NEIGHBORING ASSISTANCE OF A HYDROXYL GROUP ON MANGANESE DIOXIDE OXIDATION OF BENZYL ALCOHOLS TO LACTONES †

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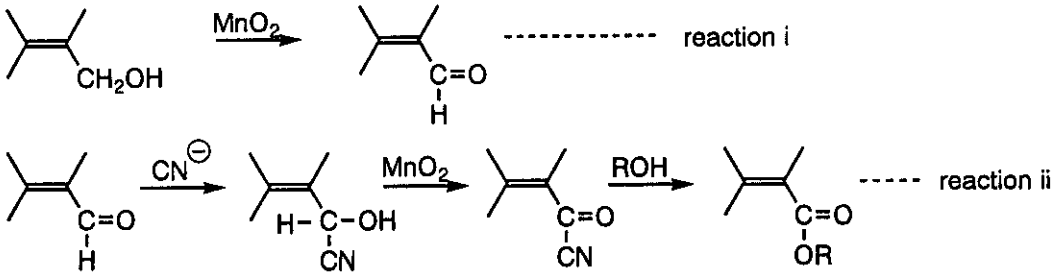
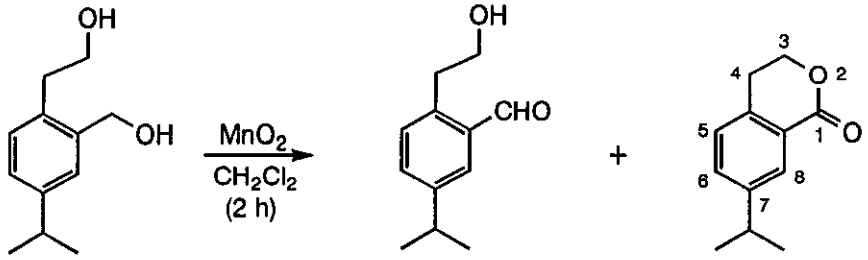
Abstract - *o*-Hydroxymethylbenzyl alcohol and *o*-hydroxyethylbenzyl alcohols have been converted to phthalide and dihydroisocoumarins, very easily and in high yields, by oxidation with non-activated manganese dioxide. In contrast, the reaction of *o*-hydroxypropylbenzyl alcohol stopped at the aldehyde level, and afforded only a small amount of the corresponding lactone under the same condition. This implies that the first oxidation product, a benzaldehyde, could be oxidized further *via* a hemiacetal, but the second oxidation to lactone is very much dependent on the ability of stable intramolecular hemiacetal formation, and not on the intermolecular mode at all.

Oxidation of allyl alcohols and benzyl alcohols with activated manganese dioxide is known to yield the corresponding aldehydes selectively (reaction i), and usually it dose not go further to carboxylic acids or esters.[1] However under exceptional conditions where cyanide ion is present, cyanohydrins formed are oxidized again to furnish carboxylic acids or esters (reaction ii).[2] During our studies on oxidative modification of benzyl alcohols, their oxidation to the level of carboxylic acids was noted, when the aldehydes were able to form intramolecular hemiacetals. Thus, oxidation of 2-hydroxyethyl-5-isopropylbenzyl alcohol (**1**) with a reagent grade manga-

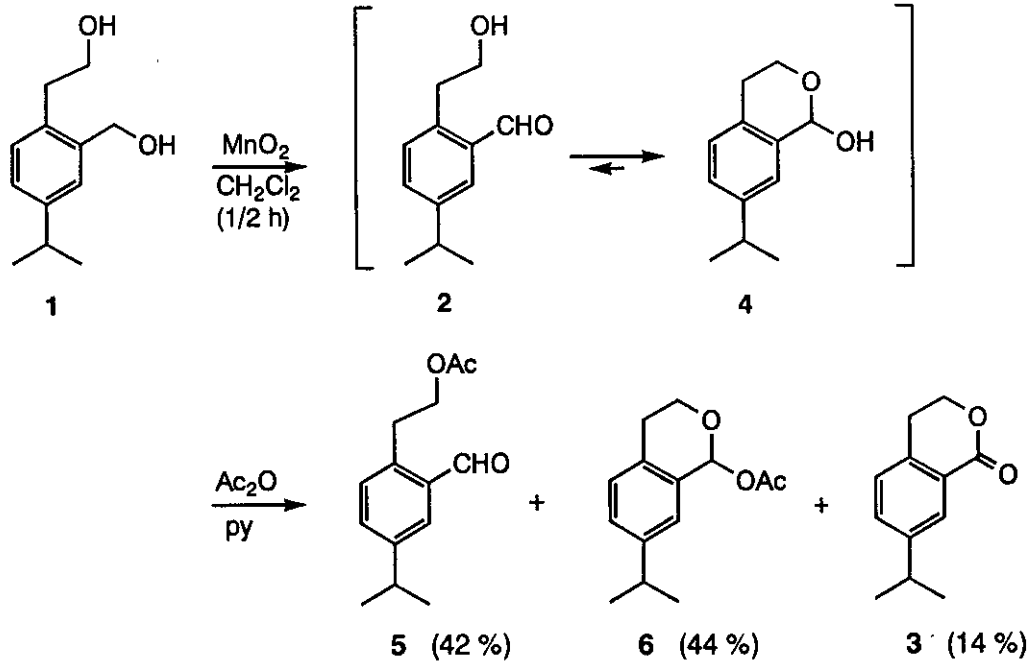
† This paper is dedicated to the memory of late Professor Emeritus of Hokkaido University, Dr. Yoshio Ban.



nese dioxide, in dichloromethane for 2 hours at room temperature yielded, instead of the aldehyde (**2**), 7-isopropyl-3,4-dihydroisocoumarin (**3**) as a major product.

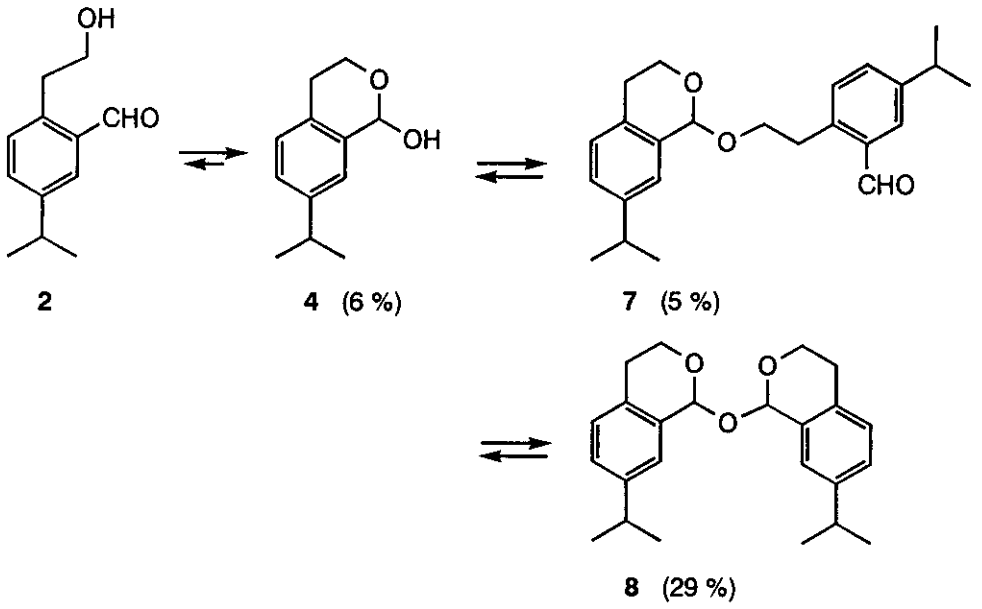


When the reaction was stopped in a half way by removal of the oxidant, ^{1}H nmr spectrum of the mixture exhibited a distinct signal for the hemiacetal anomeric hydrogen at δ 5.95.



Neither an aldehydic methine hydrogen signal near δ 10.2 nor a deshielded aromatic hydrogen signal, ortho to the carbonyl group, near δ 7.6 were observed.

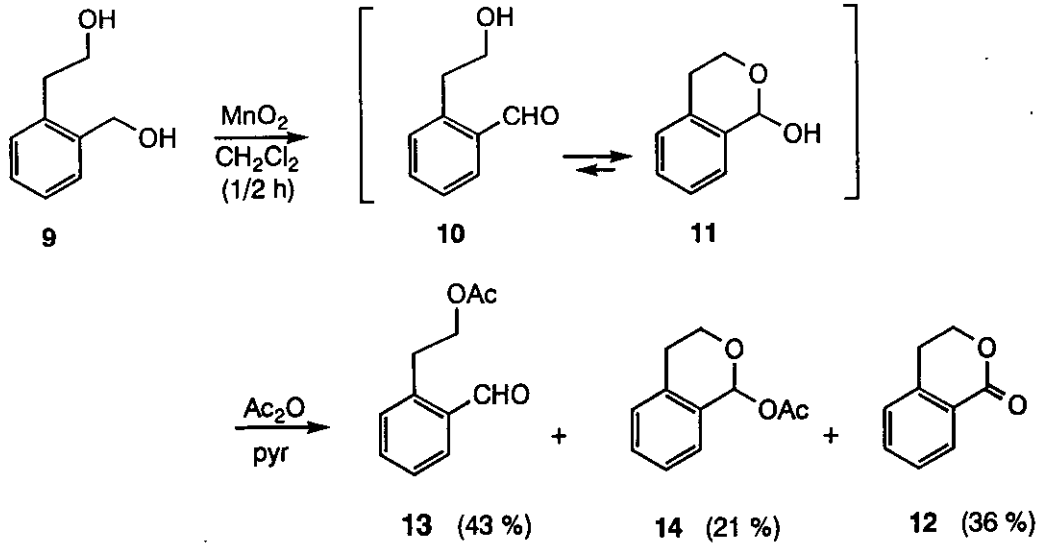
This indicated the initial reaction product to be the aldehyde (**2**), which was in equilibrium and existed exclusively in the hemiacetal structure as **4**. In fact, acetylation of the mixture afforded **5** and **6** in 42 % and 44 % yields, respectively, in addition to the lactone (**3**, 14 %).



2 **4** (6 %) **7** (5 %)

8 (29 %)

Furthermore, standing of the reaction products in dichloromethane for 24 hours at room temperature, extensive equilibration of the hydroxy aldehyde (**2**) took place, and afforded two dimeric acetals (**7**) and (**8**), together with the monomer (**4**), in a ratio of 5 : 29 : 6.



9 **10** **11**

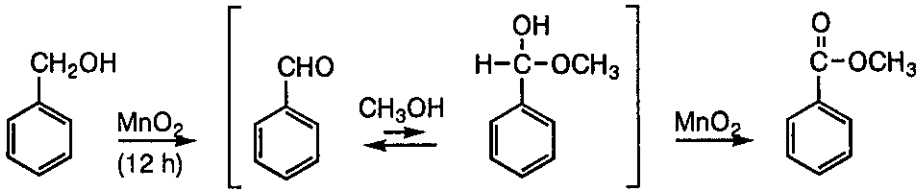
13 (43 %) **14** (21 %) **12** (36 %)

Analogus results have also been obtained with 2-hydroxyethylbenzyl alcohol (**9**), yielding dihydroisocoumarin (**12**) on oxidation, and two acetates (**13** and **14**) on acetylation of the equilibrating intermediates (**10** and **11**).

These observation clearly indicates that benzyl alcohols are oxidized to corresponding aldehydes, as expected, but if the aldehydes are converted to hemiacetals, the newly formed hydroxyl group at the benzylic position becomes susceptible to oxidation once again to give carboxylic acid derivatives.

In comparison, the effect of methanol, the smallest alcohol effective in intermolecular hemiacetal formation, was examined by a series of experiments, and the results are summarized in the Table 1. Namely, benzyl alcohol (**15**, 200 mg) was not oxidized to benzaldehyde (**16**) and methyl benzoate (**18**), or benzoic acid, in the absence of the oxidant (Expt. i), while **15** was transformed efficiently to **16** by the oxidant, irrespective of the solvent used (Expts. ii ~ iv).

Table 1. Effect of methanol on the manganese dioxide oxidation of benzyl alcohol



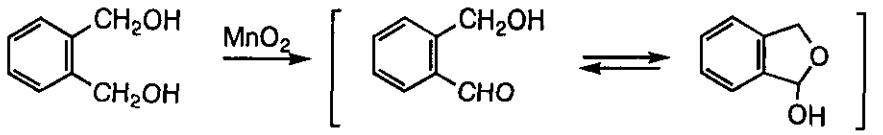
15 **16** **17** **18**

Expt.	Solvent	MnO_2	15*	16*	17*	18*
i	CH_2Cl_2 (10 ml)	0 g	100 %	–	–	–
ii	CH_2Cl_2 (10 ml)	2 g	6 %	94 %	–	–
iii	CH_2Cl_2 (10 ml) + CH_3OH (0.18 ml)	2 g	9 %	91 %	ND	ND
iv	CH_3OH (10 ml)	2 g	67 %	33 %	ND	ND

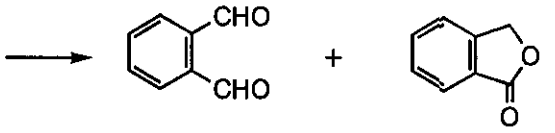
* Characterization made by tlc and ^1H nmr. ND : not detected.

In the presence of methanol (2 mole eq. to **15**, Expt. iii) or even in methanol alone (Expt. iv), the reaction yielded only benzaldehyde (**16**), and failed to exhibit anomeric hydrogen signal for the hemiacetal structure (**17**), or esteric methoxyl signal at δ 3.70 in the ^1H nmr spectrum of the reaction mixture. Therefore, the extent of intermolecular hemiacetal formation of **17** from benzaldehyde (**16**) was proven neglisible, and hence, it was not oxidized further to benzoic acid or an ester (**18**). In oder to confirm the importance of stable intramolecular hemiacetal

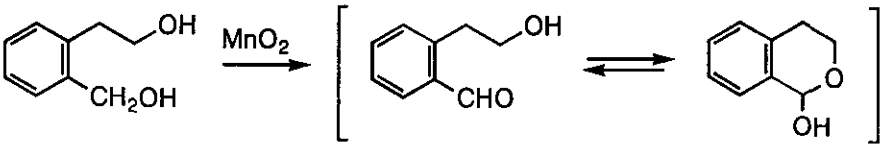
formation on the over oxidation of benzaldehydes to lactones, reaction of a series of *ortho*-subsutituted hydroxyalkylbenzyl alcohols are examined. Treatment of *o*-hydroxymethybenzyl alcohol (**19**) with manganese dioxide in dichloromethane for 2 hours yielded phthalic dialdehyde (**22**, 15 %) and phthalide (**23**, 77 %), while *o*-hydroxypropylbenzyl alcohol (**24**) afforded normal hydroxy aldehyde (**25**, 90 %) as the main product, and only a small fraction (7 %) was converted to the lactone (**27**). Under the same condition, the hydroxyethyl analog



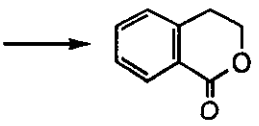
19 **20** (3 %) **21** (5 %)



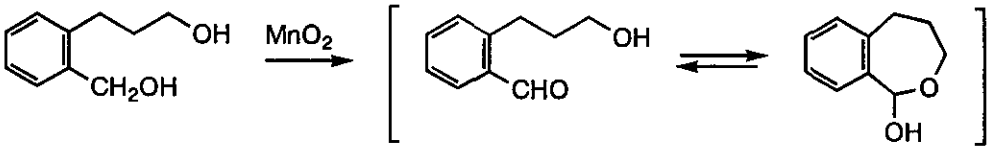
22 (15 %) **23** (77 %)



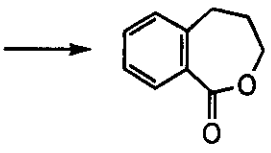
9 **10** (< 0.1 %) **11** (2 %)



12 (98 %)



24 **25** (90 %) **26** (3 %)



27 (7 %)

(**9**) afforded the aldehyde (**11**) and the lactone (**12**) in 2 % and 98 % yields, respectively. Furthermore, ^{1}H nmr spectra of these reaction mixtures revealed the relative composition of each equilibrating pairs to be 38 % of **20** and 62 % of **21**, exclusive of **11**, and 97 % of **25** and 3 % of **26**. Consequently, the yield of lactones (**23**, **12** and **27**) corresponded well to the stability of hemiacetal rings, namely to the order of the ring size of hemiacetal as 6-membered > 5-membered > 7-membered.

EXPERIMENTAL

^{1}H nmr spectra were recorded on a JEOL EX-270 (270 MHz) spectrometer with tetramethylsilane as an internal standard. High-ms (EI) spectral data were obtained on a JOEL JMS DX-303 GC-mass spectrometer.

General procedure of the oxidation of benzyl alcohols - To a solution of benzyl alcohol (1 mmol) in CH_2Cl_2 (10 ml) manganese dioxide (4 g, large excess) was added, and the mixture was stirred at room temperature for 2 h. Then the oxidant was removed by filteration and the filtrate was concentrated under a reduced pressure. The residue was subjected to a silica gel column chromatography using hexane-AcOEt (4:1) as an eluent.

7-Isopropyl-3,4-dihydroisocoumarin (3) - Oil. ^{1}H Nmr ($CDCl_3$) δ : 1.03 (6H, d, *J* 6.9 Hz), 2.95 (1H, septet, *J* 6.9 Hz), 3.03 (2H, t, *J* 5.9 Hz), 4.53 (2H, t, *J* 5.9 Hz), 7.19 (1H, d, *J* 7.6 Hz), 7.41 (1H, d, *J* 7.6 Hz), 7.98 (1H, s). High-ms *m/z*: Calcd $C_{12}H_{14}O_2$: 190.0994; found 190.0979.

Acetates (5 and 6) - A solution of **1** (200 mg, 1.03 mmol) in CH_2Cl_2 was treated with manganese dioxide (4g) at room temperature for 1/2 h, and the products were acetylated with Ac_2O (1 ml) and pyridine (1 ml) followed by chromatographic fractionation to yield **5** (102 mg), **6** (106 mg), and **3** (26 mg).

2-Acetoxyethyl-5-isopropylbenzaldehyde (5) - Oil. ^{1}H Nmr ($CDCl_3$) δ : 1.23 (6H, d, *J* 6.9 Hz), 2.05 (3H, s), 3.01 (1H, septet, *J* 6.9 Hz), 3.34 (2H, t, *J* 6.9 Hz), 4.29 (2H, t, *J* 6.9 Hz), 7.21 (1H, d, *J* 7.6 Hz), 7.40 (1H, d, *J* 7.6 Hz), 7.62 (1H, s), 10.21 (1H, s). High-ms *m/z*: Calcd $C_{14}H_{18}O_3$: 234.1256; found 234.1163.

1-Acetoxy-7-isopropylisochroman (6) - Oil. ^{1}H Nmr ($CDCl_3$) δ : 1.21 (6H, d, *J* 6.9 Hz), 2.12 (3H, s), 2.62 (1H, dd, *J* 16.5, 1.7 Hz), 2.90 (1H, ddd, *J* 16.5, 11.2, 3.3 Hz), 2.95 (1H, septet, *J*

6.9 Hz), 4.04 (1H, ddd, *J* 11.2, 11.2, 1.7 Hz), 4.13 (1H, dd, *J* 11.2, 3.3 Hz), 6.94 (1H, s), 7.24 (1H, s), 7.11 (1H, d, *J* 7.6 Hz), 7.19 (1H, d, *J* 7.6 Hz). High-ms *m/z*: Calcd $C_{14}H_{18}O_3$: 234.1256; found 234.1163.

*Oxidation of diol (**1**) to lactone (**3**), hemiacetal (**4**), and acetals (**7** and **8**)* - A solution of diol (**1**) (200 mg, 1.03 mmol) in CH_2Cl_2 was treated with manganese dioxide (4g) for about 1 h, until tlc monitoring indicated disappearence of the starting material **1**. The manganese dioxide was then removed by filtration, and the filtrate was allowed to stand for 24 h. Then products were isolated as usual to furnish the lactone (**3**) (108 mg, 55 %), hemiacetal (**4**) (12 mg, 6 %), acetals (**7**) (9 mg, 5 %) and (**8**) (55 mg, 29 %).

*7-Isopropylisochroman-1-ol (**4**)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 1.24 (6H, d, *J* 6.9 Hz), 2.65 (1H, ddd, *J* 16.5, 3.6, 2.6 Hz), 2.89 (1H, septet, *J* 6.9 Hz), 2.92 (1H, ddd, *J* 16.5, 11.2, 5.6 Hz), 3.04 (1H, d, *J* 5.3 Hz), 3.93 (1H, ddd, *J* 11.2, 5.6, 2.6 Hz), 4.20 (1H, ddd, *J* 11.2, 11.2, 3.6 Hz), 5.95 (1H, d, *J* 5.3 Hz), 7.07 (1H, d, *J* 7.9 Hz), 7.12 (1H, d, *J* 7.9 Hz), 7.18 (1H, s). High-ms *m/z*: Calcd $C_{12}H_{16}O_2$: 192.1150; found 192.1185.

*7-Isopropyl-1-(2-(2-formyl-4-isopropylphenyl)ethoxy)isochroman (**7**)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 1.22 (6H, d, *J* 6.9 Hz), 1.28 (1H, d, *J* 6.9 Hz), 2.55 (1H, dd, *J* 16.9, 2.6 Hz), 2.85 (1H, septet, *J* 6.9 Hz), 2.91 (1H, ddd, *J* 16.9, 13.0, 6.1 Hz), 2.98 (1H, septet, *J* 6.9 Hz), 3.38 (2H, t, *J* 6.8 Hz), 3.81 (1H, dd, *J* 13.0, 6.1 Hz), 3.85 (1H, m), 4.07 (1H, ddd, *J* 13.0, 13.0, 2.6 Hz), 4.17 (1H, m), 5.48 (1H, s), 6.91 (1H, s), 7.02 (1H, d, *J* 7.9 Hz), 7.11 (1H, d, *J* 7.9 Hz), 7.32 (1H, d, *J* 7.9 Hz), 7.40 (1H, d, *J* 7.9 Hz), 7.72 (1H, d, *J* 7.9 Hz), 10.28 (1H, s). High-ms *m/z*: Calcd $C_{24}H_{30}O_3$: 366.2195; found 366.2193.

*7-Isopropyl-1-(7-isopropyl-1-isochromanyloxy)isochroman (**8**)* - mp 78 ~ 80 ℃. ^{1}H Nmr ($CDCl_3$) δ: 1.22 (12H, d, *J* 6.9 Hz), 2.51 (2H, dd, *J* 16.0, 2.6 Hz), 2.85 (2H, septet, *J* 6.9 Hz), 3.08 (2H, ddd, *J* 16.0, 12.5, 6.1 Hz), 4.08 (2H, dd, *J* 12.5, 6.1 Hz), 4.34 (2H, ddd, *J* 12.5, 12.5, 2.6 Hz), 6.09 (2H, s), 7.04 (2H, d, *J* 8.3 Hz), 7.07 (2H, s), 7.09 (2H, d, *J* 8.3 Hz). High-ms *m/z*: Calcd $C_{24}H_{30}O_3$: 366.2195; found 366.2206.

*Dihydroisocoumarin (**12**) from **9** (98 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 3.07 (2H, t, *J* 5.9 Hz), 4.52 (2H, t, *J* 5.9 Hz), 7.25 (1H, d, *J* 7.6 Hz), 7.42 (1H, t, *J* 7.6 Hz), 7.53 (1H, t, *J* 7.6 Hz), 8.11 (1H, d, *J* 7.6 Hz). High-ms *m/z*: Calcd $C_9H_8O_2$: 148.0524; found 148.0548.

*2-Acetoxyethylbenzaldehyde (**13**) from **9** (43 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 2.00 (3H, s), 3.38 (2H, d, *J* 6.9 Hz), 4.32 (2H, d, *J* 6.9 Hz), 7.20 - 7.40 (2H, m), 7.42 (1H, t, *J* 7.6 Hz), 7.83

(1H, d, *J* 7.6 Hz), 10.22 (1H, s).

*1-Acetoxyisochroman (**14**) from **9** (21 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 2.22 (3H, s), 2.67 (1H, dd, *J* 16.5, 1.7 Hz), 3.10 (1H, ddd, *J* 16.5, 11.9, 3.3 Hz), 4.05 (1H, dd, *J* 11.9, 3.3 Hz), 4.15 (1H, ddd, *J* 11.9, 11.9, 1.7 Hz), 6.95 (1H, s), 7.20 - 7.40 (4H, m).

*Phthalic semialdehyde (**20** and **21**)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 5.06 (2H, s), 10.55 (1H, s) for **20**; and 3.19 (1H, d, *J* 8.4 Hz), 5.33 (2H, br), 6.50 (1H, d, *J* 8.4 Hz) for **21**.

*Phthalic dialdehyde (**22**) from **19** (15 %)* - mp 55 ~ 58 ℃. ^{1}H Nmr ($CDCl_3$) δ: 7.79 (2H, dd, *J* 5.6, 3.3 Hz), 7.99 (1H, dd, *J* 5.6, 3.3 Hz), 10.55 (2H, s). High-ms *m/z*: Calcd $C_8H_6O_2$: 134.0368; found 134.0339.

*Isochroman-1-ol (**11**) from **9** (2 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 2.68 (1H, ddd, *J* 16.5, 3.6, 2.6 Hz), 2.95 (1H, ddd, *J* 16.5, 11.2, 5.6 Hz), 3.04 (1H, d, *J* 5.3 Hz), 3.95 (1H, ddd, *J* 11.2, 11.2, 3.6 Hz), 4.22 (1H, ddd, *J* 11.2, 11.2, 3.6 Hz), 5.98 (1H, d, *J* 5.3 Hz), 7.14 (1H, d, *J* 7.9 Hz). 7.25 (1H, t, *J* 7.9 Hz), 7.28 (1H, t, *J* 7.9 Hz), 7.41 (1H, d, *J* 7.9 Hz).

*o-Hydropropylbenzaldehyde (**25**) from **24** (90 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 1.89 (2H, tt, *J* 7.6, 6.1 Hz), 2.2 (1H, br), 3.15 (1H, t, *J* 7.6 Hz), 3.67 (2H, t, *J* 6.1 Hz), 7.32 (1H, d, *J* 7.6 Hz). 7.40 (1H, t, *J* 7.4 Hz), 7.50 (1H, t, *J* 7.6 Hz), 7.81 (1H, d, *J* 7.6 Hz), 10.23 (1H, s).

*Benzo[c]oxepan-1-ol (**26**)* - ^{1}H Nmr ($CDCl_3$) δ: 5.67 (1H, s).

*Benzo[c]oxepan-1-one (**27**) from **24** (7 %)* - Oil. ^{1}H Nmr ($CDCl_3$) δ: 2.13 (2H, tt, *J* 7.3, 6.3 Hz), 2.91 (2H, t, *J* 7.3 Hz), 4.16 (2H, t, *J* 6.3 Hz), 7.22 (1H, d, *J* 7.6 Hz), 7.37 (1H, t, *J* 7.6 Hz), 7.50 (1H, t, *J* 7.6 Hz), 7.73 (1H, d, *J* 7.6 Hz). High-ms *m/z*: Calcd $C_{10}H_{10}O_2$: 162.0681; found 162.0675.

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