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Convenient Synthesis of 2,2-Disubstituted-2,3-Dihydro-1,4-Benzodioxins from 2-Substituted-2-Hydroxy-2,3-Dihydro-1,4-Benzodioxins

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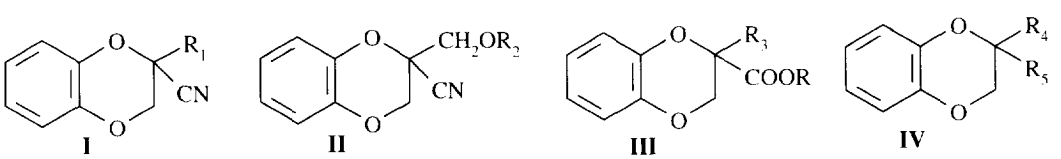
Abstract: Convenient syntheses of relatively rare 2,2-disubstituted-2,3-dihydro-1,4-benzodioxins from 2-substituted-2-hydroxy-2,3-dihydro-1,4-benzodioxins, as key synthetic intermediates, are reported. These new synthetic approaches require Lewis acid BF_3-Et_2O mediated nucleophilic substitution reaction or cyclization of suitable hydroxyphenols.

Present in many natural and synthetic products, the 2,3-dihydro-1,4-benzodioxinic ring has generated much interest in chemistry. The 2,3-dihydro-1,4-benzodioxinic derivatives are important pharmaceutical commodities of wide medical use; some of these are cardiovascular agents as adrenoreceptor antagonists[1], while other compounds with a high affinity for 5-HT receptor subtypes[2] have been shown to exhibit neuroleptic activity. In the course of our work on the synthesis of therapeutically valuable 2,3-dihydro-1,4-benzodioxinic compounds with antioxidant properties[3], we needed 2,2-disubstituted-2,3-dihydro-1,4-benzodioxins bearing various alkyl, aryl and functionalized groups at C-2 as shown in scheme 1 with the structures **I-IV** .

Scheme 1



R_1= R_2= R_3= R_4= R_5= alkyl, aryl.

Up to now, only few synthetic methods are available for the preparation of 2,2-disubstituted-2,3-dihydro-1,4-benzodioxin derivatives. In fact, the introduction of alkyl substituents at C-2 cannot be achieved by direct base-catalyzed alkylation, the reaction leading to immediate ring opening[4].

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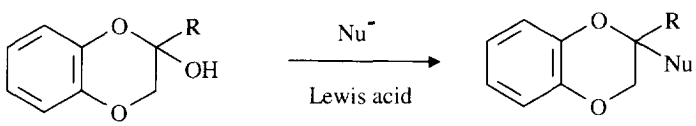
Access to these compounds requires as key synthetic intermediate 2-substituted-2-hydroxy-2,3-dihydro-1,4-benzodioxin derivatives. Katritzky *et al* first related, in poor yield below 30%, the preparation of 2-hydroxy-2,3-dihydro-1,4-benzodioxin derivatives bearing at C-2 a methyl or a phenyl group by condensation of corresponding α-chloroketone on catechol under alkaline conditions[5]. Later, Chapleo *et al* briefly outlined the synthesis of the 2-cyano-2-methyl-2,3-dihydro-1,4-benzodioxin from the 2-hydroxy-2-methyl-2,3-dihydro-1,4-benzodioxin[6]. The hydroxyl compound in dichloromethane was chlorinated in the presence of hydrochloric acid gas and immediatly treated with trimethylsilyl cyanide, because of the great instability of 2-chloro intermediate, to give the expected nitrile in good yield. In other respects, Salimbeni *et al* related the preparation of some 2-substituted-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin derivatives but not in pure form[7].

In light of the published results, we anticipated to prepare in a straightforward manner the wanted structures **I-IV**, without exploiting the reactive nature of α-haloethers as Chapleo *et al* but by Lewis acid mediated nucleophilic substitution reactions of the 2-hydroxy-2,3-dihydro-1,4-benzodioxinic derivatives, following a synthetic procedure usually used in carbohydrate chemistry[8] (scheme 2).

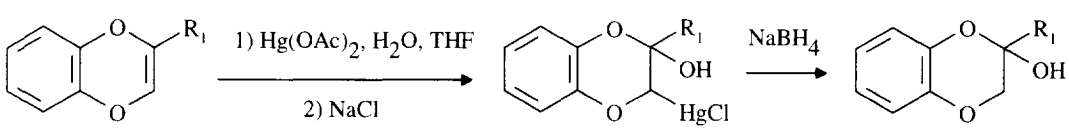
Scheme 2



R= alkyl, aryl, functionalized group.

In order to improve significantly the yield of the suitable starting material, the 2,3-dihydro-1,4-benzodioxinic hemiketals, we first reported at the outset of our work, a new efficient synthetic route to 2-substituted-2-hydroxy-2,3-dihydro-1,4-benzodioxin derivatives without limitations *via* an oxymercuration-demercuration reaction[9] of the corresponding 2-substituted 1,4-benzodioxinic derivatives[10] (scheme3).

Scheme 3



1-6 **7-12**

R_1 = alkyl, phenyl, hydroxymethyl.

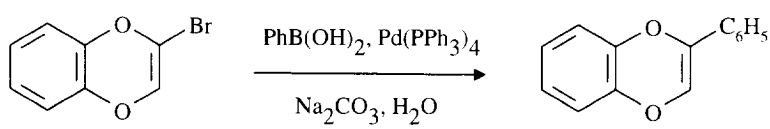
As depicted below in table 1, the oxymercuration reaction of various benzodioxins **1-6** performed in the presence of a suspension of mercuric acetate in water/THF followed by a treatment *in situ* with sodium chloride and then with sodium borohydride as a reducting agent provided in excellent yields the expected hemiketals **7-12**.

Table 1: Synthesis of the Hemiketals **7-12**

Starting material	**R_1**	**Product**	**Yield**
1	CH_3	**7**	72%
2	C_4H_9	**8**	87%
3	C_6H_5	**9**	90%
4	CH_2OH	**10**	76%
5	CH_2OBz	**11**	78%
6	CH_2OCH_3	**12**	86%

Apart from the compound **3**, the 1,4-benzodioxinic materials **1**, **2**, **4**, **5, 6** were prepared according to literature procedures[11, 12, 13]. The 2-phenyl-1,4-benzodioxin **3** was readily obtained upon palladium-catalyzed cross-coupling reaction[14] of phenylboronic acid with 2-bromo-1,4-benzodioxin **13**[11] (scheme 4).

Scheme 4



13 **96%** **3**

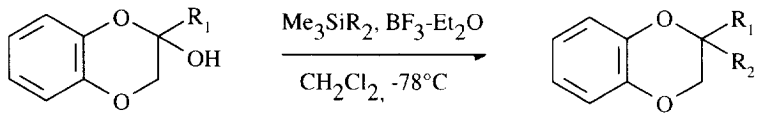
In continuation of our synthetic program, we treated the hemiketals **7-12** with silylated reagents such as trimethylsilyl cyanide and allyltrimethylsilane in the presence of various Lewis acids[15].

Performed at low temperature or room temperature, the reactions of hemiketals in the presence of trimethylsilyl cyanide using tin (IV) chloride ($SnCl_4$) or titanium (IV) chloride ($TiCl_4$) gave black messy mixtures. In each case, the starting material was predominantly recovered beside a poor yield of expected nitriles (yield<10%). In other respects, under these conditions, we noticed the debenzylation of the compound **5** in quantitative yield.

Nevertheless the use of boron trifluoride diethyl etherate (BF_3-Et_2O) gave much cleaner reactions with good yield of expected nitrile (scheme 5, table 2). However, whatever the ratios of the components, the duration, the temperature of the reaction, substantial amounts of starting material were always recovered. On the other hand, under similar conditions, the reaction using the allytrimethylsilane furnished more efficiently the 2-allyl derivatives, no trace of starting material being recovered.

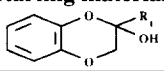
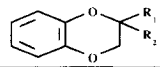
It appears that boron trifluoride diethyl etherate promoted reaction of 2,3-dihydro-1,4-benzodioxinic hemiketals **7-12** with silylated reagents is a mild efficient technique to obtain easily in good yields the corresponding analogs **14-24** bearing henceforth a functionalized group such as a cyano or an allyl group instead of the tertiary hydroxy group (scheme 5, table 2).

Scheme 5



7-12 **14-24**

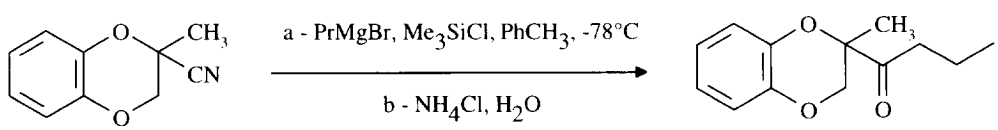
Table 2 : Lewis acid (BF_3-Et_2O) Promoted Reactions

Starting material 	R_1	R_2	Product 	Yield	
7	CH_3	CN	**14**	56%[a]	85%[b]
8	C_4H_9	CN	**15**	57%[a]	81%[b]
9	C_6H_5	CN	**16**	55%[a]	76%[b]
10	CH_2OH	CN	**17**	40%[a]	45%[b]
11	CH_2OBz	CN	**18**	62%[a]	78%[b]
12	CH_2OCH_3	CN	**19**	58%[a]	76%[b]
7	CH_3	CH_2=CH-CH_2	**20**	74%	
8	C_4H_9	CH_2=CH-CH_2	**21**	76%	
9	C_6H_5	CH_2=CH-CH_2	**22**	76%	
10	CH_2OH	CH_2=CH-CH_2	**23**	73%	
11	CH_2OBz	CH_2=CH-CH_2	**24**	76%	

[a]: the yield was calculated on the basis of the amount of starting hemiketal.
[b]: the yield was calculated on the basis of the amount of recovered starting hemiketal.

The obtained nitriles are also key synthetic intermediates for the synthesis of new functionalized derivatives. For example, after treatment with 2.5 equivalents of propyl magnesium bromide in the presence of an excess of chlorotrimethylsilane[16], the cyano derivative **14** yielded 66% of the corresponding ketone **25** (scheme 6).

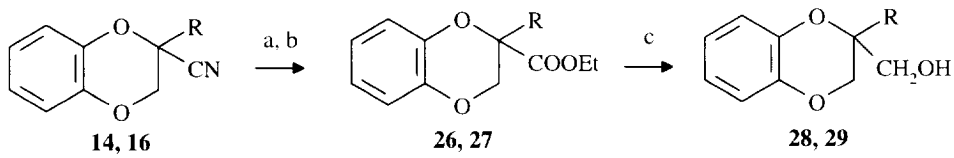
Scheme 6



14 **66%** **25**

The cyano groups of compounds **14** and **16** were converted in good yields to hydroxymethyl groups (table 3) *via* an ester intermediate by using established procedures shown in scheme 7.

Scheme 7



14, 16 **26, 27** **28, 29**

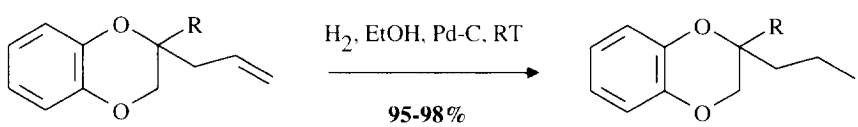
(a) *i*-KOH, EtOH; *ii*-HCl (b) PTSA, EtOH (c) $LiAlH_4$, Et_2O.

Table 3 : Conversion of Nitrile Derivatives to Hydroxymethyl Derivatives

Nitrile	R	Ester		Alcohol	
		Product	Yield	Product	Yield
14	CH_3	**26**	70%	**28**	88%
16	C_6H_5	**27**	72%	**29**	85%

In other respects, some dialkyl derivatives are available at this stage by catalytic hydrogenation of allylic analogs (**20-22**) in ethanol with 10% palladium on charcoal (Pd-C) under hydrogen atmosphere (scheme 8, table 4).

Scheme 8



20-22 **30-32**

Table 4 : Catalytic Hydrogenation of Allylic Derivatives

Starting material	R	Product	Yield
20	CH_3	**30**	98%
21	C_4H_9	**31**	95%
22	C_6H_5	**32**	97%

With the view to find a route that would allow the preparation of all 2,3-dihydro-1,4-benzodioxins bearing at C-2 two alkyl groups or an alkyl group with a phenyl group as the structure **IV** (scheme 1), we

investigated the reaction of the hemiketal **7** with a Grignard reagent in the presence of boron trifluoride diethyl etherate[17] as Lewis acid. The reaction proved fruitless, a complicated mixture of cleaved products being recovered. Nevertheless, while our work was in progress, we noticed that the exposure of alkyl hemiketals to Grignard reagents without the use of Lewis acid led readily and cleanly in high yields to hydroxyphenols resulting from a ring opening (scheme 9, table 5).

Scheme 9

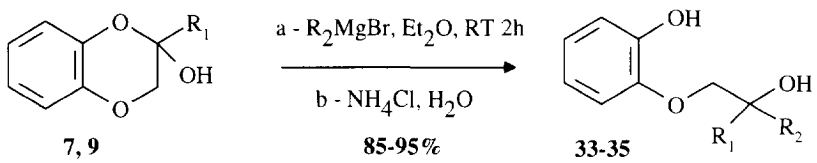


Table 5 : Ring Opening Reaction: Synthesis of Hydroxyphenols

Starting material	R_1	R_2	Product	Yield
7	CH_3	C_2H_5	**33**	95%
7	CH_3	C_3H_7	**34**	85%
9	C_6H_5	CH_3	**35**	89%

In light of these facts, within the context of developing a new efficient synthetic route to all expected products **IV** (scheme 1), the ring closure of the hydroxyphenol **33** by dehydrative cyclization was studied.

After various attempts of cyclization following established procedures[18] reported in table 6, it appeared that the procedure performed by short heating in toluene with the strongly acid ion exchanger Amberlyst-15 as catalyst gave the best result with 52% of expected benzodioxin **36**. However, similar yields were obtained with cyclization methods **E**, **F** using respectively a catalytic amount of *p*-toluenesulfonic acid in 1,2-dichloromethane or oxalyl chloride[19] in the presence of triethylamine. Procedures **A**, **B**, **D** were inefficient.

Table 6 : Dehydrative Cyclization of Hydroxyphenol **33**

	Method	Yield of obtained compound 36
A	PPA	unchanged starting material
B	P_2O_5 / CH_2Cl_2	decomposition
C	Amberlyst-15 / toluene	52%
D	2% sulfuric acid in acetic acid	complicated mixture
E	PTSA / $(CH_2Br)_2$	50%
F	$(COCl)_2$, TEA, DMF	50%

Under similar conditions using the ion exchanger Amberlyst-15 in toluene, the cyclization of the compounds **33-35** gave in modest yields the expected 2,3-dihydro-1,4-benzodioxinic analogs **36**, **30**, **37** (scheme 10, table 7). It must be noted that additional evidence for the proposal structures related upon came from the comparison of the structural assignments of the compound **30** previously obtained by catalytic reduction of the allylic analog.

Scheme 10

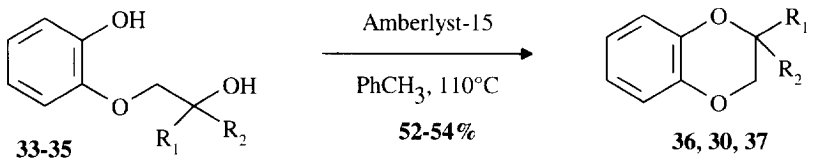


Table 7 : Cyclization of Hydroxyphenols

Starting material	R_1	R_2	Product	Yield
33	CH_3	C_2H_5	**36**	52%
34	CH_3	C_3H_7	**30**	54%
35	C_6H_5	CH_3	**37**	54%

In summary, the present article developed new efficient synthetic routes to rare 2,2-disubstituted-2,3-dihydro-1,4-benzodioxinic derivatives *via* oxymercuration-demercuration reaction, Lewis acid promoted nucleophilic substitution reaction and cyclization of suitable hydroxyphenols.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Melting points were determined on a Kofler apparatus and were uncorrected. The IR spectra were obtained on a Perkin-Elmer 196 infrared-spectrometer. The ^{1}H-NMR spectra were recorded at 300 MHz with a Bruker AM 300WB spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as an internal standard (δ units). Mass spectra were measured on a Nermag R-10-10C spectrometer. Analytical thin layer chromatography (tlc) was performed on Merck 60F-254 silica gel plates. Preparative column chromatography was performed by using Merck silica gel (70-230 mesh). The unsaturated and saturated benzodioxinic precursors **1**, **2**, **4-6**, **13** were obtained according to the literature procedures[11, 12, 13].

2-Phenyl-1,4-benzodioxin (3)

To a stirred suspension of tetrakis(triphenylphosphine)palladium (0.163 g, 0.14 mmol) in 15 ml of toluene in the presence of 0.470 ml of an aqueous solution of 2M Na_2CO_3 were added 0.630 g (5.2 mmol) of phenylboronic acid in 2 ml of ethanol and 1 g of 2-bromo-1,4-benzodioxin **13**[11] (4.7 mmol). The mixture was refluxed for 8 hours under vigorous stirring. After the reaction was complete, the residual phenylboronic acid was oxidized by 30%-H_2O_2 (0.2 ml) at room temperature for 30 minutes. The solvent was concentrated with a vacuum rotatory evaporator. The product was extracted with ether, washed by a satured NaCl solution, and finally dried over magnesium sulfate. Column chromatography (eluent: petroleum ether 100%) gave the product as colorless needles. Yield : 96%. mp 65°C [lit.[11] mp 65°C]. IR (KBr) : ν (cm^{-1}) : 1250 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.48-7.24 (m, 5H, $H_{arom.}$), 6.90-6.68 (m, 4H, $H_{arom.}$), 6.48 (s, 1H, H_3).

2-Substituted-2-hydroxy-2,3-dihydro-1,4-benzodioxins 8-12: General Procedure

To a stirred suspension of mercuric acetate (2.088 g, 6 mmol) in THF/H_2O (5 ml / 5 ml) were added 3 mmol of 2,3-dihydro-1,4-benzodioxinic derivatives (**1-6**). The mixture was stirred at room temperature. After the reaction was complete, 0.351 g (6 mmol) of NaCl were incorporated and 15 minutes later 0.228 g (6 mmol) of $NaBH_4$ were added dropwise to the mixture at low temperature. After the reduction was complete, the mixture was saturated with NaCl. The products were extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and evaporated *in vacuo*. Column chromatography (eluent: petroleum ether / ethyl acetate: 8/2) gave the products.

2-Butyl-2-hydroxy-2,3-dihydro-1,4-benzodioxin (8)

This compound was obtained as colorless needles. Yield : 87%. mp 45°C. IR (KBr) : ν (cm^{-1}) : 3580-3270 (OH), 1275 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.98-6.79 (m, 4H, $H_{arom.}$), 4.08 (d, J = 11.0Hz, 1H, H_3), 3.87 (d, J = 11.0Hz, 1H, $H_{3'}$), 3.35 (s, 1H, OH), 1.92-1.27 (m, 6H, 3xCH_2), 0.96 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 226 (M+18). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21 ; H, 7.74. Found : C, 69.42 ; H, 7.84.

2-Hydroxy-2-phenyl-2,3-dihydro-1,4-benzodioxin (9)

This compound was obtained as colorless needles. Yield : 90%. mp 122°C. IR (KBr) : ν (cm^{-1}) : 3550-3230 (OH), 1250 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.73-6.92 (m, 9H, $H_{arom.}$), 4.22 (d, J = 11.0Hz, 1H, H_3), 3.88 (d, J = 11.0Hz, 1H, $H_{3'}$), 3.50 (s, 1H, OH). MS (CI/NH_3) *m/z* : 246 (M+18). Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67 ; H, 5.30. Found : C, 73.85 ; H, 5.65.

2-Hydroxy-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin (10)

This compound was obtained as colorless needles. Yield : 76%. mp 116°C. IR (KBr) : ν (cm^{-1}) : 3510-3265 (OH), 1265 (C-O). ^{1}H-NMR ($CDCl_3$-D_2O) : δ ppm 6.97-6.86 (m, 4H, $H_{arom.}$), 4.18 (d, J = 11.7Hz, 1H, H_3), 4.02 (d, J = 11.7Hz, 1H, $H_{3'}$), 3.85 (d, J = 11.0Hz, 1H, CH_2OD), 3.72 (d, J = 11.0Hz, 1H, CH_2OD). MS (CI/NH_3) *m/z* : 200 (M+18). Anal. Calcd for $C_9H_{10}O_4$: C, 59.33 ; H, 5.54. Found : C, 59.45 ; H, 5.35.

2-Benzyloxymethyl-2-hydroxy-2,3-dihydro-1,4-benzodioxin (11)

This compound was obtained as colorless needles. Yield : 76%. mp 78°C. IR (KBr) : ν (cm^{-1}) : 3520-3255 (OH), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.41-7.24 (m, 5H, $H_{arom.}$), 6.96-6.82 (m, 4H, $H_{arom.}$) 4.72 (d, J = 11.0Hz, 1H, OCH_2Ph), 4.65 (d, J = 11.0Hz, 1H, OCH_2Ph), 4.10 (d, J = 11.5Hz, 1H, H_3), 3.99 (d, J = 11.5Hz, 1H, $H_{3'}$), 3.76 (s, 1H, OH), 3.60 (d, J = 10.4Hz, 1H, CH_2O), 3.55 (d, J = 10.4Hz, 1H, CH_2O). MS (CI/NH_3) *m/z* : 290 (M+18). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57 ; H, 5.94. Found : C, 70.65 ; H, 5.85.

2-Hydroxy-2-methoxymethyl-2,3-dihydro-1,4-benzodioxin (12)

This compound was obtained as a colorless oil. Yield : 78%. IR (neat) : ν (cm^{-1}) : 3500-3250 (OH). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.96-6.83 (m, 4H, $H_{arom.}$), 4.13 (d, J = 11.0Hz, 1H, H_3), 4.01 (d, J = 11.0Hz, 1H, $H_{3'}$), 3.79 (s, 1H, OH), 3.65 (d, J = 10.3Hz, 1H, $\mathbf{CH_2}OCH_3$), 3.58 (d, J = 10.3Hz, 1H, $\mathbf{CH_2}OCH_3$), 3.49 (s, 3H, OCH_3). MS (CI/NH_3) *m/z* : 214 (M+18). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.21 ; H, 6.16. Found : C, 61.31 ; H, 5.98.

2-Substituted-2-cyano or 2-allyl-2,3-dihydro-1,4-benzodioxins : General Procedure

Under an argon atmosphere at -78°C, 12 mmol of silylated reagents and then dropwise 18 mmol (0.225 ml) of BF_3-etherate were added to a stirred solution of 6 mmol of hydroxy derivative (**7-12**) in 30 ml of dry dichloromethane. After 3 hours at low temperature, the cooling bath was removed and the mixture was stirred at room temperature. After hydrolysis with methanol and water, the product was extracted with dichloromethane. The organic layers were washed with a concentrated $NaHCO_3$ solution, dried over magnesium sulfate and evaporated *in vacuo*. Column chromatography (eluent: petroleum ether/ethyl acetate: 9/1) gave the product.

2-Methyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (14)

This compound was obtained as colorless needles. Yield : 85%. mp 88°C. IR (KBr) : ν (cm^{-1}) : 2220 (CN), 1250 (C-O).^{1}H-NMR ($CDCl_3$) : δ ppm 7.02-6.89 (m, 4H, $H_{arom.}$), 4.4 (d, J = 11.6Hz, 1H, H_3), 3.93 (d, J = 11.6Hz, 1H, $H_{3'}$), 1.78 (s, 3H, CH_3). MS (CI/NH_3) *m/z* : 193 (M+18).

2-Butyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (15)

This compound was obtained as colorless oil. Yield : 81%. IR (neat) : ν (cm^{-1}) : 2205 (CN), 1265 (C-O).^{1}H-NMR ($CDCl_3$) : δ ppm 6.98-6.86 (m, 4H, $H_{arom.}$), 4.40 (d, J = 11.5Hz, 1H, H_3), 3.96 (d, J = 11.5Hz, 1H, $H_{3'}$), 2.03-1.33 (m, 6H, $3xCH_2$), 0.98 (t, J = 7.1Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 235 (M+18). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86 ; H, 6.97 ; N,6.44. Found : C, 71.68 ; H, 7.04 ; N, 6.51.

2-Phenyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (16)

This compound was obtained as colorless needles. Yield : 76%. mp 44°C. IR (KBr) : ν (cm^{-1}) : 2230 (CN), 1260 (C-O).^{1}H-NMR ($CDCl_3$) : δ ppm 7.69-7.63 (m, 5H, $H_{arom.}$), 7.56-7.47 (m, 4H, $H_{arom.}$), 4.48 (d, J = 11.7Hz, 1H, H_3), 4.02 (d, J = 11.7Hz, 1H, $H_{3'}$). MS (CI/NH_3) *m/z* : 255 (M+18). Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.93 ; H, 4.67 ; N, 5.91. Found : C, 75.78 ; H, 4.84 ; N, 6.11.

2-Hydroxymethyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (17)

This compound was obtained as colorless oil. Yield : 45%. IR (neat) : ν (cm^{-1}) : 3400-3250 (OH), 2240 (CN), 1265 (C-O).^{1}H-NMR ($CDCl_3$-D_2O) : δ ppm 7.24-6.89 (m, 4H, $H_{arom.}$), 4.51 (dd, J = 11.7Hz, J = 1.4Hz, 1H, H_3), 4.16 (dd, J = 11.7Hz, J = 1.4Hz, 1H, $H_{3'}$), 4.02 (d, J = 11.5Hz, 1H, CH_2OD), 3.95 (d, J = 11.5Hz, 1H, CH_2OD). MS (CI/NH_3) *m/z* : 209 (M+18). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82 ; H, 4.75 ; N, 7.33. Found : C, 62.98 ; H, 4.84 ; N, 7.21.

2-Benzyloxymethyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (18)

This compound was obtained as colorless oil. Yield : 78%. IR (neat) : ν (cm^{-1}) : 2210 (CN), 1265 (C-O).^{1}H-NMR ($CDCl_3$) : δ ppm 7.5-6.85 (m, 9H, $H_{arom.}$), 4.86 (s, 2H, CH_2Ph), 4.50 (d, J = 11.7Hz, 1H, H_3), 4.27 (d, J = 11.7Hz, 1H, $H_{3'}$), 3.95 (dd, J = 11.0Hz, J = 1.4Hz, 1H, **CH_2**O), 3.66 (dd, J = 11.0Hz, J = 1.4Hz, 1H, **CH_2**O). MS (CI/NH_3) *m/z* : 254 (M+18). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58 ; H, 5.38 ; N, 4.97. Found : C, 72.74 ; H, 5.54 ; N, 5.01.

2-Methyloxymethyl-2,3-dihydro-1,4-benzodioxin-2-carbonitrile (19)

This compound was obtained as colorless needles. Yield : 76%. mp 68°C. IR (KBr) : ν (cm^{-1}) : 2210 (CN), 1260 (C-O).^{1}H-NMR ($CDCl_3$) : δ ppm 7.02-6.88 (m, 4H, $H_{arom.}$), 4.51 (d, J = 11.7Hz, 1H, H_3), 4.12 (d, J = 11.7Hz, 1H, $H_{3'}$), 3.87 (d, J = 9.6Hz, 1H, **CH_2**OCH_3), 3.73 (d, J = 9.6Hz, 1H, **CH_2**OCH_3), 3.52 (s, 3H, OCH_3). MS (CI/NH_3) *m/z* : 223 (M+18). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.39 ; H, 5.40 ; N, 6.82. Found : C, 64.42 ; H, 5.44 ; N, 6.91.

2-Allyl-2-methyl-2,3-dihydro-1,4-benzodioxin (20)

This compound was obtained as colorless oil. Yield : 74%. IR (neat) : ν (cm^{-1}) : 1645 (C=C), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.91-6.79 (m, 4H, $H_{arom.}$), 5.94-5.78 (m, 1H, **CH**=CH_2), 5.18-5.10 (m, 2H, CH=**CH_2**), 3.96 (d, J = 11.0Hz, 1H, H_3), 3.85 (d, J = 11.0Hz, 1H, $H_{3'}$), 2.48-2.31 (m, 2H, **CH_2**CH), 1.3 (s, 3H, CH_3). MS (CI/NH_3) *m/z* : 208 (M+18). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76 ; H, 7.42. Found : C, 75.81 ; H, 7.54.

2-Allyl-2-butyl-2,3-dihydro-1,4-benzodioxin (21)

This compound was obtained as colorless oil. Yield : 76%. IR (neat) : ν (cm^{-1}) : 1650 (C=C), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.90-6.77 (m, 4H, $H_{arom.}$), 5.92-5.77 (m, 1H, **CH**=CH_2), 5.16-5.10 (m, 2H, CH=**CH_2**), 3.97 (d, J = 11.0Hz, 1H, H_3), 3.88 (d, J = 11.0Hz, 1H, $H_{3'}$), 2.49-2.34 (m, 2H, **CH_2**CH), 1.71-1.25 (m, 6H, 3xCH_2), 0.90 (t, J = 7.1Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 250 (M+18). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.56 ; H, 8.67. Found : C, 77.62 ; H, 8.70.

2-Allyl-2-phenyl-2,3-dihydro-1,4-benzodioxin (22)

This compound was obtained as colorless oil. Yield : 76%. IR (neat) : ν (cm^{-1}) : 1640 (C=C), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.48-6.75 (m, 9H, $H_{arom.}$), 5.75-5.58 (m, 1H, **CH**=CH_2), 5.05-4.96 (m, 2H, CH=**CH_2**), 4.31 (d, J = 1.4Hz, 1H, H_3), 4.19 (d, J = 1.4Hz, 1H, $H_{3'}$), 2.81-2.62 (m, 2H, **CH_2**CH). MS (CI/NH_3) *m/z* : 270 (M+18). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.92 ; H, 6.40. Found : C, 80.84 ; H, 6.54.

2-Allyl-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxin (23)

This compound was obtained as colorless oil. Yield : 73%. IR (neat) : ν (cm^{-1}) : 3520-3420 (OH), 1660 (C=C), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.95-6.80 (m, 4H, $H_{arom.}$), 5.94-5,78 (m, 1H, **CH**=CH_2), 5.21-5.15 (m, 2H, CH=**CH_2**), 4.13 (d, J = 11.1Hz, 1H, H_3), 4.02 (d, J = 11.1Hz, 1H, $H_{3'}$), 3.79-3.74 (m, 2H, CH_2OH), 2.57-2.42 (m, 2H, **CH_2**CH), 1.80 (m, 1H, OH). MS (CI/NH_3) *m/z* : 224 (M+18). Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88 ; H, 6.84. Found : C, 69.94 ; H, 6.64.

2-Allyl-2-benzyloxymethyl-2,3-dihydro-1,4-benzodioxin (24)

This compound was obtained as colorless oil. Yield : 76%. IR (neat) : ν (cm^{-1}) : 1645 (C=C), 1260 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.39-7.19 (m, 5H, $H_{arom.}$), 6.91-6.74 (m, 4H, $H_{arom.}$), 5.95-5.80 (m, 1H, **CH**=CH_2), 5.20-5.10 (m, 2H, CH=**CH_2**), 4.57 (s, 2H, CH_2Ph), 4.20 (d, J = 11.0Hz, 1H, H_3), 3.98 (d, J = 11.0Hz, 1H, $H_{3'}$), 3.55 (s, 2H, CH_2OBz), 2.62-2.44 (m, 2H, **CH_2**CH). MS (CI/NH_3) *m/z* : 314 (M+18). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00 ; H, 6.80. Found : C, 77.12 ; H, 6.74.

1-(2-Methyl-2,3-dihydro-1,4-benzodioxin-2-yl)-butan-1-one (25)

Under an argon atmosphere at -78°C, 0.520 g (4.08 mmol) of chlorotrimethylsilane was added dropwise to 0.200 g (1.14 mmol) of nitrile **14** in 3 ml of dry toluene. To the stirred mixture was added 1,5 ml (20.4 mmol) of propyl magnesium bromide in ether. After the reaction was complete, the mixture was hydrolyzed with a concentrated NH_4Cl solution. The product was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and evaporated *in vacuo*. Column chromatography (eluent: petroleum ether / ethyl acetate: 8/2) gave the product as colorless oil. Yield : 66%. IR (neat) : ν (cm^{-1}) : 1720 (C=O), 1260 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.98-6.80 (m, 4H, $H_{arom.}$), 4.48 (d, J = 11.0Hz, 1H, H_3), 3.82 (d, J = 11.0Hz, 1H, $H_{3'}$), 2.78-2.30 (m, 2H, CH_2), 1.60-1.46 (m, 2H, CH_2CH_3), 1.40 (s, 3H, CH_3), 0.83 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 221 (M+1). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.88 ; H, 7.32. Found : C, 71.02 ; H, 7.45.

2-Substituted-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester derivatives : General Procedure

A stirred solution of product **14** or **16** (0.500 g) in 5 ml of ethanol was treated with 10% aqueous potassium hydroxyde (5 eq.). After 3 hours at room temperature and evaporation under reduced pressure of ethanol, the aqueous phase was acidified with HCl 2N. The combined extracts were dried over magnesium sulfate. Evaporation of the solvent yielded the crude acid which was immediatly used without further purification. The acid intermediate was refluxed for 2 hours in ethanol in the presence of a catalytic amount of *p*-toluene sulfonic acid. The solvent was removed under reduced pressure. Column chromatography (eluent: petroleum ether/ethyl acetate: 8/2) gave the products.

2-Methyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (26)

This compound was obtained as colorless needles. Yield : 70%. mp 40°C. IR (KBr) : ν (cm^{-1}) : 1745 (C=O), 1260 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.98-6.80 (m, 4H, $H_{arom.}$), 4.51 (d, J = 11.2Hz, 1H, H_3), 4.28-4.09 (m, 2H, CH_2CH_3), 3.88 (d, J = 11.2Hz, 1H, $H_{3'}$), 1.59 (s, 3H, CH_3), 1.21 (t, J = 6.9Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 240 (M+18). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85 ; H, 6.36. Found : C, 64.98 ; H, 6.44.

2-Phenyl-2,3-dihydro-1,4-benzodioxin-2-carboxylic acid ethyl ester (27)

This compound was obtained as a colorless oil. Yield : 72%. IR (neat) : ν (cm^{-1}) : 1750 (C=O), 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.68-6.84 (m, 9H, $H_{arom.}$), 4.89 (d, J = 11.0Hz, 1H, H_3), 4.27-4.11 (m, 3H, CH_2CH_3, $H_{3'}$), 1.15 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 303 (M+18). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82 ; H, 5.67. Found : C, 71.85 ; H, 5.72.

2-Substituted-2-hydroxymethyl-2,3-dihydro-1,4-benzodioxins : General Procedure

Under an argon atmosphere, 1 mmol of product **26** or **27** was added at low temperature to 1,5 mmol of $LiAlH_4$ in suspension in 10 ml of dry THF. After the reaction was complete, the product was hydrolyzed then extracted with diethylether. The combined extracts were dried over magnesium sulfate and evaporated under reduced pressure. Column chromatography (eluent: petroleum ether/ ethyl acetate: 8/2) gave the product.

2-Hydroxymethyl-2-methyl-2,3-dihydro-1,4-benzodioxin (28)

This compound was obtained as colorless needles. Yield : 88%. mp 60°C. IR (KBr) : ν (cm^{-1}) : 3500-3205 (OH), 1270 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.92-6.78 (m, 4H, $H_{arom.}$), 4.15 (d, J = 11.1Hz, 1H, H_3), 3.89 (d, J = 11.1Hz, 1H, $H_{3'}$), 3.69 (d, J = 12.0Hz, 1H, CH_2OH), 3.62 (d, J = 12.0Hz, 1H, CH_2OH), 2.50 (s, 1H, OH). MS (CI/NH_3) *m/z* : 198 (M+18). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65 ; H, 6.72. Found : C, 66.59 ; H, 6.68.

2-Hydroxymethyl-2-phenyl-2,3-dihydro-1,4-benzodioxin (29)

This compound was obtained as colorless needles. Yield : 85%. mp 82°C. IR (KBr) : ν (cm^{-1}) : 3580-3200 (OH), 1265 (C-O). ^{1}H-NMR ($CDCl_3$-D_2O) : δ ppm 7.48-6.80 (m, 9H, $H_{arom.}$), 4.51 (d, J = 11.0Hz, 1H, H_3), 4.43 (d, J = 11.0Hz, 1H, $H_{3'}$), 3.93 (d, J = 11.5Hz, 1H, CH_2OD), 3.82 (d, J = 11.5Hz, 1H, CH_2OD). MS (CI/NH_3) *m/z* : 260 (M+18). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36 ; H, 5.82. Found : C, 74.65 ; H, 5.87.

General procedure of catalytic hydrogenation

The allylic compounds **20-22** (2 mmol) and 10% palladium on charcoal (0.125 g) were suspended in 5 ml of ethanol and stirred in a Parr bottle under H_2 pressure (30 psi) for 3 hours at room temperature. The mixture was filtered through Celite and evaporated. Pure materials **30-32** were obtained as colorless oil by purification on silica gel column chromatography (eluent: petroleum ether/ethyl acetate: 8/2).

2-Methyl-2-propyl-2,3-dihydro-1,4-benzodioxin (30)

This compound was obtained as colorless oil. Yield : 98%. IR (neat) : ν (cm^{-1}) : 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.90-6.77 (m, 4H, $H_{arom.}$), 3.94 (d, J = 11.0Hz, 1H, H_3), 3.85 (d, J = 11.0Hz, 1H, $H_{3'}$), 1.73-1.37 (m, 4H, $(\mathbf{CH_2})_2CH_3$), 1.28 (s, 3H, CH_3), 0.94 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 193 (M+1). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97 ; H, 8.38. Found : C, 74.85 ; H, 8.56.

2-Butyl-2-propyl-2,3-dihydro-1,4-benzodioxin (31)

This compound was obtained as colorless oil. Yield : 95%. IR (neat) : ν (cm^{-1}) : 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.02-6.89 (m, 4H, $H_{arom.}$), 3.98 (d, J = 11.0Hz, 1H, H_3), 3.88 (d, J = 11.0Hz, 1H, $H_{3'}$),

1.76-1.41 (m, 10H, 3xCH_2, 2xCH_2), 1.30 (t, J = 7.4Hz, 3H, CH_2CH_3), 0.94 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 235 (M+1). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.89 ; H, 9.46. Found : C, 76.92 ; H, 9.56.

2-Phenyl-2-propyl-2,3-dihydro-1,4-benzodioxin (32)

This compound was obtained as colorless oil. Yield : 97%. IR (neat) : ν (cm^{-1}) : 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.45-7.2 (m, 5H, $H_{arom.}$), 7.10-6.76 (m, 4H, $H_{arom.}$), 4.23 (d, J = 11.0Hz, 1H, H_3), 4.11 (d, J = 11.0Hz, 1H, $H_{3'}$), 2.02-1.71 (m, 2H, CH_2), 1.44-1.01 (m, 2H, CH_2), 0.78 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 272 (M+18). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28 ; H,.7.14 Found : C, 80.34 ; H, 7.16.

Synthesis of hydroxyphenols 33-35 : General Procedure

Under an argon atmosphere at 0°C, 1.2 equivalents of Grignard reagent were added dropwise to 0.500 g of alcohol **7** or **9** in 8 ml of dry diethylether. After the reaction was complete, the mixture was treated with a concentrated NH_4Cl solution. The product was extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and evaporated *in vacuo*. Column chromatography (eluent: petroleum ether/ethyl acetate: 8/2) gave the products as colorless oil.

2-(2-Hydroxy-2-methyl-butoxy)-phenol (33)

This compound was obtained as colorless needles. Yield : 95%. mp 82°C. IR (KBr) : ν (cm^{-1}) : 3570-3055 (OH), 1245 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.50 (s, 1H, OH), 6.99-6.75 (m, 4H, $H_{arom.}$), 3.86 (d, J = 9.5Hz, 1H, OCH_2), 3.79 (d, J = 9.5Hz, 1H, OCH_2), 3.40 (s, 1H, OH), 1.70 (q, J = 7.3Hz, 2H, CH_2CH_3), 1.30 (s, 3H, CH_3), 0.97 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 214 (M+18). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32 ; H, 8.22. Found : C, 67.54 ; H, 8.42.

2-(2-Hydroxy-2-methyl-pentoxy)-phenol (34)

This compound was obtained as colorless oil. Yield : 85%. IR (neat) : ν (cm^{-1}) : 3510-3200 (OH), 1245 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.25 (s, 1H, OH), 6.97-6.73 (m, 4H, $H_{arom.}$), 3.86 (d, J = 9.6Hz, 1H, OCH_2), 3.80 (d, J = 9.6Hz, 1H, OCH_2), 3.00 (s, 1H, OH), 1.71-1.30 (m, 4H, CH_2CH_2), 1.31 (s, 3H, CH_3), 0.94 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 228 (M+18). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54 ; H, 8.63. Found : C, 68.74 ; H, 8.57.

2-(2-Hydroxy-2-phenyl-propoxy)-phenol (35)

This compound was obtained as colorless oil. Yield : 85%. IR (neat) : ν (cm^{-1}) : 3400-3150 (OH), 1245 (C-O). ^{1}H-NMR ($CDCl_3$-D_2O) : δ ppm 7.53-7.27 (m, 5H, $H_{arom.}$), 6.97-6.74 (m, 4H, $H_{arom.}$), 4.12 (d, J = 9,5Hz, 1H, CH_2), 4.08 (d, J = 9.5Hz, 1H, CH_2), 1.80 (s, 3H, CH_3). MS (CI/NH_3) *m/z* : 262 (M+18). Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75 ; H, 6.60. Found : C, 73.86 ; H, 6.84.

General procedure of dehydrative cyclization

Diols (**33-35**) were refluxed for 24 hours in 5 ml of dry toluene in the presence of a drop of Amberlyst-15. The mixture was filtered, concentrated, and column chromatographed (eluent: petroleum ether/ethyl acetate: 8/2).

2-Ethyl-2-methyl-2,3-dihydro-1,4-benzodioxin (36)

This compound was obtained as colorless oil. Yield : 52%. IR (neat) : ν (cm^{-1}) :1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 6.90-6.77 (m, 4H, $H_{arom.}$), 3.94 (d, J = 11.0Hz, 1H, OCH_2), 3.86 (d, J = 11.0Hz, 1H, OCH_2), 1.86-1.47 (m, 2H, CH_2CH_3), 1.28 (s, 3H, CH_3), 0.97 (t, J = 7.3Hz, 3H, CH_2CH_3). MS (CI/NH_3) *m/z* : 179 (M+1). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13 ; H, 7.92. Found : C, 74.35 ; H, 7.86.

2-Methyl-2-phenyl-2,3-dihydro-1,4-benzodioxin (37)

This compound was obtained as colorless oil. Yield : 54%. IR (neat) : ν (cm^{-1}) : 1265 (C-O). ^{1}H-NMR ($CDCl_3$) : δ ppm 7.51-6.76 (m, 9H, $H_{arom.}$), 4.26 (d, J = 11.0Hz, 1H, H_3), 4.12 (d, J = 11.0Hz, 1H, $H_{3'}$), 1.64 (s, 3H, CH_3). MS (CI/NH_3) *m/z* : 244 (M+18). Anal. Calcd for $C_{15}H_{14}O_2$: C, 74.97 ; H, 8.38. Found : C, 74.85 ; H, 8.56.

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