

Regioselective Protection of the 4-Hydroxyl of 3,4-Dihydroxybenzaldehyde

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Abstract: The regioselective protection of the 4-hydroxyl group of 3,4-dihydroxybenzaldehyde was accomplished with seven different protecting groups (benzyl, p-methoxybenzyl, o-nitrobenzyl, 2,6-dichlorobenzyl, 3,4-dichlorobenzyl, vinyl and propargyl) in yields ranging between 67-75%.

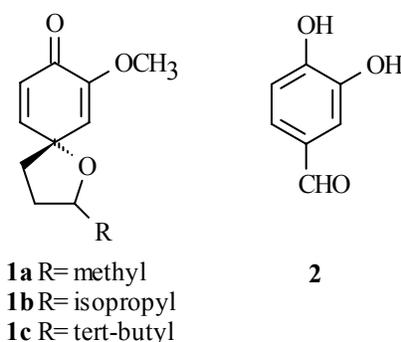
Keywords: regioselective, protection, catechol, 3,4-dihydroxybenzaldehyde

Introduction

We recently reported our study of the diastereoselective spiroannulation of simple phenols producing spiroethers **1a-c** shown in Figure 1 [1]. In a continuation of this work, we needed to replace the methoxy group with other substituents in order to study the effect these groups would have on the spiroannulation reaction. To accomplish this task, we first needed to selectively protect the 4-hydroxyl group of 3,4-dihydroxybenzaldehyde **2** (Figure 1). Unfortunately, a literature survey showed that little had been done in terms of selective protection of this type of catechol. We found a few examples dealing with the selective protection of 2,4- and 2,5-dihydroxybenzaldehydes [2,3], 2,5-dihydroxyacetophenone [4], and methyl 2,5-dihydroxybenzoate [5], with protective groups such as methyl [4], benzyl [2,5], and *t*-butyldimethylsilyl [3]. More recently, we reported the protection of 2,4-dihydroxybenzaldehyde using the methoxymethyl ether (MOM) protecting group [6]. The

selectivity in these cases is normally attributed to the intramolecular H-bonding that exists between the 2-hydroxyl and the carbonyl group preventing the 2-position from being alkylated. In another example, the pivaloyl protecting group was used to selectively protect the 5-hydroxyl group of 1-*t*-butyl-2,5-dihydroxy-benzene with the selectivity being controlled by steric hindrance [7]. In the case of catechols such as 3,4-dihydroxyacetophenone or 3,4-dihydroxybenzaldehyde, where the acidity of the phenolic hydroxyls controls the selectivity, we found only a few examples of selective protection of the 4-hydroxyl position. One example used the methyl protecting group in the protection of the 4-hydroxyl group of 3,4-dihydroxyacetophenone [8]. However, we considered this protecting group inappropriate for our purpose because Lewis acids would usually be required to remove it from the targeted product. Examples of selective protection of 3,4-dihydroxybenzaldehyde were also found, but typically these reactions provided low yields of the 4-protected products. For instance, the protection of 3,4-dihydroxybenzaldehyde was accomplished in ~ 40% using the allyl protecting groups [9,10], while the benzyl and *p*-methoxybenzyl protecting groups gave only between 30-57% yield of the 4-protected benzaldehyde [11,12]. Hence, there was a need to find a better method to introduce a protecting group that can be easily removed from the target molecules under mild conditions. We now wish to report our findings on the successful regioselective protection of the 4-hydroxyl group of **2** using seven different protecting groups.

Figure 1



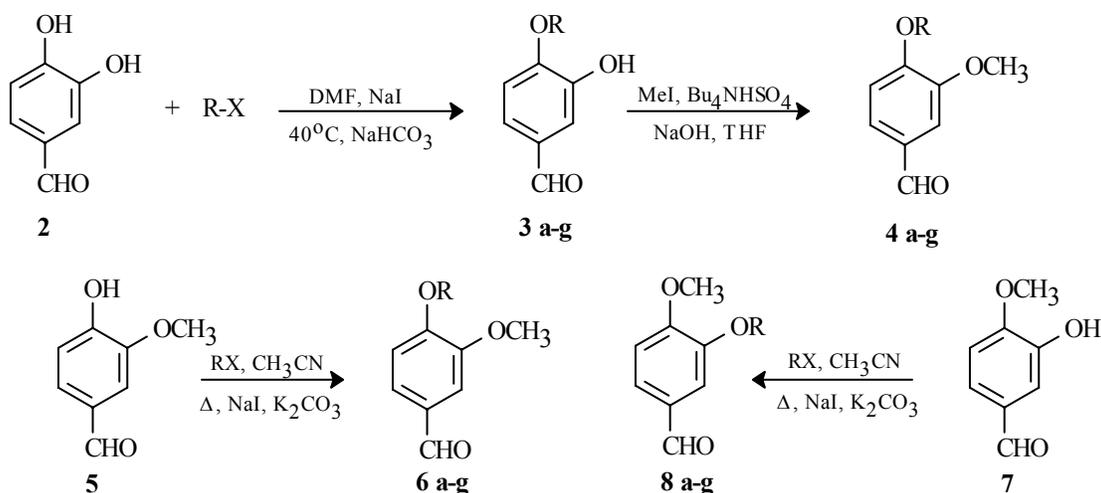
Results and Discussion

Since we had success in the protection of 2,4-dihydroxybenzaldehyde with the MOM protecting group [6], we decided to begin this investigation with that protecting group. Following our reported procedure [MOMCl, K₂CO₃, acetone, rt, 20h], compound **2** gave primarily one product by thin layer chromatography (tlc). Flash chromatography of the crude reaction mixture provided a colourless solid (87%), but ¹H-NMR suggested that two aldehydes (δ 9.84 and 9.81) were present in a 8/2 ratio. GC-MS analysis of this mixture confirmed the ratio of these two products, and further indicated that the two products were a mixture of the 4-monoprotected and the 3-monoprotected isomers, since each product showed *m/z* 182 [M⁺]. Changing the base to the weaker NaHCO₃ in an attempt to deprotonate only the 4-hydroxyl group did not succeed, and only **2** was recovered in a

quantitative amount after stirring either at room temperature for 2 days, or for 20h at reflux. Under the conditions used by Wymann for the methyl protecting group [Li_2CO_3 , DMF, 60°C , 20h] [8], only benzaldehyde **2** was recovered when MOMCl was used as the alkylating agent. We also carried out these reactions with MEMCl as the alkylating agent and obtained the same results, *i.e.* a 8/2 mixture of isomeric monoprotected aldehydes using the conditions we previously reported for 2,4-dihydroxybenzaldehyde [MEMCl, K_2CO_3 , acetone, rt, 20h] [6], and complete recovery of the starting material under the conditions used by Wymann [MEMCl, Li_2CO_3 , DMF, 60°C , 20h] [8].

Having no success with the MOM and MEM protecting groups, we looked at more reactive alkyl halides and tried using benzyl chloride. Under the first set of conditions [benzyl chloride, K_2CO_3 , NaI, acetone, rt, 20h], we obtained a mixture of products consisting of both monoprotected aldehydes, as well as the diprotected product. However, with the second set of conditions [benzyl chloride, K_2CO_3 , DMF, NaI], **2** produced a mixture of the monoprotected products (δ 9.80 and 9.76) in 67% yield in a 9/1 ratio when stirred for 6 days at room temperature. Changing the base to NaHCO_3 and heating the reaction mixture [benzyl chloride, DMF, NaHCO_3 , NaI, 40°C , 20h] as shown in Scheme 1 had a positive effect on the yield, as well as the purity of the product. In this case, we were able to isolate only one monoprotected aldehyde ($^1\text{H-NMR}$ in CDCl_3 : δ 9.80; GCMS m/z : 228 [M^+]) in 71% yield as a colourless solid (mp: $118\text{--}120^\circ\text{C}$).

Scheme 1



a R: PhCH_2 - X: Cl; **b** R: $p\text{-MeOPhCH}_2$ - X: Cl; **c** R: $o\text{-NO}_2\text{PhCH}_2$ - X: Br; **d** R: $2,6\text{-diClPhCH}_2$ - X: Br;
e R: $3,4\text{-diClPhCH}_2$ - X: Cl; **f** R: H_2CCHCH_2 - X: Br; **g** R: HCCCH_2 - X: Br

Alkylations of **2** with other alkyl halides using these reaction conditions were also successful and we were able to prepare six other monoprotected benzaldehydes in 67–75% yields as shown in Scheme 1. $^1\text{H-NMR}$ data for the aldehyde signal as well as the GC-MS data confirmed the presence of only one monoprotected product in all cases: $^1\text{H-NMR}$ in CDCl_3 : δ 9.84 (**3b**), 9.86 (**3c**), 9.87 (**3d**), 9.86 (**3e**), 9.85 (**3f**), 9.86 (**3g**); GCMS m/z : 258 [M^+] (**3b**), 273 [M^+] (**3c**), 296 [M^+] (**3d**), 296 [M^+] (**3e**), 178

[M⁺] (**3f**), 176 [M⁺] (**3g**). The yields and melting points of all the compounds shown in Scheme 1 are summarized in Table 1.

Table 1. Yields and Melting Points

Series	R	Yield ^a				Melting Point (°C) ^b			
		3	4	6	8	3	4	6	8
a	benzyl	71	83	89	82	118-120	58-60	60-61	59-60
b	p-methoxybenzyl	75	100	90	78	125-127	105-107	106-107	80-81
c	o-nitrobenzyl	67	85	83	86	147-149	126-127	127-129	138-139
d	2,6-dichlorobenzyl	69	85	80	80	125-126	124-125	125-126	167-168
e	3,4-dichlorobenzyl	68	85	86	93	153(d)	113(d)	115(d)	82(d)
f	allyl	72	91	94	86	55-56	24-26	24-25	n/a ^c
g	propargyl	69	94	86	88	77-78	84-85	85-86	71-72

^a isolated yields after column chromatography

^b melting points were recorded on a hot stage instrument and are uncorrected

^c **8** is an oil at room temperature

In order to conclusively identify the major product produced in these reactions, we methylated [2M NaOH, THF, CH₃I, Bu₄NHSO₄] the products **3a-g** to give the derivatives **4a-g** as shown in Scheme 1. We also prepared compounds **6a-g** and **8a-g** from vanillin (**5**) and isovanillin (**7**) respectively, and compared the spectroscopic data of these compounds with that of **4a-g**, looking for spectroscopic evidence that would confirm the identity of these compounds. As previously mentioned, we already knew from GC-MS that only monoprotected benzaldehydes were produced. We compared the ¹H-NMR and IR spectra of **4a-g** to those of **6a-g** and **8a-g**, but we did not find any significant difference between any of these spectra that would help in confirming the structures of the monoprotected benzaldehydes **3a-g**. However, careful analysis of the ¹³C-NMR spectra for the same compounds showed one significant difference in all cases. We noticed that the signals for the aromatic carbons C₂ and C₅ were further apart in the case of **4a-g** and **6a-g** (C₂ ~112.5ppm and C₅ ~109.5ppm), while the signals for the same carbons almost collapse to only one line for compounds **8a-g** (C₂ ~111.5 ppm and C₅ ~111.0 ppm). The results shown in Table 2 suggest that compounds **4a-g** and **6a-g** are identical based on the chemical shifts of these two carbons. Further evidence can be observed when comparing the entire ¹³C-NMR spectra. When comparing **4a-g** and **6a-g**, the spectra appear to be duplicates of one another. However, when comparing **4a-g** and **8a-g** differences other than those for C₂ and C₅ can be observed, although much less significant, confirming that **4a-g** and **8a-g** are different compounds. Mass spectral analysis and mixed melting point experiments also indicated that **4a-g** and **6a-g** were identical compounds.

Table 2. ^{13}C -NMR Data^a

Series	R	2		4		6		8	
		C ₂	C ₅						
a	benzyl	114.6	111.7	112.6	109.5	112.5	109.4	111.4	110.9
b	p-methoxybenzyl	114.6	111.6	112.0	109.4	112.0	109.3	110.9	110.8
c	o-nitrobenzyl	115.1	112.1	112.6	109.6	112.6	109.6	112.2	111.2
d	2,6-dichlorobenzyl	114.8	112.1	113.2	110.0	113.2	110.1	112.6	111.3
e	3,4-dichlorobenzyl	115.0	111.7	112.5	109.6	112.5	109.6	111.3	111.1
f	allyl	114.6	111.6	112.0	109.4	112.0	109.3	110.9	110.8
g	propargyl	115.0	112.0	112.6	109.5	112.6	109.5	111.9	111.0

^a ^{13}C -NMR data were obtained in CDCl_3 on a Bruker AMX300 spectrometer at 75.4 MHz using CHCl_3 as the internal standard. Chemical shifts are expressed in δ units.

We also attempted the regioselective protection of **2** with two other alkyl halides, phenacyl bromide and α -bromoacetonitrile. In the case of phenacyl bromide [DMF, NaI, NaHCO_3 , 40°C , 20h], we obtained a mixture of products (8 spots by tlc) that were unseparable and not identified. Under the other set of conditions [K_2CO_3 , acetone, rt, 20h] the reaction did not show any selectivity and the ^1H -NMR spectrum of the crude reaction mixture showed that both possible monoprotected aldehydes were obtained along with some of the diprotected product. In the case of α -bromoacetonitrile, only benzaldehyde **2** was recovered in quantitative yield under either set of conditions.

Conclusions

We have successfully protected the 4-hydroxyl group of 3,4-dihydroxybenzaldehyde in 70% yield with active halides such as benzyl chloride derivatives, allyl bromide and propargyl bromide. The reaction showed higher regioselectivity than with other alkyl halides such as MOMCl, MEMCl, phenacyl bromide or α -bromoacetonitrile. Given the number of available benzyl halide derivatives, this method should be a valuable tool for the protection of other catechols bearing an electron-withdrawing substituent para to one of the hydroxyl groups. It may also find usefulness in industry, for example in the synthesis of alkaloids such as galanthamine [13], as well as in the synthesis of antimycotic agents (benzylidene thiazolidinediones) which requires the selective protection of the 4-hydroxyl group of 3,4-dihydroxybenzaldehyde [12].

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Experimental

Melting points were determined on a hot stage instrument and are uncorrected. Infrared spectra were recorded either as KBr pellets or neat on a Perkin Elmer System 2000 FTIR. $^1\text{H-NMR}$ spectra were recorded on a Bruker AMX300 spectrometer at 300MHz and chemical shifts are expressed in ppm using TMS as internal standard. $^{13}\text{C-NMR}$ spectra were recorded on a Bruker AMX300 spectrometer at 75.4MHz and chemical shifts are expressed in ppm using chloroform as internal standard. Mass spectra were recorded on a Hewlett Packard 5898B spectrometer.

General procedure for the selective protection of 3,4-dihydroxybenzaldehyde:

To a solution of 3,4-dihydroxybenzaldehyde **2** (~1.0 mmol) in DMF (5 mL) was added sodium bicarbonate (~1.5 mmol), the alkyl halide (~2.0 mmol) and sodium iodide (~0.3 mmol). The resulting mixture was stirred at 40°C for 24h. 10% Aqueous HCl (10 mL) was added and the solution was extracted with ethyl acetate (3 x 10 mL). The organic fractions were combined, washed with brine (10 mL), dried (anhydrous MgSO_4) and the solvent was evaporated *in vacuo* to give a brown liquid. Subsequent chromatography on silica gel using the solvent systems indicated afforded a colourless solid in all cases.

4-Benzyloxy-3-hydroxybenzaldehyde (3a). From 137 mg of **2**, we obtained **3a** (160 mg, 71%) after chromatography (20% EtOAc/hexanes); Mp: 118-120°C. Spectral data were identical to those previously reported [12].

3-Hydroxy-4-(p-methoxybenzyloxy)-benzaldehyde (3b). From 116 mg of **2**, we obtained **3b** (163 mg, 75%) after chromatography (15% acetone/hexanes); Mp: 125-127°C. Spectral data were identical to those previously reported [12].

3-Hydroxy-4-(o-nitrobenzyloxy)-benzaldehyde (3c). From 115 mg of **2**, we obtained **3c** (153 mg, 67%) after chromatography (25% EtOAc/hexanes); Mp: 147-149°C; IR (KBr) cm^{-1} : 3410 (OH), 1685 (CO); $^1\text{H-NMR}$ (CDCl_3) δ : 5.68 (s, 2H, OCH_2), 5.82 (s, 1H, exchangeable with D_2O , OH), 6.97 (d, 1H, $J=8.3\text{Hz}$, H_5), 7.57 (m, 5H, aromatic Hs), 8.22 (d, 1H, $J=8.2\text{Hz}$, benzyl Ar- H_3), 9.86 (s, 1H, CHO); $^{13}\text{C-NMR}$ (CDCl_3) δ : 68.3 (OCH_2), 112.1 (C_2), 115.1 (C_5), 124.6 (benzyl Ar- C_3), 125.7 (C_6), 128.7 (benzyl Ar- C_6), 129.5 (benzyl Ar- C_4), 131.5 (C_1), 132.1 (benzyl Ar- C_1), 134.5 (benzyl Ar- C_5), 146.4 (C_3), 147.3 (benzyl Ar- C_2), 150.4 (C_4), 191.1 (CO); MS m/z (relative %): 273 [M^+] (2), 119 (100), 92 (93), 64 (63), 63 (31).

4-(2,6-Dichlorobenzyloxy)-3-hydroxybenzaldehyde (3d). From 112 mg of **2**, we obtained **3d** (166 mg, 69%) after chromatography (20% EtOAc/hexanes); Mp: 125-126°C; IR (KBr) cm^{-1} : 3419 (OH), 1681 (CO); $^1\text{H-NMR}$ (CDCl_3) δ : 5.45 (s, 2H, OCH_2), 5.79 (s, 1H, exchangeable with D_2O , OH), 7.29 (m, 6H, aromatic Hs), 9.87 (s, 1H, CHO); $^{13}\text{C-NMR}$ (CDCl_3) δ : 66.4 (OCH_2), 112.1 (C_5), 114.8 (C_2),

124.4 (C₆), 128.9 (benzyl Ar-C₃), 131.0 (C₁), 131.4 (benzyl Ar-C₄), 131.5 (benzyl Ar-C₂), 137.2 (benzyl Ar-C₁), 146.8 (C₃), 150.9 (C₄), 191.2 (CO); MS m/z (relative %): 296 [M⁺] (7), 254 (100), 253 (77), 207 (46).

4-(3,4-Dichlorobenzyloxy)-3-hydroxybenzaldehyde (3e). From 125 mg of **2**, we obtained **3e** (181 mg, 68%) after chromatography (15% EtOAc/hexanes); Mp: 153°C (decomposed); IR (KBr) cm⁻¹: 3423 (OH), 1683 (CO); ¹H-NMR (CDCl₃) δ: 5.16 (s, 2H, OCH₂), 5.77 (s, 1H, exchangeable with D₂O, OH), 6.99 (d, 1H, J=8.3Hz, H₅), 7.42 (m, 5H, aromatic Hs), 9.86 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 70.0 (OCH₂), 111.7 (C₅), 115.0 (C₂), 124.5 (C₆), 127.2 (benzyl Ar-C₆), 129.9 (benzyl Ar-C₂), 131.2 (C₁), 131.4 (benzyl Ar-C₅), 133.2 (benzyl Ar-C₃), 133.4 (benzyl Ar-C₄), 135.6 (benzyl Ar-C₁), 146.4 (C₃), 150.6 (C₄), 191.1 (CO); MS m/z (relative %): 296 [M⁺] (4), 254 (63), 253 (27), 207 (100).

4-Allyloxy-3-hydroxybenzaldehyde (3f). From 125 mg of **2**, we obtained **3f** (116 mg, 72%) after chromatography (20% EtOAc/hexanes); Mp: 55-56°C. Spectral data were identical to those previously reported [9].

3-Hydroxy-4-propargyloxybenzaldehyde (3g). From 112 mg of **2**, we obtained **3g** (99 mg, 69%) after chromatography (20% EtOAc/hexanes); Mp: 77-78°C; IR (KBr) cm⁻¹: 3422 (OH), 2129 (alkyne), 1679 (CO); ¹H-NMR (CDCl₃) δ: 2.63 (s, 1H, propargyl CH), 4.87 (s, 2H, OCH₂), 5.95 (s, 1H, exchangeable with D₂O, OH), 7.10 (d, 1H, J=8.2Hz, H₅), 7.45 (d, 1H, J=8.2Hz, H₆), 7.48 (s, 1H, H₂), 9.86 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 57.0 (OCH₂), 76.7 (propargyl CH), 77.3 (propargyl C₂), 112.1 (C₅), 115.0 (C₂), 124.3 (C₆), 131.5 (C₁), 146.5 (C₃), 149.8 (C₄), 191.3 (CO); MS m/z (relative %): 176 [M⁺] (100), 147 (33), 137 (64), 109 (57), 81 (47).

General procedure for the methylation of derivatives 3a-g

To a solution of monoprotected benzaldehydes **3a-g** (~0.5 mmol) in THF (5 mL) was added 2M NaOH solution (5 mL), CH₃I (~2 mmol) and Bu₄NHSO₄ (~100 mg). The resulting yellow solution was stirred at room temperature for 24h. Water (20 mL) was added and the solution was extracted with ethyl acetate (3 x 10 mL). The organic fractions were combined, dried (MgSO₄) and the solvent was evaporated *in vacuo*. In all cases the crude products gave colourless solids after purification by chromatography on silica gel using the indicated solvent systems.

4-Benzyloxy-3-methoxybenzaldehyde (4a). From 150 mg of **3a**, we obtained **4a** (132 mg, 83%) after chromatography (20% EtOAc/hexanes); Mp: 58-60°C. Spectral data were identical to those obtained from an authentic sample purchased from Aldrich Chemical Co.

4-(p-Methoxybenzyloxy)-3-methoxybenzaldehyde (4b). From 84 mg of **3b**, we obtained **4b** (88 mg, 100%) after chromatography (20% EtOAc/hexanes); Mp: 105-107°C (lit: 102-103°C) [14]; IR (KBr) cm⁻¹: 1682 (CO); ¹H-NMR (CDCl₃) δ: 3.84 (s, 3H, benzyl OCH₃), 3.93 (s, 3H, OCH₃), 5.18 (s, 2H,

OCH₂), 6.92 (d, 2H, J=8.5Hz, benzyl Ar-H₃), 7.01 (d, 2H, J=8.0Hz, H₅), 7.39 (m, 4H, aromatic Hs), 9.84 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 55.5 (benzyl OCH₃), 56.2 (OCH₃), 70.9 (OCH₂), 109.4 (C₅), 112.5 (C₂), 114.3 (benzyl Ar-C₃), 126.8 (C₆), 128.0 (benzyl Ar-C₁), 129.2 (benzyl Ar-C₂), 130.3 (C₁), 150.2 (C₃), 153.9 (C₄), 159.8 (benzyl Ar-C₄), 191.2 (CO); MS m/z (relative %): 272 [M⁺] (3), 122 (10), 121 (100), 91 (5).

3-Methoxy-4-(o-nitrobenzyloxy)benzaldehyde (4c). From 99 mg of **3c**, we obtained **4c** (88 mg, 85%) after chromatography (20% EtOAc/hexanes); Mp: 126-127°C; IR (KBr) cm⁻¹: 1681 (CO); ¹H-NMR (CDCl₃) δ: 4.00 (s, 3H, OCH₃), 5.65 (s, 2H, OCH₂), 7.01 (d, 1H, J=8.2Hz, H₅), 7.44 (dd, 1H, J=1.8, 8.2Hz, H₆), 7.48 (d, 1H, J=1.8Hz, H₂), 7.53 (t, 1H, J=7.6Hz, benzyl Ar-H₄), 7.72 (t, 1H, J=7.6Hz, benzyl Ar-H₅), 7.93 (d, 1H, J=7.9Hz, benzyl Ar-H₆) 8.22 (d, 1H, J=8.3Hz, benzyl Ar-H₃), 9.86 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 56.3 (OCH₃), 67.9 (OCH₂), 109.6 (C₅), 112.6 (C₂), 125.4 (benzyl Ar-C₃), 126.9 (C₆), 128.5 (benzyl Ar-C₆), 128.8 (benzyl Ar-C₄), 131.0 (C₁), 133.2 (benzyl Ar-C₁), 134.5 (benzyl Ar-C₅), 146.9 (C₃), 150.3 (C₄), 153.1 (benzyl Ar-C₂), 191.1 (CO); MS m/z (relative %): 287 [M⁺] (3), 153 (7), 137 (10), 136 (100), 78 (43).

4-(2,6-Dichlorobenzyloxy)-3-methoxybenzaldehyde (4d). From 166 mg of **3d**, we obtained **4d** (148 mg, 85%) after chromatography (15% EtOAc/hexanes); Mp: 124-125°C; IR (KBr) cm⁻¹: 1683 (CO); ¹H-NMR (CDCl₃) δ: 3.90 (s, 3H, OCH₃), 5.40 (s, 2H, OCH₂), 7.18 (d, 1H, J=8.1Hz, H₅), 7.37 (m, 5H, aromatic Hs), 9.89 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 56.4 (OCH₃), 66.5 (OCH₂), 110.0 (C₅), 113.2 (C₂), 126.7 (C₆), 128.7 (benzyl Ar-C₃), 128.9 (benzyl Ar-C₂), 130.9 (benzyl Ar-C₄), 131.5 (C₁), 137.4 (benzyl Ar-C₁), 150.6 (C₃), 154.0 (C₄), 191.2 (CO); MS m/z (relative %): 312 [M⁺+2] (14), 310 [M⁺] (20), 161 (67), 159 (100), 123 (7).

4-(3,4-Dichlorobenzyloxy)-3-methoxybenzaldehyde (4e). From 105 mg of **3e**, we obtained **4e** (93 mg, 85%) after chromatography (15% EtOAc/hexanes); Mp: 113°C (decomposed); IR (KBr) cm⁻¹: 1684 (CO); ¹H-NMR (CDCl₃) δ: 3.97 (s, 3H, OCH₃), 5.13 (s, 2H, OCH₂), 6.94 (d, 1H, J=8.1Hz, H₅), 7.28 (d, 1H, J=8.1Hz, H₆), 7.43 (m, 3H, aromatic Hs), 7.55 (s, 1H, H₂), 9.85 (s, 1H, CHO); ¹³C-NMR (CDCl₃) δ: 56.2 (OCH₃), 69.6 (OCH₂), 109.6 (C₅), 112.5 (C₂), 126.6(C₆ and benzyl Ar-C₆), 129.3 (benzyl Ar-C₂), 130.8 (C₁), 130.9 (benzyl Ar-C₅), 132.5 (benzyl Ar-C₃), 133.1 (benzyl Ar-C₄), 136.4 (benzyl Ar-C₁), 150.2 (C₃), 153.1 (C₄), 191.1 (CO); MS m/z (relative %): 312 [M⁺+2] (9), 310 [M⁺] (13), 161 (70), 159 (100), 123 (7).

4-Allyloxy-3-methoxybenzaldehyde (4f). From 268 mg of **3f**, we obtained **4f** (262 mg, 91%) after chromatography (20% EtOAc/hexanes); Mp: 24-25°C. Spectral data were identical to those previously reported [15].

3-Methoxy-4-propargyloxybenzaldehyde (**4g**). From 96 mg of **3g**, we obtained **4g** (97 mg, 94%) after chromatography (20% EtOAc/hexanes). Mp: 84-85°C. Spectral data were identical to those previously reported [16].

References

1. Plourde, G.L., *Tetrahedron Lett.*, **2002**, *43*, 3597.
2. Mendelson, W.L.; Holmes, M.; Dougherty, J., *Synth. Commun.* **1996**, *26*, 593.
3. Liu, A.; Dillon, K.; Campbell, R.M.; Cox, D.C.; Huryn, D.M., *Tetrahedron Lett.*, **1996**, *37*, 3587.
4. Vyas G.N.; Shah, N.M., *Org. Synt., Collect. Vol. IV*, **1963**, 836.
5. Kotecha, N.R.; Ley, S.V.; Montégani, S., *Synlett*, **1992**, 395.
6. Plourde, G.L.; Fisher, B.B., *Molecules*, **2002**, *7*, 315.
7. Lam, L.K.T.; Farhat, K., *Org. Prep. Proced. Int.*, **1978**, *10*, 79.
8. Wymann, W.E.; Davis, R.; Patterson Jr., J.W.; Pfister, J.R., *Synth. Commun.*, **1988**, *18*, 1379.
9. Reitz, A.; Avery M.A.; Verlander M.S.; Goodman M., *J. Org. Chem.*, **1981**, *46*, 4859.
10. Kessar, S.V.; Gupta, Y.P.; Mohammad, T.; Goyal, M.; Sawal, K.K., *J. Chem. Soc. Chem. Comm.*, **1983**, 400.
11. Markey, S.P.; Powers, K.; Dubinsky, D.; Kapin, I.J., *J. Labelled Comp. and Radiopharm.*, **1979**, *17*, 103.
12. Orchard, M.G.; Neuss, J.C.; Galley, C.M.S., *PCT Int. Appl.*, **2002**, 99 pp., WO 02/17915 A1.
13. Kuenburg, B.; Czollner, L.; Frohlich, J.; Jordis, U., *Org. Process R & D*, **1999**, *3*, 425.
14. Vig, O.P.; Bari, S.S.; Sharma, A.; Sattar, M.M., *Ind. J. Chem.*, **1990**, *29B*, 284.
15. Ayer, W.A.; Craw, P.A., *Can. J. Chem.*, **1991**, *69*, 1909.
16. Ishii, H.; Ishikawa, T.; Wada, H.; Miyazaki, H.; Kaneko, Y.; Harayama, T., *Chem. Pharm. Bull.*, **1992**, *40*, 2614.

Sample availability: all compounds are available from MDPI.

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