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Convenient Synthesis of 5-Substituted-6-Methoxy or 6-Hydroxy-2,3-Dihydro-1,4-Benzodioxins via Lithiated Intermediates

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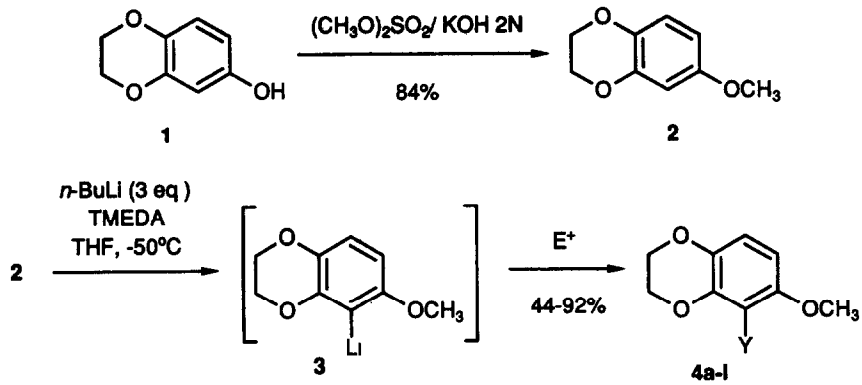
Abstract: The 6-methoxy and 6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxins can be lithiated at the 5-position to give intermediate lithio derivatives which react with various electrophiles to afford, after hydrolysis, 5-substituted-6-methoxy and 6-hydroxy-2,3-dihydro-1,4-benzodioxins

The 2,3-dihydro-1,4-benzodioxin subunit is present in many natural products such as neoglycans[1], purpurenol[2], and synthetic derivatives exhibiting biological activity[3]. Moreover, this structure constitutes an ideal precursor for access to 1,4-benzodioxins, constituting a heterocyclic system which has recently been gaining attention[4] Procedures permitting regioselective functionalization on the homo- and heterocycle of 2,3-dihydro-1,4-benzodioxin are thus of great interest

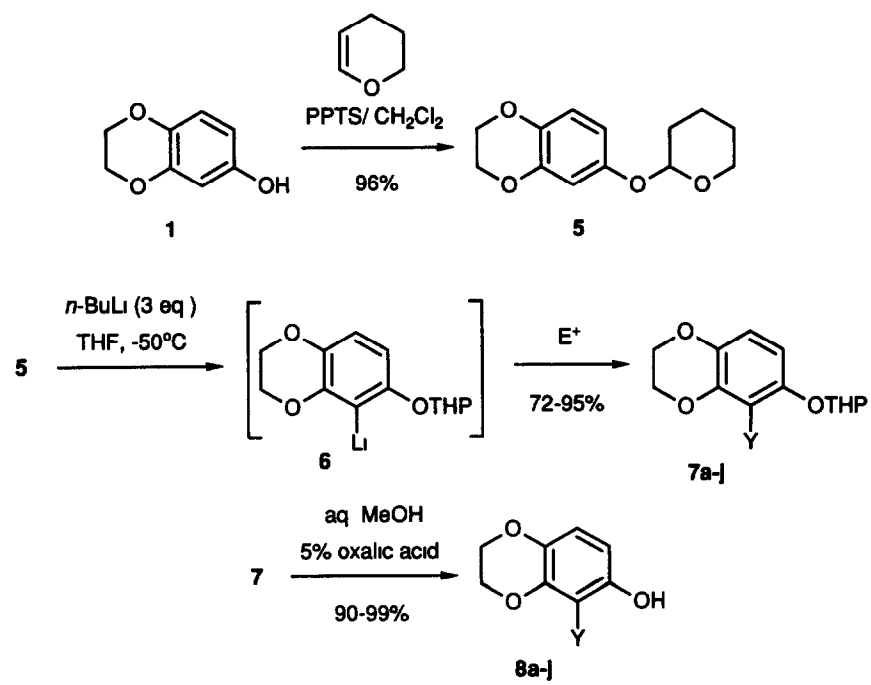
The most direct access to derivatives **8** involved the *ortho*-lithiation[5] at C_5 of the unprotected 6-hydroxy-2,3-dihydro-1,4-benzodioxin **1**[6], followed by reaction with various electrophiles. Unfortunately the experimental conditions required for lithiation[7] induced the cleavage of the heterocyclic ring[8] We therefore had to find a protective group for the phenolic function allowing both direct *ortho*-lithiation at C_5 and the conservation of the integrity of the heterocyclic system First, we have shown that 5-substituted-6-methoxy-2,3-dihydro-1,4-benzodioxins could be obtained in fair to good yields via the 5-lithio derivative[9] After experimentation with various temperatures, bases and molecular ratio, treatment of **2** with 3.0 equivalents of butyllithium at -50°C in tetrahydrofuran in the presence of 6 equivalents of N,N,N',N'-tetramethylenediamine (TMEDA), was found to be the most effective in converting **2** into the 5-lithio derivative **3** This carbanion subsequently reacted, at -50°C, with various electrophiles (6 equivalents) to give compounds **4** in fair to good yields (Scheme 1, Table 1) When the reaction was performed at lower temperatures (<-50°C), incomplete deprotonation was observed whereas higher ones induced a cleavage of the 2,3-dihydro-1,4-benzodioxin ring[8]

In the course of our work concerning access to new polyheterocyclic systems with potential pharmacological value such as coumarins[10] and benzodioximic analogs of psoralens[11], we needed a direct method for preparing substituted 6-hydroxy-2,3-dihydro-1,4-benzodioxin derivatives bearing hydroxyalkyl or hydroxyaryl groups at the 5-position In the later case, however, conditions for cleaving of the methoxy group were incompatible with the presence of the sensitive hydroxyl group in compounds **4**



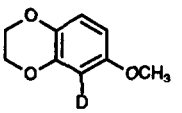
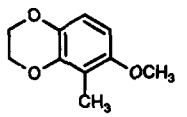
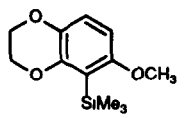
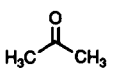
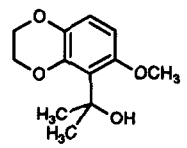
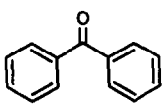
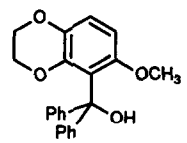
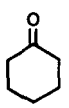
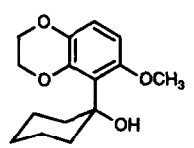
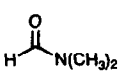
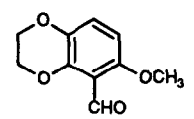
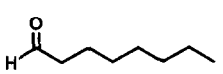
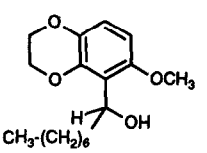
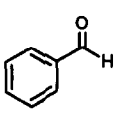
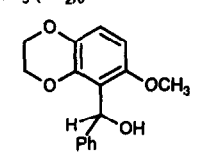
Scheme 1

We therefore had to protect the phenol with a group allowing both direct *ortho*-lithiation at C_5 and the conservation of the derivatives **8** during the deprotection of the phenolic group. After disappointing results obtained with the OMOM[12] and $OCONEt_2$[13] groups as functionalities promoting and stabilizing *ortho*-metalation, we opted for the tetrahydropyranyl ether group (OTHP) Indeed, this old underdeveloped *ortho*-directing group in the masked phenol metalation[14] appeared very attractive for our purpose because of its easy cleavage We found that the experimental conditions previously described for the metalation of **2** (except for the presence of TMEDA which is not necessary), also gave the best results for the functionalization of **5** Compounds **8** were obtained in good yields after easy deprotection of the tetrahydropyranyl ether protecting group (Scheme 2, Table 2)



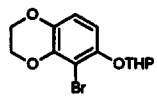
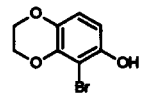
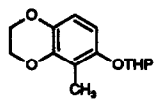
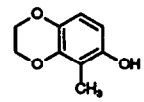
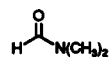
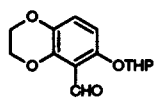
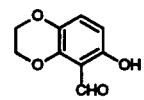
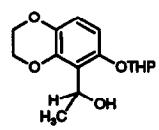
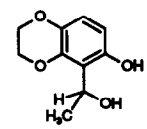
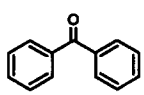
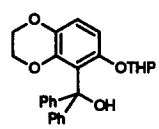
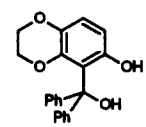
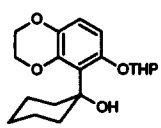
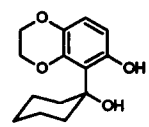
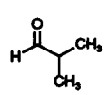
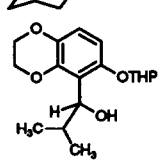
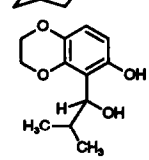
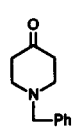
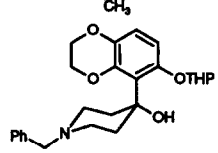
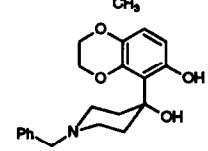
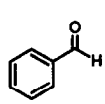
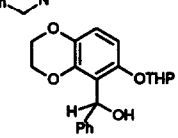
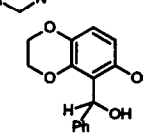
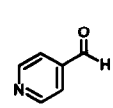
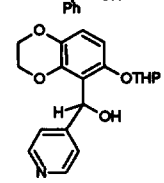
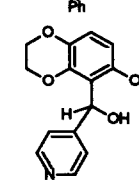
Scheme 2

Table 1. Synthesis of 5-substituted-6-methoxy-2,3-dihydro-1,4-benzodioxins **4** from **2**.

	Electrophile (E^+)	Compound **4**	Yield[a] (%)
a	D_2O		80
b	ICH_3		72
c	$ClSi(CH_3)_3$		92
d			44
e			72
f			82
g			66
h			87
i			84

[a] Yields of pure isolated product based on **2**

Table 2. Synthesis of 5-substituted-6-tetrahydropyranyloxy and 6-hydroxy-2,3-dihydro-1,4-benzodioxins 7 and 8 from 5.

	Electrophile (E^+)	Compound 7	Yield[a] (%)	Compound 8	Yield[a] (%)
a	$BrCF_2CF_2Br$		95		97
b	ICH_3		73		99
c			72		90
d			89		92
e			76		94
f			85		94
g			89		95
h			73		90
i			76		91
j			76		95

[a] Yields of pure isolated product based on 5 and 7, respectively

Using the directed *ortho*-metalation reactions, we developed a convenient and regiospecific general method for preparing 6-methoxy or 6-hydroxy-2,3-dihydro-1,4-benzodioxins variously substituted at C_5.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were obtained using a Perkin-Elmer 196 and the ^{1}H-NMR spectra were recorded at 60 MHz on a Hitachi-Perkin R 24B spectrometer (compounds **4**) and at 300 MHz on a Bruker AM 300WB spectrometer (compounds **1**, **2**, **5**, **7** and **8**). Chemical shifts are reported in parts per million downfield from tetramethylsilane (δ units) Analytical thin layer chromatography (tlc) was performed on Merk 60F-254 silica gel plates. Preparative column chromatography was performed by using Merk silica gel (70-230 mesh) Mass spectra were measured on a Nermag R-10-10C spectrometer Tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone ketyl prior to use.

6-Hydroxy-2,3-dihydro-1,4-benzodioxin (1):
Compound **1** was readily obtained from the commercialy available 6-amino-2,3-dihydro-1,4-benzodioxin by a method previously described[6]. Yield 90%, IR (film) ν = 3600-3000 (OH), 1180 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ = 4 17-4 26 (m, 4H, OCH_2CH_2O), 6 33 (dd, $J_{5,7}$ = 2.76 Hz and $J_{7,8}$ = 8.69 Hz, 1H, H_7), 6 40 (d, $J_{5,7}$ = 2.76 Hz, 1H, H_5), 6 71 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_8), MS m/z = 153 (M+1) Anal Calcd for $C_8H_8O_3$ C 63 15, H 5 30 Found C 63 05, H 5 15

6-Methoxy-2,3-dihydro-1,4-benzodioxin (2):
To a stirred solution of **1** (0 5g, 3 29 mmol) in potassium hydroxide (KOH 2N, 2 ml), dimethylsulfate (0 456 g, 0 342 ml, 3 62 mmol) was slowly added. The mixture was then stirred at 60°C for 30 min and allowed to cool After extraction with diethyl ether, the product was purified by silica gel column chromatography (eluent petroleum ether/diethyl ether, 9.1) The solvent was evaporated to dryness to provide 0 454 g of **2** as a colorless oil. Yield 84%, IR (film) ν = 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$). δ = 3 73 (s, 3H, OCH_3), 4 18-4 26 (m, 4H, OCH_2CH_2O), 6 41 (dd, $J_{5,7}$ = 2 76 Hz and $J_{7,8}$ = 8 69 Hz, 1H, H_7), 6 45 (d, $J_{5,7}$ = 2 76 Hz, 1H, H_5), 6 76 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_8), MS m/z = 167 (M+1) Anal Calcd for $C_9H_{10}O_3$ C 65 05, H 6 06 Found C 64 96, H 5 95

6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxin (5):
To a solution of **1** (3 8 g, 25 6 mmol) and pyridinium *p*-toluene sulfonate (PPTS, 0 64 g, 0 385 mmol) in methylene chloride (15 ml), dihydropyran (3 23 g, 3 5 ml, 38.5 mmol) was added and the mixture was stirred at room temperature for 2 h The solution was washed with a basic solution (NaOH 5%) and the product purified by silica gel column chromatography (eluent petroleum ether/ diethyl ether, 9 1). The solvent was evaporated to give 5 78 g of **5** as a colorless oil Yield 98%, IR (film) ν = 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ = 1 5-2 04 (m, 4H, H_{THP}), 3 46-3.52 (m, 2H, H_{THP}), 3 84-3 97 (m, 2H, H_{THP}), 4.17-4 26 (m, 4H, OCH_2CH_2O), 5 27 (t, J = 3 16 Hz, 1H, H_{THP}), 6 54 (dd, $J_{5,7}$ = 2 76 Hz and $J_{7,8}$ = 8 69 Hz, 1H, H_7), 6 63 (d, $J_{5,7}$ = 2 76 Hz, 1H, H_5), 6 76 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_8), MS m/z = 237 (M+1)

Synthesis of 5-substituted-6-methoxy-2,3-dihydro-1,4-benzodioxins (4) General procedure:
To a stirred solution of **2** (0 5 g, 3 01 mmol) in THF (15 ml) were added TMEDA (3 ml, 18 06 mmol) and *n*-butyllithium 1 6 M in hexane (5 65 ml, 9 03 mmol) at -50°C under an argon atmosphere The mixture was stirred at -50°C for 2 h, then the electrophile (15 06 mmol) was added The solution was stirred at -50°C for 2 h and then allowed to warm to room temperature After hydrolysis and extraction at neutral pH with diethyl ether, the crude products were purified by chromatography on silica gel (eluent petroleum ether/diethyl ether, 7 3)

5-Deuterio-6-methoxy-2,3-dihydro-1,4-benzodioxin (4a):
Reaction with deuterium oxide (0 302 g, 0.27 ml) gave 0 484 g of compound **4a** as a colorless oil. Yield. 80%, IR (film)· ν = 1100 cm^{-1}, ^{1}H-NMR (CCl_4) δ = 3 66 (s, 3H, OCH_3), 4 10-4 20 (m, 4H, OCH_2CH_2O), 6.24 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6.48 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}) Anal. Calcd. for $C_9H_9O_3$· C 53.73, H 4 51. Found: C 53.50; H 4.60

5-Methyl-6-methoxy-2,3-dihydro-1,4-benzodioxin (4b):
Reaction with iodomethane (2 14 g, 0.937 ml) gave 0.39 g of compound **4b** as colorless needles Yield. 72%; mp = 38-39°C; IR (KBr)· ν = 1120 (ether) cm^{-1}; ^{1}H-NMR (CCl_4)· δ = 2.00 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4 11-4 21 (m, 4H, OCH_2CH_2O), 6 21 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 54 (d, $J_{7,8}$ = 9.00 Hz, 1H, H_{arom}) Anal. Calcd for $C_{10}H_{12}O_3$ C 66 65, H 6 71 Found C 66 48; H 6 62

5-Trimethylsilyl-6-methoxy-2,3-dihydro-1,4-benzodioxin (4c):
Reaction with chlorotrimethylsilane (1 64 g, 1 91 ml) gave 0.657 g of compound **4c** as a colorless oil Yield 92%, IR (film) ν = 1100 cm^{-1}; ^{1}H-NMR (CCl_4) δ = 0 00 (s, 9H, $Si(CH_3)_3$), 3 80-3 86 (m, 4H, OCH_2CH_2O), 5.98 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 46 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}). Anal Calcd. for $C_{12}H_{18}O_3Si$· C 60 47, H 7 61 Found· C 60 63; H 7 85

2-[5-(6-Methoxy-2,3-dihydro-1,4-benzodioxinyl)]propan-2-ol (4d):
Reaction with acetone (0 875 g, 1 10 ml) gave 0.296 g of compound **4d** as a colorless oil Yield. 44%, IR (film) ν = 3600-3200 (OH), 1090 (ether) cm^{-1}, ^{1}H-NMR (CCl_4 + D_2O) δ = 1 60 (s, 6H, $CH(CH_3)_2$), 3 80 (s, 3H, OCH_3), 4 15-4 25 (m, 4H, OCH_2CH_2O), 6 20 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 50 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}) Anal. Calcd for $C_{12}H_{16}O_4$ C 64 27, H 7 19 Found C 64.20, H 7 12

1-[5-(6-Methoxy-2,3-dihydro-1,4-benzodioxinyl)]-1,1-diphenylmethanol (4e):
Reaction with benzophenone (2 74 g) gave 0 752 g of compound **4e** as colorless needles Yield: 72%, mp = 143-144°C; IR (KBr)· ν = 3500-3000 (OH), 1090 (ether) cm^{-1}, ^{1}H-NMR (CCl_4 + D_2O) δ = 3 33 (s, 3H, OCH_3), 4 05-4 15 (m, 4H, OCH_2CH_2O), 6 41 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 78 (d, $J_{7,8}$ = 9.00 Hz, 1H, H_{arom}), 7 15-7 50 (m, 10H, H_{arom}) Anal Calcd for $C_{22}H_{20}O_4$· C 75 84, H 5 69 Found· C 75 73, H 5 53

1-[5-(6-Methoxy-2,3-dihydro-1,4-benzodioxinyl)]cyclohexan-1-ol (4f):
Reaction with cyclohexanone (1 48 g, 1 56 ml) gave 0 65 g of compound **4f** as a colorless oil Yield 82%, IR (film) ν = 3600-3100 (OH), 1100 (ether) cm^{-1}, ^{1}H-NMR (CCl_4 + D_2O) δ = 0.66-2 50 (m, 8H, H_{cy}), 3 73 (s, 3H, OCH_3), 4 05-4 15 (m, 4H, OCH_2CH_2O), 6 31 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 58 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}) Anal Calcd for $C_{15}H_{20}O_4$· C 68 16; H 7 62 Found C 68 06; H 7 55

5-Formyl-6-methoxy-2,3-dihydro-1,4-benzodioxin (4g):
Reaction with dimethylformamide (1 1 g, 1 07 ml) gave 0 384 g of compound **4g** as colorless needles Yield 66%; mp = 122-123°C, IR (KBr) ν = 1670 (C=O), 1070 (ether) cm^{-1}, ^{1}H-NMR (CCl_4) δ = 3 86 (s, 3H, OCH_3), 4 20-4 50 (m, 4H, OCH_2CH_2O), 6 46 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 7 06 (d, $J_{7,8}$ = 9.00 Hz, 1H, H_{arom}), 10 46 (s, 1H, CHO) Anal Calcd for $C_{10}H_{10}O_4$ C 61 86, H 5 15 Found 61 98, H 5 23

1-[5-(6-Methoxy-2,3-dihydro-1,4-benzodioxinyl)]octan-1-ol (4h):
Reaction with octanal (1 93 g, 2 35 ml) gave 0 768 g of compound **4h** as a colorless oil Yield 87%, IR (film) ν = 3600-3100 (OH), 1100 (ether) cm^{-1}, ^{1}H-NMR (CCl_4 + D_2O): δ = 0.80-1.03 (m, 3H, $-(CH_2)_7CH_3$), 1 13-1 50 (m, 14H, $-(CH_2)_7CH_3$), 3 80 (s, 3H, OCH_3), 4 11-4 21 (m, 4H, OCH_2CH_2O), 4 73-5 00 (m, 1H, CHOH), 6 29 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6 59 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}) Anal Calcd for $C_{17}H_{25}O_4$ C 69 60, H 8 59 Found C 69 36, H 8 70

1-[5-(6-Methoxy-2,3-dihydro-1,4-benzodioxinyl)]-1-phenylmethanol (4i):
Reaction with benzaldehyde (1 6 g, 1 53 ml) gave 0.685 g of compound **4i** as a colorless oil. Yield: 84%, IR (film): ν = 3600-3000 (OH), 1100 (ether) cm^{-1}; ^1H-NMR (CCl_4 + D_2O)· δ = 3.60 (s, 3H, OCH_3), 4.05-4 15 (m, 4H, OCH_2CH_2O), 6.20 (s, 1H, CHOH), 6.26 (d, $J_{7,8}$ = 9 00 Hz, 1H, H_{arom}), 6.55 (d, $J_{7,8}$ = 9.00 Hz, 1H, H_{arom}), 6 93-7 36 (m, 5H, H_{arom}) Anal Calcd for $C_{16}H_{16}O_4$ C 70 57; H 5 92. Found· C 70 72; H 5 70

Synthesis of 5-substituted-6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxins (7). General procedure:
To a stirred solution of **5** (0 2 g, 0 847 mmol) in THF (10 ml) was added *n*-butyllithium 1 6 M in hexane (1 6 ml, 2.55 mmol) at -50°C under an argon atmosphere The mixture was stirred at -50°C for 2 h, then the electrophile (4 25 mmol) was added The solution was stirred at -50°C for 1 h and then allowed to warm to room temperature After hydrolysis and extraction at neutral pH with diethyl ether, the crude products were purified by chromatography on silica gel (eluent petroleum ether/diethyl ether, 9 1)

5-Bromo-6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxin (7a):
Reaction with 1,2-dibromotetrafluoroethane (0 48 ml) gave 0 264 g of compound **7a** as a colorless oil. Yield 95-99%, IR (film) ν = 1260 (ether) cm^{-1} ^1H-NMR ($CDCl_3$) δ = 1.5-2 16 (m, 4H, H_{THP}), 3.44-3.62 (m, 2H, H_{THP}), 3 84-4 05 (m, 2H, H_{THP}), 4 18-4 23 (m, 2H, OCH_2CH_2O), 4.31-4.36 (m, 2H, OCH_2CH_2O), 5 37 (t, J = 2 76 Hz, 1H, H_{THP}), 6 68 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), 6 77 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), MS· m/z = 315 (M), 317 (M+2)

5-Methyl-6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxin (7b):
Reaction with iodomethane (0 6 g, 0 27 ml) gave 0 155 g of compound **7b** as a colorless oil. Yield: 73%; IR (film) ν = 1260 (ether) cm^{-1}, ^1H-NMR ($CDCl_3$) δ = 1 5-2 09 (m,4H, H_{THP}), 2.12 (s, 3H, CH_3), 3 54-3 63 (m, 2H, H_{THP}), 3.89-3 97 (m, 2H, H_{THP}), 4 15-4 20 (m, 2H, OCH_2CH_2O), 4 24-4 29 (m, 2H, OCH_2CH_2O), 5 26 (t, J = 3,36 Hz, 1H, H_{THP}), 6 63 (s, 2H, H_{arom}), MS m/z = 251 (M+1)

5-Formyl-6-tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxin (7c):
Reaction with dimethylformamide (0 31 g, 0 33 ml) gave 0 16 g of compound **7c** as yellow needles Yield 72%, mp 84°C, IR (KBr) ν = 1680 (C=O), 1245 (ether) cm^{-1}; ^1H-NMR ($CDCl_3$). δ = 1 5-1.93 (m, 4H, H_{THP}), 3 47-3 55 (m, 2H, H_{THP}), 3 83-3 92 (m, 2H, H_{THP}), 4 22-4 29 (m, 2H, OCH_2CH_2O), 4 33-4 40 (m, 2H, OCH_2CH_2O), 4 96 (t, J = 2 60 Hz, 1H, H_{THP}), 6 43 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), 7,04 (d, $J_{7,8}$ = 9.08 Hz, 1H, H_{arom}), 10,28 (s, 1H, CHO), MS m/z = 265 (M+1)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]-1-methylmethanol (7d):
Reaction with acetaldehyde (0 19 g, 0 24 ml) gave 0 21 g of compound **7d** as a colorless oil Yield. 89%, IR (film) ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^1H-NMR ($CDCl_3$ + D_2O). δ = 1 56 (d, J = 6 95 Hz, 3H, CH_3), 1 58-2 05 (m, 4H, H_{THP}), 3 56-3 65 (m, 2H, H_{THP}), 3 85-3 96 (m, 2H, H_{THP}), 4.18-4 22 (m, 2H, OCH_2CH_2O), 4 26-4 30 (m, 2H, OCH_2CH_2O), 5 28 (t, J = 3 36 Hz, 1H, CHOH), 5 37 (t, J = 2 96 Hz, 1H, H_{THP}), 6 67 (d, $J_{7,8}$ = 2 37 Hz, 1H, H_{arom}), 6 69 (d, $J_{7,8}$ = 2 37 Hz, 1H, H_{arom}), MS m/z = 263 (M-17)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]-1,1-diphenylmethanol (7e):
Reaction with benzophenone (0,774 g) gave 0 269 g of compound **7e** as a colorless oil Yield 76%, IR (film). ν = 3600-3100 (OH), 1260 (ether) cm^{-1}. ^1H-NMR ($CDCl_3$ + D_2O). δ = 1.25-1.64 (m, 4H, H_{THP}), 3 42-3 57 (m, 2H, H_{THP}), 3 71-3 77 (m, 3H, OCH_2CH_2O et H_{THP}), 4 05-4 11 (m, 3H, OCH_2CH_2O + H_{THP}), 5 06 (t, J = 2 58 Hz, 1H, H_{THP}), 6 79 (d, $J_{7,8}$ = 2 37 Hz, 2H, H_{arom}), 7 15-7 39 (m, 5H, H_{arom}); MS m/z = 401 (M-17)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]cyclohexan-1-ol (7f):

Reaction with cyclohexanone (0.417g) gave 0 24 g of compound **7f** as a colorless oil. Yield: 85%; IR (film): ν = 3600-3100 (OH), 1240 (ether) cm^{-1}; ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 1.16-2 03 (m, 14H, H_{THP} et H_{cy}), 2.23-2.36 (m, 2H, H_{THP}), 3.59-3.67 (m, 1H, H_{THP}), 3.88-3.97 (m, 1H, H_{THP}), 4 17-4.26 (m, 4H, OCH_2CH_2O), 5.29 (t, J = 2 69 Hz, 1H, H_{THP}), 6 67 (d, $J_{7,8}$ = 9.08 Hz, 1H, H_{arom}), 6 79 (d, $J_{7,8}$ = 9.08 Hz, 1H, H_{arom}); MS· m/z = 317 (M-17)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]-1-isopropylmethanol (7g):
Reaction with isobutyraldehyde (0 29 g, 0 37 ml) gave 0.232 g of compound **7g** as a yellow oil Yield. 89%; IR (film). ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O): δ = 0.79 (dd, J = 1 87 Hz and J = 6.71 Hz, 3H, CH_3), 1.13 (dd, J = 1.87 Hz and J = 6,71 Hz, 3H, CH_3), 1.53-2 22 (m, 5H, H_{THP} et $CH(CH_3)_2$), 3.56-3.66 (m, 2H, H_{THP}), 3.81-3.94 (m, 2H, H_{THP}), 4.17-4 28 (m, 4H, OCH_2CH_2O), 5 27 (t, J = 3.35 Hz, 1H, CHOH), 5.38 (t, J = 2.76 Hz, 1H, H_{THP}), 6 18 (d, J = 3,95 Hz, 2H, H_{arom}), MS m/z = 391 (M-17).

4-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]-*N*-benzylpiperidin-4-ol (7h):
Reaction with 4-*N*-benzylpiperidone (0 81 g, 0 78 ml) gave 0.263 of compound **7h** as a yellow oil. Yield· 73%; IR (film) ν = 3700-3100 (OH), 1260 (ether) cm^{-1}. ^{1}H-NMR ($CDCl_3$ + D_2O). δ = 1 29-1.67 (m, 4H, H_{THP}), 2.22-2.64 (m, 8H, $H_{piperidine}$), 2.75-2 87 (m, 1H, H_{THP}), 2 98-3 08 (m, 1H, H_{THP}), 3.17-3 24 (m, 1H, H_{THP}), 3 50 (s, 2H, NCH_2Ph), 3 84-3 94 (m, 1H, H_{THP}), 4 15-4 20 (m, 2H, OCH_2CH_2O), 4 21-4 26 (m, 2H, OCH_2CH_2O), 5.29 (t, J = 3 16 Hz, 1H, H_{THP}), 6,67 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), 6 76 (d, $J_{7,8}$ = 9.08 Hz, 1H, H_{arom}), 7 17-7 39 (m, 5H, H_{arom}); MS m/z = 426 (M+1)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl)]-1-phenylmethanol (7i):
Reaction with benzaldehyde (0 451 g, 0.432 ml) gave 0.22 g of compound **7i** as a colorless oil Yield. 76%, IR (film) ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O). δ = 1.26-1 81 (m, 4H, H_{THP}), 3 24-3 42 (m, 2H, H_{THP}), 3 54-3.62 (m, 1H, H_{THP}), 3 83-3.93 (m, 1H, H_{THP}), 4 19-4 31 (m, 4H, OCH_2CH_2O), 5.44 (t, J = 2.58 Hz, 1H, H_{THP}), 6 23 (s, 1H, CHOH), 6 66 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), 6 77 (d, $J_{7,8}$ = 9 08 Hz, 1H, H_{arom}), 7 16-7 41 (m, 5H, H_{arom}); MS m/z = 325 (M-17)

1-[5-(6-Tetrahydropyranyloxy-2,3-dihydro-1,4-benzodioxinyl]-4-pyridinylmethanol (7j):
Reaction with 4-pyridine carboxaldehyde (0.454 g, 0.4 ml) gave 0.221 g of compound **7j** as a colorless oil Yield 76%; IR (film): ν = 3600-3100 (OH), 1230 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O). δ = 1 23-1 81 (m, 4H, H_{THP}), 3 17-3 26 (m, 1H, H_{THP}), 3.29-3 36 (m, 1H, H_{THP}), 3 53-3 60 (m, 1H, H_{THP}), 3 74-3 85 (m, 1H, H_{THP}), 4 14-4 28 (m, 4H, OCH_2CH_2O), 5 05 (m, 1H, CHOH)), 5 36 (t, J = 2.96 Hz, 1H, H_{THP}), 6 62-6 76 (m, 2H, H_{arom}), 7 22-7 28 (m, 2H, H_{pyr}), 8 41-8 52 (m, 2H, H_{pyr}), MS m/z = 344 (M+1)

Synthesis of 5-substituted-6-hydroxy-2,3-dihydro-1,4-benzodioxins (8). General procedure:
Compounds **7** (0.05 g) were dissolved in 90% aqueous methanol (1 8 ml) and 5% oxalic acid aqueous solution (0 2 ml) The solution was stirred at room temperature and the reaction was followed by tlc The methanol was eliminated and water added After extraction with diethyl ether, the products were purified by column chromatography on silica gel (eluent petroleum ether/diethyl ether, 8 2)

5-Bromo-6-hydroxy-2,3-dihydro-1,4-benzodioxin (8a):
Treatment of **7a** gave 0.035 g of compound **8a** as a colorless oil Yield. 97%; IR (film). ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 4 17-4 22 (m, 2H, OCH_2CH_2O), 4 32-4 37 (m, 2H, OCH_2CH_2O), 6 54 ($d_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 76 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), MS m/z = 231 (M), 233 (M+2) Anal Cald for $C_8H_7O_3Br$ C 41 59, H 3 05 Found C 41 72, H 3 29

5-Methyl-6-hydroxy-2,3-dihydro-1,4-benzodioxin (8b):
Treatment of **7b** gave 0 035 g of compound **8b** as white needles Yield. 99%; mp = 50°C, IR (KBr): ν = 3600-3000 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 2.09 (s, 3H, CH_3), 4.15-4.20 (m, 2H, OCH_2CH_2O), 4 24-4.29 (m, 2H, OCH_2CH_2O), 6.31 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6.59 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), MS· m/z = 167 (M+1). Anal. Calcd for $C_9H_{10}O_3$: C 65.06, H 6.07. Found: C 64.85, H 5 81

5-Formyl-6-hydroxy-2,3-dihydro-1,4-benzodioxin (8c):
Treatment of **7c** gave 0 031 g of compound **8c** as yellow needles Yield. 90%; mp = 62°C; IR (KBr) ν = 3600-3000 (OH), 1700 (C=O), 1250 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 4.22-4 29 (m, 2H, OCH_2CH_2O), 4 33-4 39 (m, 2H, OCH_2CH_2O), 6.42 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 7 04 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 11.30 (s, 1H, CHO), MS. m/z = 181 (M+1) Anal Calcd. for $C_9H_8O_4$· C 60.01, H 4 48 Found· C 60 28, H 4 66

1-[5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-1-methylmethanol (8d):
Treatment of **7d** gave 0 032 g of compound **8d** as a colorless oil Yield. 92%, IR (film): ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 1 52 (d, J = 6.52 Hz, 3H, CH_3), 4 10-4 27 (m, 4H, OCH_2CH_2O), 5 47 (q, J = 6 57 Hz, 1H, CHOH), 6 37 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 66 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), MS m/z = 179 (M-17) Anal Calcd for $C_{10}H_{12}O_4$ C 61 23, H 6 17 Found C 61 47, H 6 32

1-[5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-1,1-diphenylmethanol (8e):
Treatment of **7e** gave 0 038 g of compound **8e** as white needles Yield 94%, mp = 178°C, IR (KBr) ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 3 68-3 73 (m, 2H, OCH_2CH_2O), 4 00-4 05 (m, 2H, OCH_2CH_2O), 6 45 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 76 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 7 28-7 44 (m, 10H, H_{arom}), MS m/z = 317 (M-17) Anal Calcd for $C_{21}H_{18}O_4$· C 75 44, H 5 43 Found C 75 20, H 5 38

1-[5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]cyclohexan-1-ol (8f):
Treatment of **7f** gave 0 035 g of compound **8f** as white needles Yield 94%, mp = 140°C, IR (KBr) ν = 3600-3100 (OH), 1240 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 1 65-1 86 (m, 5H, H_{cy}) 2 18-2 31 (m, 5H, H_{cy}), 4 15-4 25 (m, 4H, OCH_2CH_2O), 6 45 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 67 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), MS m/z = 233 (M-17) Anal Calcd for $C_{14}H_{18}O_4$ C 67 19, H 7 25 Found C 67 27, H 7 13.

1-(5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-1-isopropylmethanol (8g):
Treatment of **7g** gave 0 034 g of compound **8g** as white needles Yield 95%, mp = 80-82°C, IR (KBr) ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 0 90 (d, J = 6 71 Hz, 3H, CH_3), 1 13 (d, J = 6 71 Hz, 3H, CH_3), 2 09 (m, 1H, $CH(CH_3)_2$), 4 14-4 22 (m, 4H, OCH_2CH_2O), 4 98 (d, J = 5 56 Hz, 1H, CHOH), 6 37 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 67 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), MS m/z = 207 (M-17) Anal Calcd for $C_{12}H_{16}O_4$ C 64 28, H 7 19 Found 64 54, H 7 47

4-[5-(6-hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-*N*-benzylpiperidin-4-ol (8h):
Treatment of **7h** gave 0 036 g of compound **8h** as white needles Yield 95%, mp = 165-166°C, IR (KBr) ν = 3700-3100 (OH), 1240 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O) δ = 1 80-1 90 (m, 2H, $H_{piperidine}$), 2 43-2 57 (m, 2H, $H_{piperidine}$), 2 74-2 97 (m, 4H, $H_{piperidine}$), 3.62 (s, 2H, NCH_2Ph), 4 13-4.17 (m, 2H, OCH_2CH_2O), 4 20-4 25 (m, 2H, OCH_2CH_2O), 6 37 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 67 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 7 25-7 40 (m, 5H, H_{arom}), MS m/z = 342 (M+1), 324 (M-17) Anal Calcd for $C_{20}H_{23}NO_4$ C 70 36, H 6 77, N 4 10 Found C 70 01, H 7 09, N 4 32

1-[5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-1-phenylmethanol (8i):
Treatment of **7i** gave 0 034 g of compound **8i** as white needles Yield. 91%; mp = 162°C; IR (KBr) ν = 3600-3100 (OH), 1260 (ether) cm^{-1}, ^{1}H-NMR ($CDCl_3$ + D_2O)· δ = 4.11-4 22 (m, 4H, OCH_2CH_2O), 6 34 (s, 1H, CHOH), 6.40 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 6 71 (d, $J_{7,8}$ = 8.69 Hz, 1H, H_{arom}), 7.24-7.46 (m, 5H, H_{arom}), MS m/z = 241 (M-17). Anal. Calcd for $C_{15}H_{14}O_4$: C 69 76; H 5 46 Found· C 69 46; H 5 68

1-[5-(6-Hydroxy-2,3-dihydro-1,4-benzodioxinyl)]-4-pyridinylmethanol (8j):
Treatment of **7j** gave 0 036 g of compound **8j** as white needles. Yield. 95%, mp = 214°C, IR (KBr). ν = 3600-3150 (OH), 1230 (ether) cm^{-1}; ^{1}HNMR ($CDCl_3$ + D_2O). δ = 4.18-4 28 (m, 4H, OCH_2CH_2O), 6.30 (s, 1H, CHOH), 6.38 (d, $J_{7,8}$ = 8.69 Hz, 1H, H_{arom}), 6 73 (d, $J_{7,8}$ = 8 69 Hz, 1H, H_{arom}), 7.36 (d, J = 5.33 Hz, 2H, H_{pyr}), 8 48 (d, J = 5 33 Hz, 2H, H_{pyr}); MS. m/z = 260 (M+1), 243 (M-17) Anal. Calcd for $C_{14}H_{13}NO_4$. C 64 86; H 5 05; N 5.40 Found C 64 57, H 4 95, N 5 21.

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