), 110.11, 115.82, 120.97, 121.66, 125.89, 128.43, 128.53 and 128.88 (d, Ar C), 126.01 and 126.89 (s, C-2 and/or C-3′a), 153.69 (s, C-1), 158.08 (s, C-7′a). Minor epimer: ^{1}H NMR ($CDCl_3$) δ 4.37 (1 H, br s, OH-1), 4.84 (1 H, d, ^3J = 6.8 Hz, H-3′), 6.15 (1 H, dd, ^3J = 6.8 and 6.5 Hz, H-2′), 6.35 (1 H, d, ^3J = 6.5 Hz, OH-2′), 6.7–7.4 (8 H, m, Ar H); ^{13}C NMR ($CDCl_3$) δ 49.56 (d, C-3′), 102.18 (d, C-2′), 110.16, 116.76, 121.11, 121.52, 125.18, 128.65, 129.36 and 131.55 (d, Ar C), 122.34 and 126.88 (s, C-2 and/or C-3′a), 154.27 (s, C-1), 157.45 (s, C-7′a); IR (neat) ν_{max} 3380 (OH), 1600, 1480, 1460, 1220, 1100, 940 cm^{-1}; MS, *m/e* 228 ($M^{\bullet+}$, 17), 210 ($M^{\bullet+}$ – H_2O, 100, *m** = 193.4), 199 (66), 181 (50), 153 (18), 152 (18), 121 (25), 107 (50).

2-(Benzofuran-3-yl)phenol (5a). **5a** was formed in quantitative yield as a thick oil upon heating at 50 °C for a few minutes a solution of either **6a′** (100 mg) or **3a** (100 mg) in acetic acid (1.5 mL) containing concentrated hydrochloric acid (1 mL); IR (neat) ν_{max} 3500 (OH), 1450, 1220, 1100, 960 cm^{-1}; MS, *m/e* 210 ($M^{\bullet+}$, 100), 181 (50), 153, 152.

2-(7-Methoxybenzofuran-2-yl)-6-methoxyphenol (2b) and 4,7-Dimethoxy-(5a*r*,10b*c*)-5a,10b-dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furan (3b). Reduction of **1b** (2.28 g, 15 mmol) was done at 50 °C. After workup, the resulting reddish solid material (2.0 g) was chromatographed with 20% ethyl acetate–hexane. The first eluted fraction was **3b** (0.32 g, 16%): mp 180–2 °C from chloroform; IR (Nujol) ν_{max} 1620, 1490, 1280, 1190, 1090, 1070, 950 cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 228 (16). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.18; H, 5.20. The second eluted fraction was **2b** (1.5 g, 75%): mp 160–1 °C from ethanol; IR (Nujol) ν_{max} 3420 (OH) cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 255, 241. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.22; H, 5.23.

2-(6-Methoxybenzofuran-2-yl)-5-methoxyphenol (2c) and 3,8-Dimethoxy-(5a*r*,10b*c*)-5a,10b-dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furan (3c). Reduction of **1c** (1.52 g, 10 mmol) was done at 80 °C. After workup, 1.5 g of brown residue was obtained. The solid was taken up in hot methanol. On standing overnight at 0 °C, **3c** (0.6 g, 45%) crystallized out as white thin needles: mp 165–6 °C; IR (Nujol) ν_{max} 1600, 1490, 1275, 1190, 1140, 980 cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 255 (M – CH_3, 60). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.20; H, 5.25. The mother liquor of the above crystallization was stripped of solvent and chromatographed with 20% ethyl acetate–hexane to give unreacted **1c** (0.45 g, 30%) at first and **2c** (0.27 g, 20%) afterward: mp 155–6 °C; IR (Nujol) ν_{max} 3390 (OH) cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 255 (M – CH_3, 95), 135 (21). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.05; H, 5.24.

2-(5-Methoxybenzofuran-2-yl)-4-methoxyphenol (2d) and 2,9-Dimethoxy-(5a*r*,10b*c*)-5a,10b-dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furan (3d). Reduction of **1d** (1.52 g, 10 mmol) was done at 50 °C. The crude reaction mixture was carefully extracted with ethyl acetate (5 × 75 mL) until all the red-brown sticking solid was dissolved. After workup, 1.3 g of a reddish solid was recovered. Chromatography with 20% ethyl acetate–hexane gave in order unreacted **1d** (0.3 g, 20%), **3d** (0.28 g, 21%), and **2d** (0.75 g, 54%). Upon recrystallization from methanol, **3d** was obtained as white needles: mp 179–80 °C (lit. mp 177–8 °C);[30] IR (Nujol) ν_{max} 1490, 1220, 1180, 1030, 980 cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 255 (M – CH_3, 20), 241, 218. After recrystallization from aqueous methanol, **2d** was obtained as yellow needles: mp 108–9 °C; IR (Nujol) ν_{max} 3200 (OH), 1210, 1030 cm^{-1}; MS, *m/e* 270 ($M^{\bullet+}$, 100), 255. Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.25; H, 5.18.

2-(7-Hydroxybenzofuran-2-yl)-6-hydroxyphenol (2e) and 2-(7-Hydroxybenzofuran-3-yl)-6-hydroxyphenol (5e). Reduction of **1e** (1.38 g, 10 mmol) was done at 80 °C. After workup, 0.7 g of a reddish solid was recovered. A brown precipitate,[6] insoluble in the common organic solvents, remained in the aqueous layer. Purification of the solid residue by chromatography with 30% ethyl acetate–hexane afforded 0.6 g (50%) of a pale-pink powder (mp 115–90 °C) which, by NMR analysis, was a mixture of **2e** (60%) and **5e** (40%). Their separation was not accomplished. Isomeric mixture: ^{1}H NMR (DMSO-d_6) δ 6.7–7.5 (6 H for each isomer, m, Ar H), 7.35 (1 H, s, H-3′ of isomer **2e**), 8.13 (1 H, s, H-2′ for isomer **5e**), 9.60 (3 H for each isomer, br s, OH); ^{13}C NMR (DMSO-d_6) δ 105.66 (d, $^1J_{C,H}$ = 180 Hz, C-3′ of isomer **2e**), 110.16 (d), 110.33 (d), 111.49 (d), 111.51 (d), 114.19 (d), 114.97 (d), 116.45 (d), 117.22 (s), 117.72 (s), 119.01 (s), 119.01 (d), 119.10 (d), 119.68 (d), 123.31 (d), 123.39 (d), 128.56 (s), 131.04 (s), 141.82 (s), 142.18 (s), 142.80 (s), 142.85 (s), 143.12 (s), 143.44 (s), 143.44 (d, $^1J_{C,H}$ = 205.5 Hz, C-2′ of isomer **5e**), 145.40 (s), 145.54 (s), 152.18 (s); MS, *m/e* 242 ($M^{\bullet+}$, 100), 213 (14). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.51; H, 4.10.

2-(5-Hydroxybenzofuran-2-yl)-4-hydroxyphenol (2f) and 2-(5-Hydroxybenzofuran-3-yl)-4-hydroxyphenol (5f). Reduction of **1f** (1.38 g, 10 mmol) was done at 80 °C. After workup, 1.3 g of brown solid was recovered. Chromatography of the solid with 20% ethyl acetate–hexane gave first **5f** (0.24 g, 20%) as reddish crystals [mp 180–3 °C; IR (Nujol) ν_{max} 3300–3100 (OH), 1200, 1170 cm^{-1}; MS, *m/e* 242 ($M^{\bullet+}$, 100), 213 (M – CHO, 27). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.38; H, 4.20] and then **2f** (0.95 g, 78%) as reddish crystals [mp 208–10 °C from aqueous ethanol; IR (Nujol) ν_{max} 3500–3100 (OH), 1190 cm^{-1}; MS, *m/e* 242 ($M^{\bullet+}$, 100), 213 (20), 204 (25), 105 (50), 104 (50), 77 (20). Anal. Calcd for $C_{14}H_{10}O_4$: C, 69.42; H, 4.16. Found: C, 69.47; H, 4.12].

2-(5-Bromobenzofuran-2-yl)-4-bromophenol (2g), 2,9-Dibromo-(5a*r*,10b*c*)-5a,10b-dihydrobenzo[*b*]benzo[4,5]furo[3,2-*d*]furan (3g), and 3,8-Dibromo-(4b*r*,9b*c*)-4b,9b-dihydrobenzo[*b*]benzo[4,5]furo[2,3-*d*]furan (4g). Reduction of **1g** (2.0 g, 10 mmol) was done at 80 °C. After workup, the crude residue (2.1 g) was taken up in 40% ethyl acetate–methanol. On standing overnight at room temperature, a yellow solid was formed (0.85 g), which, by NMR analysis was a mixture of **3g** (40%) and **4g** (60%). The solid was then dissolved in acetone and stored at 0 °C for 2 days. **4g** (0.45 g, 24%) crystallized out as long white needles: mp 259–60 °C; IR (Nujol) ν_{max} 1600, 1240, 1165, 1120, 1060 cm^{-1}; MS, *m/e* [370 (49), 368 (100), 366 (51)] ($M^{\bullet+}$), (289, 287, *m** = 225) (M – Br), (261, 259) (M – COBr). Anal. Calcd for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19. Found: 45.63; H, 2.15. The mother liquor of the above crystallization, stripped of solvent, gave **3g** (0.35 g, 20%): mp 268–70 °C from ethyl acetate; IR (Nujol) ν_{max} 1330 1230, 1105, 1025, 980 cm^{-1}; MS, *m/e* [370 (49), 368 (100), 366 (51)] ($M^{\bullet+}$), (289, 287, *m** = 225) (M – Br), 261, 259, 208, 180, 152. Anal. Calcd for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19. Found: C, 45.71; H, 2.16. The crude residue left (1.2 g) was purified by column chromatography with 20% ethyl acetate–hexane to afford unreacted **1g** (0.12 g, 6%) and **2g** (0.8 g, 43%): mp 196–8 °C from chloroform; IR (Nujol) ν_{max} 3480 (OH) cm^{-1}; MS, *m/e* [370 (49), 368 (100), 366 (51)] ($M^{\bullet+}$), (342, 340, 338) (M

(29) Adam, D. J.; Crombie, L.; Siddalingajah, K. S.; Whiting, D. A. *J. Chem. Soc. C* **1966**, 544.

(30) Beilstein, *19*, E V, p 425.

– CO), (289, 287, m^* = 225) (M – Br), (261, 259) (M – COBr). Anal. Calcd for $C_{14}H_8O_2Br_2$: C, 45.69; H, 2.19. Found: C, 45.72; H, 2.16. Since **4g** was quantitatively transformed into **2g** by refluxing it in a 1:1 acetic acid/hydrochloric acid mixture, the total yield of **2g** is 67%.

2-(5-Chlorobenzofuran-2-yl)-4-chlorophenol (2h), 2,9-Dichloro-(5a*r*,10b*c*)-5a,10b-dihydrobenzo[*b*]benzo[4,5]furo-[3,2-*d*]furan (3h), and 3,8-Dichloro-(4b*r*,9b*c*)-4b,9b-dihydrobenzo[*b*]benzo[4,5]furo[2,3-*d*]furan (4h). Reduction of **1h** (1.57 g, 10 mmol) was done at 80 °C. After workup, the reddish solid (1.5 g) was taken up in 10% ethyl acetate–methanol. On standing overnight at 0 °C, a pale yellow solid was formed (0.55 g) which was a mixture of **3h** and **4h**. The solid was dissolved in hot acetone and stored at room temperature for 4 days. **4h** crystallized out (0.3 g, 21%) as long white needles: mp 248–50 °C; MS, *m/e* [282 (10), 280 (62), 278 (100)] ($M^{\bullet+}$), [217 (20), 215 (60)] (M – COCl), 151, 139. Anal. Calcd for $C_{14}H_8O_2Cl_2$: C, 60.24; H, 2.89. Found: C, 60.30; H, 2.85. The mother liquor of the above crystallization, stripped of solvent, gave 0.2 g (14%) of **3h**: mp 233–5 °C from chloroform (lit. mp 234–6 °C[13b]); MS, *m/e* [282 (10), 280 (62), 278 (100)] ($M^{\bullet+}$). The crude residue left (0.9 g) was purified on column chromatography with 20% ethyl acetate–hexane to give unreacted **1h** (0.11 g, 7%) and **2h** (0.65 g, 46%): mp 187–8 °C from chloroform; IR (Nujol) ν_{max} 3510 (OH) cm^{-1}; MS, *m/e* [282 (10), 280 (62), 278 (100)] ($M^{\bullet+}$), [253 (0.1), 252 (0.6), 249 (10)] (M – CHO), [245 (0.3), 243 (10), m^* = 212.4] (M – Cl), [217 (16), 215 (50)] (M – COCl). Anal. Calcd for $C_{14}H_8O_2Cl_2$: C, 60.24; H, 2.89. Found: C, 60.19; H, 2.91.

(7a*r*,14a*c*)-7a,14a-Dihydronaphtho[2,1-*b*]naphtho-[1′,2′:4,5]furo[2,3-*d*]furan (4k). Reduction of **1k** (1.72 g, 10 mmol) was done at 0 °C. Upon mixture of the reagents, a green color appeared, and a precipitate was formed in few minutes. The mixture was left to stir for 1 h, and then the solid was filtered off and crystallized from chloroform to give **4k** (1.5 g, 97%) as white needles: mp 262–3 °C (lit. mp 232–3 °C[19] and 261–2 °C[31]); ^1H NMR ($CDCl_3$) δ 6.91 (2 H, br s, H-7a and H-14a, ^3J = 7.5 Hz obtained by analysis of the ^{13}C–H satellites), 7.14, 7.39, 7.62, 7.80, 7.83 and 8.07 (12 H, m, naphth H); ^{13}C NMR ($CDCl_3$) δ 87.25 (d, C-7a and C-14a), 112.83, 122.51, 123.60, 127.77, 128.74 and 132.60 (d, naphth C), 116.18, 129.42, 131.01 and 158.38 (s, naphth C); MS, *m/e* 310 ($M^{\bullet+}$, 44), 281 (M – CHO, 15), 187 (16), 176 (40), 122 (72), 105 (100), 77 (76); IR (Nujol) ν_{max} 1250, 1160 cm^{-1}. Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.31; H, 4.53.

(7a*r*,14a*c*)-7a,14a-Dihydronaphtho[2,1-*b*]naphtho-[1′,2′:4,5]furo[3,2-*d*]furan (3k) and 1-Naphtho[2,1-*b*]furan-2-yl-2-naphthol (2k). Reduction of **1k** (1.72 g, 10 mmol) was done at 50 °C. After workup, 1.6 g of a solid was recovered. The crude residue was purified by flash column chromatography to give at first **3k** [0.17 g, 11%; mp 236 °C from 1:1 hexane/ethyl acetate (lit. mp 236 °C[32]); ^1H NMR ($CDCl_3$) δ 5.55 (1 H, br d, ^3J = 6.1 Hz, H-14c), 7.10 (1 H, d, ^3J = 6.1 Hz, H-7a), 7.23, 7.32, 7.51, 7.73, 7.80 and 8.27 (12 H, m, naphth H); MS, *m/e* 310 ($M^{\bullet+}$, 100), 281 (M – CHO, 50); IR (Nujol) ν_{max} 1250, 1230, 1210, 1200, 1060 cm^{-1}] and then **2k** [1.35 g, 87%; mp 135–7 °C from aqueous ethanol; ^1H NMR ($CDCl_3$) δ 6.70 (1 H, s, OH), 7.49 (1 H, d, ^5J = 0.9 Hz, H-1′), 7.2–8.2 (12 H, m, naphth H); ^{13}C NMR ($CDCl_3$) δ 107.28 (d, $^1J_{C,H}$ = 175 Hz, C-1′), 109.79 (s), 112.16 (d), 117.89 (d), 123.45 (d), 123.83 (s), 123.83 (d), 124.23 (d), 124.89 (d), 125.77 (d), 126.61 (d), 127.39 (s), 127.39 (d), 128.36 (d), 128.83 (d), 129.01 (s), 130.47 (s), 131.68 (d), 132.56 (s), 150.01 (s), 152.50 (s), 152.71 (s); MS, *m/e* 310 ($M^{\bullet+}$, 100), 281 (M – CHO, 33). Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.04; H, 4.58.

***trans*-4,5-Bis(2-hydroxyphenyl)-2-methyl-1,3-dioxolane (7a).** After workup, a thick yellow oil was recovered (1.34 g) which, upon purification on a silica gel column with 30% ethyl acetate–hexane gave at first unreacted **1a** (0.25 g, 20%) and then **7a** (1.04 g, 76%) as a colorless thick oil that solidified on standing: mp 72–3 °C; ^1H NMR ($CDCl_3$–DMSO-d_6) δ 1.56 (3 H, d, ^3J = 4.9 Hz, Me-2), 5.28 and 5.48 (2 H, d, ^3J = 7.2 Hz, H-4 and H-5), 5.60 (1 H, q, ^3J = 4.9 Hz, H-2), 6.7–7.7 (8 H, m, Ar H), 8.70 and 8.93 (2 H, br s, 2OH); MS, *m/e* 272 ($M^{\bullet+}$), 254, 228, 210, 198, 181, 150, 121, 107 (100), 105, 78, 77, 65; IR (Nujol) ν_{max} 3450–3200 (OH), 1300–1090 (dioxolane ring) cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.50; H, 5.95.

***trans*-4,5-Bis(2-hydroxy-3-methoxyphenyl)-2-methyl-1,3-dioxolane (7b).** After workup, a red thick oil was recovered (1.75 g). Purification of the crude oil on a silica gel column with 20% ethyl acetate–hexane gave unreacted **1b** (0.16 g, 11%) and **7b** (1.4 g, 84%), which recrystallized from ether as yellow needles: mp 131–3 °C; ^1H NMR ($CDCl_3$) δ 1.57 (3 H, d, ^3J = 4.8 Hz, Me-2), 3.85 (6 H, s, 2OMe, 5.33 and 5.50 (2 H, d, ^3J = 7.2 Hz, H-4 and H-5), 5.72 (1 H, q, ^3J = 4.8 Hz, H-2), 6.15 and 6.30 (2 H, br s, 2OH), 6.7–7.1 (6 H, m, Ar H); IR (Nujol) ν_{max} 3380 (OH), 1300–1000 (dioxolane ring) cm^{-1}; MS, *m/e* 332 ($M^{\bullet+}$), 288, 270, 259, 180, 151, 137 (100). Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.15; H, 6.09.

***trans*-4,5-Bis(2-hydroxy-5-methoxyphenyl)-2-methyl-1,3-dioxolane (7d).** After workup, a thick yellow oil was recovered (1.8 g). Chromatography on a silica gel column with 20% ethyl acetate–hexane afforded unreacted **1d** (0.23 g, 15%) and **7d** (1.35 g, 80%) as a colorless thick oil: ^1H NMR ($CDCl_3$) δ 1.63 (3 H, d, ^3J = 4.8 Hz, Me-2), 3.60 and 3.63 (6 H, s, 2OMe), 5.15 (2H, s, H-4 and H-5; in DMSO they resonated at 5.15 and 5.35, ^3J = 7.2 Hz), 5.60 (1 H, q, ^3J = 4.8 Hz, H-2), 6.3–6.9 (6 H, m, Ar H), 6.98 (2 H, br s, 2OH); MS, *m/e* 332 ($M^{\bullet+}$), 270, 214, 210, 181, 180, 152, 151, 137, 85, 83, 43; IR (neat) ν_{max} 3400 (OH), 1500, 1270–1030 (dioxolane ring) cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found: C, 65.20; H, 6.02.

***trans*-4,5-Bis(2-hydroxy-5-bromophenyl)-2-methyl-1,3-dioxolane (7g).** After workup, a thick oil was obtained (2.2 g). Column chromatography of the crude residue with 20% ethyl acetate–hexane as eluant afforded unreacted **1g** (0.45 g, 22%) and **7g** (1.4 g, 65%): mp 115–7 °C; ^1H NMR (DMSO-d_6) δ 1.44 (3 H, d, ^3J = 4.8 Hz, Me-2), 5.03 and 5.26 (2 H, d, ^3J = 7.2 Hz, H-4 and H-5), 5.53 (1 H, q, ^3J = 4.8 Hz, H-2), 6.70, 6.70, 7.26, 7.27, 7.47 and 7.50 (6 H, m, Ar H), 9.76 (2 H, br s, 2OH); IR (Nujol) ν_{max} 3350 (OH), 1300–1050 (characteristic bands of dioxolane ring) cm^{-1}; MS, *m/e* (432, 430, 428) ($M^{\bullet+}$), (369, 367, 365), 202, 200 (base peak). Anal. Calcd for $C_{16}H_{14}O_4Br_2$: C, 44.68; H, 3.28. Found: C, 44.63; H, 3.30.

***trans*-4,5-Bis(2-hydroxy-5-chlorophenyl)-2-methyl-1,3-dioxolane (7h) and *cis*-4,5-Bis(2-hydroxy-5-chlorophenyl)-2-methyl-1,3-dioxolane (8h).**[33] After workup, the crude oil (1.75 g) was eluted on a silica gel column with 20% ethyl acetate–hexane to afford in order unreacted **1h** (0.25 g, 16%), **7h** (1.2 g, 70%), and **8h** (0.2 g, 11%). Upon recrystallization from hexane ethyl ether (1:1), **7h** melted at 127 °C: ^1H NMR (DMSO-d_6) δ 1.45 (3 H, d, ^3J = 4.7 Hz, Me-2), 5.05 (1 H, d, ^3J = 7.1 Hz, H-5), 5.26 (1 H, d, ^3J = 7.1 Hz, H-4), 5.53 (1 H, q, ^3J = 4.7 Hz, H-2), 6.74 (2 H, d, ^3J = 8.6 Hz, H-3′ and H-3″), 7.11 (1 H, dd, ^3J = 8.6 and ^4J = 2.8 Hz, H-4″), 7.14 (1 H, dd, ^3J = 8.6 and ^4J = 2.8 Hz, H-4′), 7.36 (1 H, d, ^4J = 2.8 Hz, H-6″), 7.38 (1 H, d, ^4J = 2.8 Hz, H-6′), 9.68 (2 H, br s, 2OH); NOE experiments: irradiation of Me-2 enhanced H-2 (12%), H-5 (1.5%), and H-6′ (2.5%), irradiation of H-2 enhanced Me-2 (6%), H-4 (6%), and H-6″ (5%), irradiation of H-4 enhanced H-2 (5.5%), H-6′ (3.5%), and H-6″ (8%), and irradiation of H-5 enhanced Me-2 (0.5%), H-6′ (10%), and H-6″ (5.5%); MS, *m/e* (344, 342, 340) ($M^{\bullet+}$), (282, 280, 278) (M – CH_3CHO – H_2O), (158, 156) (base peaks), 77, 56, 51, 43; IR (Nujol) ν_{max} 3360 (OH), 1300–1020 (characteristic bands of dioxolane ring) cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_4Cl_2$: C, 56.32; H, 4.14. Found: C, 56.37; H, 4.08. **8h**, slightly contamined with **7h**, melted at 155–60 °C; ^1H NMR (DMSO-d_6) δ 1.57 (3 H, d, ^3J = 4.7 Hz, Me-2), 5.26 (1 H, q, ^3J = 4.7 Hz, H-2), 5.57 (2 H, s, H-4 and H-5), 6.56, 6.92, and 6.94 (6 H, m, Ar H), 9.61 (2 H, br s, 2OH); NOE experiments: irradiation of Me-2 enhanced H-2 (5.5%), H-6′, and H-6″ (3%), irradiation of H-2 enhanced Me-2 (2.5%), H-4, and H-5 (5.5%), and irradiation of H-4 and H-5 enhanced H-2 (10%), H-6′, and H-6″ (1%); IR (Nujol) ν_{max} 3340 (OH), 1300–1000 (characteristic bands of dioxolane ring) cm^{-1}.

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Formal 2 + 2 and 3 + 2 Cycloaddition Reactions of 2*H*-Chromenes with 2-Alkoxy-1,4-benzoquinones: Regioselective Synthesis of Substituted Pterocarpans

Thomas A. Engler,*,† Jayachandra P. Reddy, Keith D. Combrink, and David Vander Velde

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

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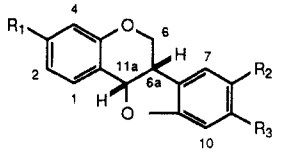
The titanium(IV)-catalyzed reaction of various 2*H*-chromenes and 2-alkoxy-1,4-benzoquinones stereoselectively yields the oxygenated pterocarpans **8** and/or the 2 + 2 adducts **7**, depending upon reaction conditions. Cyclobutanes **7** rearrange to **8** upon treatment with protic acids. Syntheses of the pterocarpan phytoalexins (±)-homopterocarpin (**2**), (±)-pterocarpin (**3**), and (±)-9-*O*-benzyl-3-*O*-methylsophoropterocarpan A (**4**) are presented, which demonstrates the synthetic utility of these formal cycloaddition reactions.

Introduction

Phytoalexins are antimicrobial compounds produced by plants in response to a stress.[1] The stress can be in a variety of forms such as attack by fungi or bacteria or by the application of an abiotic elicitor such as heavy metal salts or irradiation. It has been suggested that phytoalexins are crucial components in plant disease resistance and that they may be valuable in the development of new approaches to crop protection and perhaps in pharmaceutical applications as well.[2]

A large class of isoflavonoid phtoalexins possess a substituted pterocarpan ring system **1**. The structural requirements for biological activity and the mode of action of the pterocarpan phytoalexins have not been comprehensively studied, although oxygen-containing substituents at C_3 and C_9 appear to be necessary for potent activity, and the presence of prenyl substituents may also be important.[2a,3] For these reasons, methods for the synthesis of pterocarpans have received considerable interest recently.[4] We have developed an efficient synthesis of the structurally similar 2-aryl-2,3-dihydrobenzofurans via Lewis acid catalyzed reactions of styrenes with 1,4-benzoquinones.[5] We now report the details of the extension of this method to the regioselective preparation of substituted pterocarpan frameworks[6] including (±)-homopterocarpin (**2**), (±)-pterocarpin (**3**), and (±)-9-*O*-benzyl-3-*O*-methylsophoropterocarpan A (**4**). In addition, the method provides intermediates that should be useful in the synthesis of a number of other pterocarpan phytoalexins.



1, $R_1=R_2=R_3=H$
2, $R_1=R_3=OCH_3$, $R_2=H$
3, $R_1=OCH_3$, R_2-R_3=-OCH_2O-
4, $R_1=OCH_3$, $R_2=CH_2CH=C(CH_3)_2$, $R_3=OCH_2Ph$

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Results and Discussion

Bicyclo[4.2.0]octenediones **7** and/or pterocarpans **8** are produced by Ti(IV)-catalyzed reactions of 2*H*-chromenes **5** and 2-alkoxy-1,4-benzoquinones **6** (Scheme I and Table I). The Ti(IV) employed was in the form of a premixed combination of titanium(IV) chloride and titanium(IV) isopropoxide, and the ratio of the products formed, **7**:**8**, is dependent upon the number of equivalents of Ti^{4+}, the ratio of $TiCl_4$ to $Ti(OiPr)_4$, and the reaction temperature. Thus, at -78 °C with 1-2 equiv of Ti(IV) as catalyst, formal 2 + 2 adducts **7** are formed exclusively in most cases. However, upon warming of the reaction mixture and/or utilization of catalyst systems with >2 equiv of Ti(IV) and enriched in $TiCl_4$, the formal 3 + 2 adducts **8** are the major, if not the exclusive, products found. Attempts to obtain cycloaddition products from **5** and **6** with stannic chloride

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