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# SYNTHESIS AND REDOX RING CLEAVAGE OF *cis*-1,3,4,5-TETRAHYDROBENZO[*c*]OXEPINES

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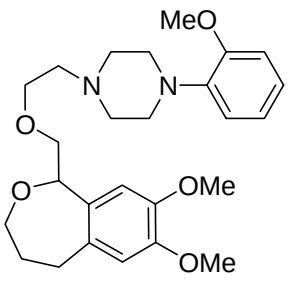
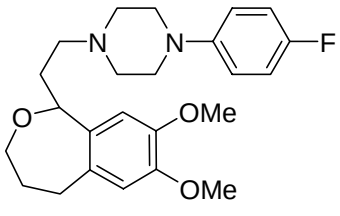
**Abstract** –A series of *cis*-1,3,4,5-tetrahydrobenzo[*c*]oxepines was conveniently prepared via the oxa-Pictet-Spengler reaction catalyzed by boron trifluoride etherate in dioxane at room temperature. Experiments proved that the construction of these heterocyclic compounds via this methodology was highly acid (catalyst)- and reaction condition-dependent. An unexpected redox ring cleavage reaction occurred when unsuitable acids or reaction conditions were employed.

## INTRODUCTION

Many natural products contain a seven-membered oxacycle such as oxepines in their molecular architecture.[1] 1,3,4,5-Tetrahydrobenzo[*c*]oxepine and its derivatives have been explored in the field of pharmaceutical research. For example, the oxepine **A** proved to be an active antianaphylactic agent while the compound **B** showed central and peripheral activities as an α-blocker.[2] Numerous synthetic approaches to these heterocyclic compounds have been reported and most of them are based on the intramolecular dehydration of a diol or Friedel-Crafts alkylation of chloride and tosylate.[3] In recent years, modern coupling reactions such as Suzuki and Heck reactions have also been utilized to construct these seven-membered oxacycles.[4] Although the oxa-Pictet-Spengler reaction has been widely used to build a variety of cumarins,[5] its application in the synthesis of 1,3,4,5-tetrahydrobenzo[*c*]oxepine receives less attention.[2, 5f]



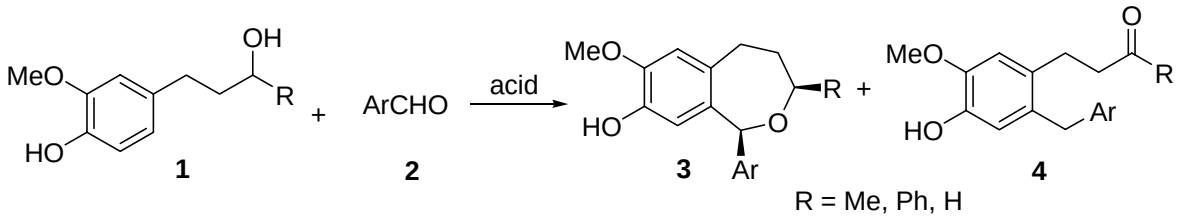

**A**




**B**

## RESULTS AND DISCUSSION

We now disclose a synthesis of *cis*-1,3,4,5-tetrahydrobenzo[*c*]oxepines via the oxa-Pictet-Spengler reaction. An unexpected redox ring cleavage reaction of 1,3,4,5-tetrahydrobenzo[*c*]oxepines is also revealed. Our research was initiated with the oxa-Pictet-Spengler reaction of **1a** (R=Me) with *p*-nitrobenzaldehyde (**2a**). The cyclization was promoted by boron trifluoride etherate in dichloromethane according to our previous procedure.[6] Unexpectedly, the reaction gives a mixture of **3a** and **4a** (Scheme **1**). Under the same reaction conditions, treatment of **1a** and benzaldehyde (**2b)** gives **4b** as the only product. Similar results are also obtained while MsOH is used as catalyst (Table 1).




**Scheme 1**

Table 1 Reactions of **1a** (R=Me) with *p*-nitrobenzaldehyde (**2a**) and benzaldehyde (**2b**)

| Entry | ArCHO | Solvent | Acid | Conditions | Yield of **3** (%)[a] | Yield of **4** (%)[a] |
|---|---|---|---|---|---|---|
| 1 | **2a** | DCM | $BF_3{\cdot}Et_2O$ | rt | 52(**3a**) | 16(**4a**) |
| 2 | **2a** | DCM | $BF_3{\cdot}Et_2O$ | reflux | 0(**3a**) | 84(**4a**) |
| 3 | **2a** | dioxane | $BF_3{\cdot}Et_2O$ | rt | 62(**3a**) | 0(**4a**) |
| 4 | **2a** | dioxane | $BF_3{\cdot}Et_2O$ | reflux | 23(**3a**) | 65(**4a**) |
| 5 | **2b** | DCM | $BF_3{\cdot}Et_2O$ | rt | 0(**3b**) | 57(**4b**) |
| 6 | **2b** | DCM | $BF_3{\cdot}Et_2O$ | reflux | 0(**3b**) | 45(**4b**) |
| 7 | **2b** | dioxane | $BF_3{\cdot}Et_2O$ | rt | 32(**3b**) | 9(**4b**) |
| 8 | **2b** | dioxane | $BF_3{\cdot}Et_2O$ | reflux | 0(**3b**) | 38(**4b**) |
| 9 | **2b** | DCM | MsOH | rt | 7(**3b**) | 20(**4b**) |
| 10 | **2b** | DCM | MsOH | reflux | 0(**3b**) | 74(**4b**) |
| 11 | **2b** | dioxane | MsOH | rt | -(**3b**)[b] | -(**4b**)[b] |
| 12 | **2b** | dioxane | MsOH | reflux | 3(**3b**) | 27(**4b**) |

[a] Isolated yield

[b] No product islated

We postulated that the ketone **4** was resulted from a redox ring cleavage of **3**.[7] Namely, the desired oxepine **3** was actually formed and then decomposed to **4** in situ. Obviously, the cyclization must be performed under such reaction conditions that the oxepine **3** can endure. The influence of the reaction

parameters such as acid, solvent and temperature were investigated and results were summarized in Table 1. It was found that boron trifluoride etherate in dioxane at room temperature turned out to be effective for the oxe-Pictet-Spengler reaction to produce the desired oxepine. A series of 1,3,4,5-tetrahydrobenzo[*c*]oxepines was thus prepared, and the results were summarized in Table 2.

Table 2 Synthesis of **3a-k** via the oxa-Pictet-Spengler reaction[a]

| Entry | R | Ar | Product | Yield (%)[b] |
|---|---|---|---|---|
| 1 | Me | *o*-$ClC_6H_4$ | **3c** | 70 |
| 2 | Me | *p*-$ClC_6H_4$ | **3d** | 58 |
| 3 | Me | *o*-$NO_2C_6H_4$ | **3e** | 42 |
| 4 | Me | *m*-$NO_2C_6H_4$ | **3f** | 45 |
| 5 | Me | *m*-$BrC_6H_4$ | **3g** | 50 |
| 6 | Me | *p*-$BrC_6H_4$ | **3h** | 50 |
| 7 | Me | 2,6-$Cl_2C_6H_3$ | **3i** | 63 |
| 8 | $C_6H_5$ | *p*-$NO_2C_6H_4$ | **3j** | 22 |
| 9 | H | *p*-$NO_2C_6H_4$ | **3k** | 47[c] |

[a] Reaction conditions: $BF_3{\cdot}Et_2O$ (200% mol), ArCHO (120% mol), rt.

[b] Isolated yield after chromatography.

[c] Catalyzed by $AlCl_3$.

The oxa-Pictet-Spengler reaction of **1** with aromatic aldehyde is remarkably stereoselective, [8] which gives a single *cis*-stereoisomer. Assignment of the *cis*-stereochemical relationship between the substituents at C-1 and C-3 is made by NOE enhancement experiments. Irradiation of the C-1 methine proton of **3a** gives an enhancement of the C-3 methine proton signal, and no change of C-3 methyl proton. The structure of **3e** was further confirmed by X-ray crystallography (Figure 1).

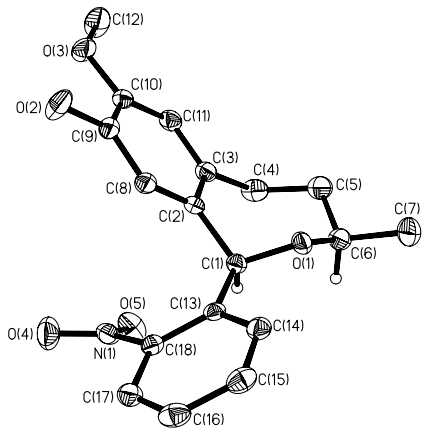
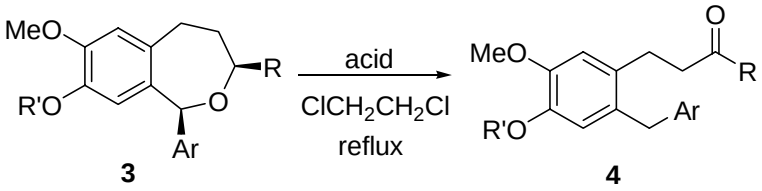



**Figure 1** Molecular structure of **3e**

We next treated the above-prepared oxepines **3a-k** with several acids to bear out that the ketones **4** were resulted from **3** through a ring cleavage reaction. It was observed that the ring cleavage reaction (except **3e** and **3k**) occurred smoothly in the presence of acids such as boron trifluoride etherate, methylsulfonic acid, and *p*-toluenesulfonic acid. The results were outlined in Table 3. In contrast, acetic acid, benzoic acid, and phenol do not promote the reaction (Table 3, entry 4). All the redox ring cleavage products **4a-l** were characterized by spectral analyses and the structure of **4c** was confirmed by X-ray crystallography (Figure 2).




**3** **4**

**Scheme 2**

Table 3 Results of redox ring cleavage of **3a-l**[a]

| Entry | R | R’ | Ar | Acid | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Me | H | *p*-$NO_2C_6H_4$ | MsOH | 80(**4a**) |
| 2 | Me | H | $C_6H_5$ | MsOH | 89(**4b**) |
| 3 | Me | H | *o*-$ClC_6H_4$ | MsOH | 78(**4c**) |
| 4 | Me | H | *p*-$ClC_6H_4$ | MsOH | 90(**4d**) |
| | Me | H | *p*-$ClC_6H_4$ | TsOH | 89(**4d**) |
| | Me | H | *p*-$ClC_6H_4$ | $BF_3{\cdot}Et_2O$ | 90(**4d**) |
| | Me | H | *p*-$ClC_6H_4$ | $C_6H_5OH$ | -[c] |
| | Me | H | *p*-$ClC_6H_4$ | $C_6H_5COOH$ | -[c] |
| | Me | H | *p*-$ClC_6H_4$ | $CH_3COOH$ | -[c] |
| 5 | Me | H | *o*-$NO_2C_6H_4$ | MsOH | -[c] |
| 6 | Me | H | *m*-$NO_2C_6H_4$ | MsOH | 71(**4f**) |
| 7 | Me | H | *m*-$BrC_6H_4$ | MsOH | 67(**4g**) |
| 8 | Me | H | *p*-$BrC_6H_4$ | MsOH | 69(**4h**) |
| 9 | Me | H | 2,6-$Cl_2C_6H_3$ | MsOH | 95(**4i**) |
| 10 | Ph | H | *p*-$NO_2C_6H_4$ | MsOH | 47(**4j**) |
| 11 | H | H | *p*-$NO_2C_6H_4$ | MsOH | -[c] |
| 12 | Me | Me | *p*-$ClC_6H_4$ | MsOH | 91(**4l**) |

[a] Conditions: 20 mol% acid, 1,2-dichloromethane, reflux, 3h.

[b] Isolated yield after chromatography.

[c] No redox ring cleavage product were obtained.

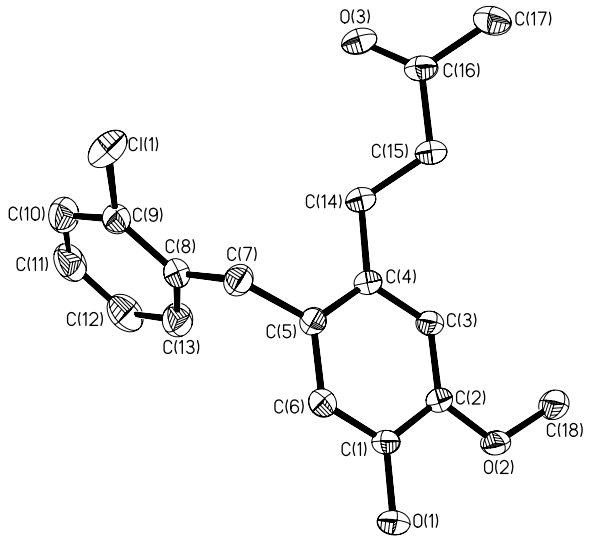
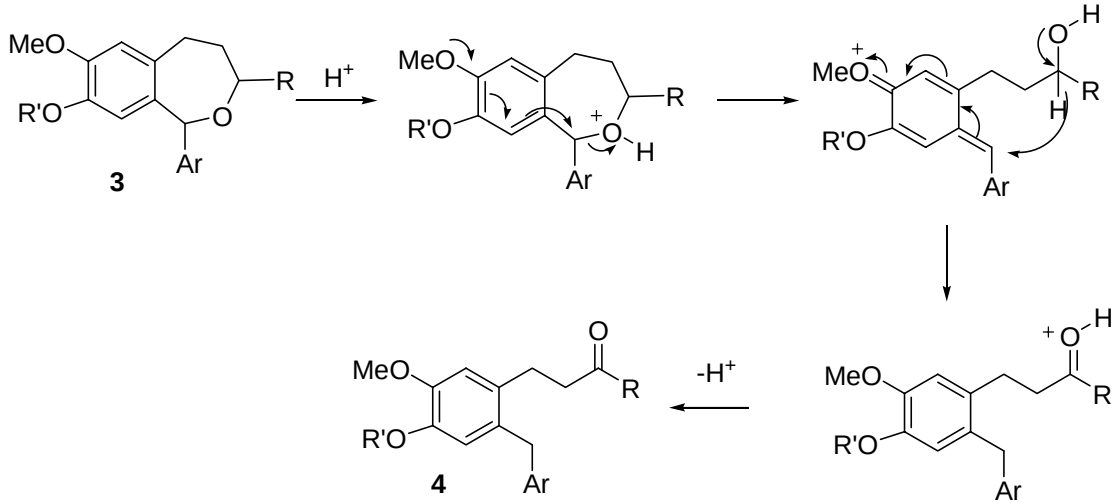



**Figure 2** Molecular structure of **4c**

It should be noted that the redox ring cleavage reaction could also occur at the absence of a hydroxyl group. For instance, the methylated product of **3d** underwent the ring cleavage in 91% isolated yield (Table 3 entry 12). A possible mechanism for this redox cleavage reaction was proposed in Scheme 3. Protonation of oxygen atom in the seven-membered ring of **3** provides an oxonium ion, which undergoes cleavage of a C-O single bond to give a conjugated carbocation. Intramolecular hydride migration to the carbocation provides a stable protonated ketone, which lose a proton to give **4**.




**Scheme 3**

In conclusion, 1,3,4,5-tetrahydrobenzo[*c*]oxepines are very sensitive to strong acids and liable to an unexpected redox ring cleavage reaction. Therefore, a suitable catalyst and reaction conditions are very important for construction of 1,3,4,5-tetrahydrobenzo[*c*]oxepines by the oxa-Pictet-Spengler reaction. We found that boron trifluoride etherate in dioxane was a suitable catalyst for this purpose and a series of *cis*-1,3,4,5-tetrahydrobenzo [*c*]oxepines was thus successfully prepared. What we reported here extended

the scope of the oxa-Pictet-Spengler reaction and was also beneficial to the investigation of the properties of 1,3,4,5-tetrahydrobenzo [*c*]oxepines.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer (500 MHz for $^1$H NMR, 125 MHz for $^{13}$C NMR). Mass spectra were performed on a TRACE MS spectrometer. IR spectra were recorded on an AVATAR 360 FT-IR spectrometer. Elemental analyses were recorded on a Vario EL apparatus. Melting points were determined on an X-6 micro-melting point apparatus and are uncorrected. Silica gel (200-300 mesh) was used for column chromatography. 4-(4-Hydroxy-3-methoxyphenyl) butan-2-ol (**1a**) was prepared according to the literature.[9]

**General procedure for preparation of 1,3,4,5-tetrahydrobenzo[*c*]oxepines 3.**

$BF_3{\cdot}Et_2O$ (0.24 mL, 2.0 mmol) was added to a dioxane (5 mL) mixed solution of **1** (1.0 mmol) and aromatic aldehyde (1.2 mmol). After this mixture was stirred at rt for one week, 30 mL of AcOEt was added. The organic layer was separated, washed with saturated aqueous solutions of $NaHCO_3$ (3 x 20 mL), $NaHSO_3$ (3 x 20 mL), then dried with anhydrous $Na_2SO_4$. Removal of the solvent and the resulting residue was purified by silica gel column chromatography (eluent: petroleum ether/ AcOEt = 5:1) to give the product **3**.

**8-Hydroxy-7-methoxy-3-methyl-1-(4-nitrophenyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3a**

Light Yellow crystals, mp 145-146 ºC (AcOEt, petroleum ether). IR (KBr): 3547, 2960, 2925, 1598, 1514, 1348, 1285, 1076, 738 cm$^{-1}$.$^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.31 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.62-1.98 (m, 2H, $CH_2$), 2.90-3.23 (m, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.08 (m, 1H, CH), 5.40 (s, 1H, OH), 5.82 (s, 1H, CH-Ar), 6.04 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.60 (d, $J$ = 8.5 Hz, 2H, aryl H), 8.26 (d, $J$ = 8.8 Hz, 2H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 148.8, 147.1, 145.5, 143.1, 134.8, 133.9, 127.9, 123.4, 113.9, 112.4, 80.7, 80.4, 56.1, 36.6, 33.6, 23.0. MS (EI, 70eV): $m/z$(%) = 329 ($M^+$, 100). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 66.08; H, 6.09; N, 4.19.

**8-Hydroxy-7-methoxy-3-methyl-1-phenyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3b**

White crystals, mp 119-120 ºC (AcOEt, petroleum ether). IR (KBr): 3463, 1596, 1509, 1286, 1106, 732, 696 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.27 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.54-1.95 (m, 2H, $CH_2$), 2.86-3.22 (m, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 4.04 (m, 1H, CH), 5.31 (s, 1H, OH), 5.70 (s, 1H, CH-Ar), 6.16 (s, 1H, aryl H), 6.71 (s, 1H, aryl H), 7.25-7.38 (m, 5H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 23.0, 33.6, 36.8, 56.0, 79.8, 81.7, 112.3, 114.5, 127.1, 127.2, 128.2, 133.7, 136.4, 141.4, 143.0, 145.1. MS (EI, 70eV): $m/z$(%) = 284 ($M^+$, 100). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.53; H, 6.90.

**1-(2-Chlorophenyl)-8-hydroxy-7-methoxy-3-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3c**

White crystals, mp 112-113 ºC (AcOEt, petroleum ether). IR (KBr): 3558, 2973, 2936, 1593, 1511, 1269, 1075, 1027, 845, 748 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.30 (d, $J$ = 6.1 Hz, 3H, $CH_3$), 1.62-1.98 (m, 2H, $CH_2$), 2.86-3.38 (m, 2H, $CH_2$), 3.89 (s, 3H, $OCH_3$), 4.11 (m, 1H, $CH_3CH$), 5.35 (s, 1H, OH), 5.99 (s, 1H, CH-Ar), 6.05 (s, 1H, aryl H), 6.77 (s, 1H, aryl H), 7.28-7.40 (m, 3H, aryl H), 7.76 (d, $J$ = 7.6 Hz, 1H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 23.1, 33.9, 36.8, 56.0, 78.2, 81.2, 112.4, 113.3, 126.9, 128.4, 128.9, 129.0, 132.0, 134.0, 135.1, 139.4, 143.1, 145.2. MS (EI, 70eV): $m/z$(%) = 318 ($M^+$, 100). Anal. Calcd for $C_{18}H_{19}O_3Cl$: C, 67.82; H, 6.01. Found: C, 67.75; H, 6.00.

**1-(4-Chlorophenyl)-8-hydroxy-7-methoxy-3-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3d**

White crystals, mp 115-117 ºC (AcOEt, petroleum ether). IR (KBr): 3559, 1589, 1504, 1278, 856, 766 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.33 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.64-2.00 (m, 2H, $CH_2$), 2.93-3.25 (m, 2H, $CH_2$), 3.93 (s, 3H, $OCH_3$), 4.09 (m, 1H, $CH_3CH$), 5.40 (s, 1H, OH), 5.74 (s, 1H, CH-Ph), 6.18 (s, 1H, aryl H), 6.77 (s, 1H, aryl H), 7.32-7.42 (m, 4H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.9, 33.5, 36.6, 56.0, 79.9, 80.9, 112.3, 114.2, 128.3, 128.4, 132.8, 133.6, 135.8, 139.9, 143.0, 145.2. MS (EI, 70eV): $m/z$(%) = 318 ($M^+$, 100). Anal. Calcd for $C_{18}H_{19}O_3Cl$: C, 67.82; H, 6.01. Found: C, 67.75; H, 5.93.

**8-Hydroxy-7-methoxy-3-methyl-1-(2-nitrophenyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3e**

Light Yellow crystals, mp 187-188 ºC (AcOEt, petroleum ether). IR (KBr): 3530, 2969, 2925, 2864, 1595, 1527, 1508, 1354, 1286, 1068, 732 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.29 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.60-1.98 (m, 2H, $CH_2$), 2.83-3.40 (m, 2H, $CH_2$), 3.88 (s, 3H, $OCH_3$), 4.11 (m, 1H, CH), 5.35 (s, 1H, OH), 5.95 (s, 1H, CH-Ar), 6.43 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.50-7.76 (m, 2H, aryl H), 8.03 (d, $J$ = 7.9 Hz, 1H, aryl H), 8.09 (d, $J$ = 8.2 Hz, 1H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 23.0, 33.8, 36.8, 56.0, 77.1, 81.3, 112.3, 112.4, 124.4, 128.1, 129.7, 133.5, 133.9, 135.3, 137.2, 143.1, 145.2, 147.1. MS (EI, 70eV): $m/z$(%) = 329 ($M^+$, 16). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.59; H, 5.80; N, 4.27.

**8-Hydroxy-7-methoxy-3-methyl-1-(3-nitrophenyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3f**

Light yellow crystals, mp 159-160 ºC (AcOEt, petroleum ether). IR (KBr): 3453, 2963, 2920, 1595, 1528, 1508, 1351, 1286, 1106, 732 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.31 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.60-1.98 (m, 2H, $CH_2$), 2.91-3.21 (m, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.07 (m, 1H, CH), 5.39 (s, 1H, OH), 5.82 (s, 1H, CH-Ar), 6.07 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.56 (t, $J$ = 7.9 Hz, 1H, aryl H), 7.75 (d, $J$ = 7.6 Hz, 1H, aryl H ), 8.19 (d, $J$ = 8.12 Hz, 1H, aryl H ), 8.30 (s, 1H, aryl H) . $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.9, 33.5, 36.6, 56.1, 80.0, 80.7, 112.5, 114.0, 122.2, 122.3, 129.0, 133.3, 133.8, 134.9, 143.2, 143.7, 145.4, 148.2. MS (EI, 70eV): $m/z$(%) = 328 ($M^+$, 44.5). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.69; H, 6.06; N, 4.35.

**1-(3-Bromophenyl)-8-hydroxy-7-methoxy-3-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3g**

White crystals, mp 111-112 ºC (AcOEt, petroleum ether). IR (KBr): 3451, 2968, 2915, 1594, 1509, 1288, 1105, 876, 762 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.26 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.52-1.94 (m, 2H, $CH_2$), 2.84-3.18 (m, 2H, $CH_2$), 3.86 (s, 3H, $OCH_3$), 4.01 (m, 1H, CH), 5.36 (s, 1H, OH), 5.66 (s, 1H, CH-Ar), 6.14 (s, 1H, aryl H), 6.70 (s, 1H, aryl H), 7.19-7.57 (m, 4H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.9, 33.5, 36.6, 56.0, 79.9, 80.9, 112.3, 114.2, 122.4, 125.7, 129.7, 130.1, 130.2, 133.6, 135.6, 143.0, 143.7, 145.2. MS (EI, 70eV): $m/z$(%) = 361 ($M^+$, 33). Anal. Calcd for $C_{18}H_{19}O_3Br$: C, 59.52; H, 5.27. Found: C, 59.60; H, 5.39.

**1-(4-Bromophenyl)- 8-hydroxy -7-methoxy-3-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3h**

White crystals, mp 131-132 ºC (AcOEt, petroleum ether). IR (KBr): 3452, 2960, 2919, 1596, 1508, 1288, 1106, 767 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.26 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.52-1.94 (m, 2H, $CH_2$), 2.83-3.18 (m, 2H, $CH_2$), 3.85 (s, 3H, $OCH_3$), 4.01 (m, 1H, CH), 5.33 (s, 1H, OH), 5.65 (s, 1H, CH-Ar), 6.11 (s, 1H, aryl H), 6.70 (s, 1H, aryl H), 7.26 (d, $J$ = 7.6 Hz, 2H, aryl H), 7.49 (d, $J$ = 8.3 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.9, 33.6, 36.7, 56.1, 79.9, 81.0, 112.4, 114.2, 121.0, 128.9, 131.2, 133.7, 135.8, 140.4, 143.1, 145.2. MS (EI, 70eV): $m/z$(%) = 361 ($M^+$, 18). Anal. Calcd for $C_{18}H_{19}O_3Br$: C, 59.52; H, 5.27. Found: C, 59.83; H, 5.58.

**1-(2,6-Dichlorophenyl)-8-hydroxy-7-methoxy-3-methyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3i**

White crystals, mp 140-141 ºC (AcOEt, petroleum ether). IR (KBr): 3553, 1591, 1513, 1434, 1273, 781 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.27 (d, $J$ = 6.2 Hz, 3H, $CH_3$), 1.72-2.05 (m, 2H, $CH_2$), 3.02-3.12 (m, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.07 (m, 1H, CH), 5.37 (s, 1H, OH), 6.26 (s, 1H, CH-Ar), 6.39 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.20 (t, $J$ = 8.0 Hz, 1H, aryl H), 7.37 (d, $J$ = 8.0 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 22.8, 33.3, 36.6, 56.0, 79.3, 80.3, 112.8, 113.4, 128.9, 132.6, 133.8, 136.8, 143.1, 145.1. MS (EI, 70eV): $m/z$(%) = 352 ($M^+$, 100). Anal. Calcd for $C_{18}H_{18}O_3Cl_2$: C, 61.20; H, 5.14. Found: C, 61.22; H, 5.15.

**8-Hydroxy-7-methoxy-1-(4-nitrophenyl)-3-phenyl-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3j**

White crystals, mp 208-209 ºC (AcOEt, petroleum ether). IR (KBr): 3535, 1518, 1346, 1072, 700 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.91-2.23 (m, 2H, $CH_2$), 3.03-3.35 (m, 2H, $CH_2$), 3.93 (s, 3H, $OCH_3$), 4.98(dd, $J$ = 10.8 Hz, 1.8 Hz, 1H, CH-Ar), 5.41 (s, 1H, OH), 5.99 (s, 1H, CH), 6.13 (s, 1H, aryl H), 6.80 (s, 1H, aryl H), 7.30-7.40 (m, 5H, aryl H), 7.63 (d, $J$ = 8.5 Hz, 2H, aryl H), 8.25 (d, $J$ = 8.7 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 33.7, 37.5, 56.1, 81.5, 85.5, 112.5, 114.2, 123.4, 125.7, 127.3, 128.0, 128.3, 133.5, 134.5, 143.3, 143.4, 145.6, 147.2, 148.5. MS (EI, 70eV): $m/z$(%) = 391 ($M^+$, 54). Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.32; H, 5.70; N, 3.25.

**8-Hydroxy-7-methoxy-1-(4-nitrophenyl)-1,3,4,5-tetrahydrobenzo[*c*]oxepine 3k**

Yellow crystals, mp 159-160 ºC (AcOEt, petroleum ether). IR (KBr): 3541, 1515, 1351, 1094, 740 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 1.86-1.97 (m, 2H, $CH_2$), 2.92-3.19 (m, 2H, $CH_2$), 3.91 (s, 3H, $OCH_3$),

3.96-4.35 (m, 2H, $CH_2$), 5.37 (s, 1H, OH), 5.78 (s, 1H, CH-Ar), 6.09 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.56 (d, $J$ = 8.5 Hz, 2H, aryl H), 8.26 (d, $J$ = 8.8 Hz, 2H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 30.0, 34.2, 56.0, 73.3, 82.2, 112.6, 114.5, 123.5, 128.1, 131.0, 134.0, 134.2, 143.2, 145.5, 148.5. MS (EI, 70eV): $m/z$(%) = 315 ($M^+$, 94). Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.50; H, 5.47; N, 4.38.

**General procedure for preparation of 4a-i.**

A catalytic amount of methylsulfonic acid (0.006 g, 0.06 mmol) was added to a 1,2-dichloroethane solution (5 mL) of 1,3,4,5-tetrahydrobenzo[*c*]oxepine **3** (0.3 mmol). This mixture was refluxed for about 2 h, cooled to rt, and 30 mL of AcOEt was added. The organic layer was separated, washed with saturated solution of $NaHCO_3$ (3 x 20 mL), then dried with anhydrous $Na_2SO_4$. Removal of the solvent and the resulting residue was purified by silica gel column chromatography to give product **4**.

**4-[2-(4-Nitrobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4a**

Yellow crystals, mp 78-79 ºC (AcOEt, petroleum ether). IR (KBr): 3459, 1710, 1594, 1513, 1345, 1284, 1103, 736cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.09 (s, 3H, $CH_3$), 2.56 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 2.77 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.03 (s, 2H, Ar-$CH_2$-Ar), 5.56 (s, 1H, OH), 6.69 (s, 1H, aryl H), 6.71 (s, 1H, aryl H), 7.29 (d, $J$ = 8.5 Hz, 2H, aryl H), 8.13 (d, $J$ = 8.6 Hz, 2H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 26.3, 30.0, 38.2, 44.7, 56.0, 112.1, 116.7, 123.6, 129.1, 129.3, 130.9, 144.1, 145.6, 146.4, 148.9, 207.6. MS (EI, 70eV): $m/z$(%) = 329 ($M^+$, 2). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.41; H, 5.94; N, 4.25.

**4-(2-Benzyl-4-hydroxy-5-methoxyphenyl)butan-2-one 4b**

White crystals, mp 78-79 ºC (AcOEt, petroleum ether). IR (KBr): 3433, 1709, 1591, 1514, 1264, 884, 723 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.03 (s, 3H, $CH_3$), 2.45 (t, $J$ = 7.6 Hz, 2H, $CH_2$), 2.81 (t, $J$ = 7.5 Hz, 2H, $CH_2$), 3.88 (s, 3H, $OCH_3$), 3.93 (s, 2H, Ar-$CH_2$-Ar), 5.52 (s, 1H, OH), 6.68 (s, 1H, aryl H), 6.76 (s, 1H, aryl H), 7.14 (d, $J$ = 7.4 Hz, 2H, aryl H), 7.20 (t, $J$ = 7.3 Hz, 1H, aryl H), 7.26-7.29 (m, 2H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 208.2, 145.1, 143.8, 141.1, 131.3, 130.9, 128.7, 128.5, 126.0, 116.9, 112.1, 56.0, 44.9, 38.6, 29.9, 26.7. MS (EI, 70eV): $m/z$(%) = 284 ($M^+$, 60). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.21; H, 7.29.

**4-[2-(2-Chlorobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4c**

White crystals, mp 115-116 ºC (AcOEt, petroleum ether). IR (KBr): 3383, 1702, 1591, 1515, 1294, 882, 754 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 2.10 (s, 3H, $CH_3$), 2.61 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 2.81 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.01 (s, 2H, Ar-$CH_2$-Ar), 5.50 (s, 1H, OH), 6.61 (s, 1H, aryl H), 6.73 (s, 1H, aryl H), 6.97 (m, 1H, aryl H), 7.14-7.19 (m, 2H, aryl H), 7.40 (m, 1H, aryl H). $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 26.7, 30.0, 35.5, 44.7, 56.0, 112.1, 116.4, 126.8, 127.6, 129.4, 129.8, 130.5, 131.0,

134.1, 138.4, 143.9, 145.2, 208.1. MS (EI, 70eV): *m*/*z*(%) = 318 ($M^+$, 93). Anal. Calcd for $C_{18}H_{19}O_3Cl$: C, 67.82; H, 6.01. Found: C, 67.84; H, 6.11.

**4-[2-(4-Chlorobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4d**

White crystals, mp 78-79 ºC (AcOEt, petroleum ether). IR (KBr): 3385, 1705, 1591, 1511, 1274, 1089, 873 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.10 (s, 3H, $CH_3$), 2.52 (t, *J* = 7.5 Hz, 2H, $CH_2$), 2.82 (t, *J* = 7.5 Hz, 2H, $CH_2$), 3.92 (s, 5H, Ph-$CH_2$-Ph +$OCH_3$), 5.54 (s, 1H, OH), 6.72 (s, 1H, aryl H), 6.75 (s, 1H, aryl H), 7.10 (d, *J* = 8.3 Hz, 2H, aryl H), 7.28 (d, *J* = 8.3 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.5, 30.0, 37.8, 44.8, 56.0, 112.0, 116.7, 128.5, 129.9, 130.7, 130.8, 131.7, 139.5, 143.8, 145.2, 207.9. MS (EI, 70eV): *m*/*z*(%) = 318 ($M^+$, 77). Anal. Calcd for $C_{18}H_{19}O_3Cl$: C, 67.82; H, 6.01. Found: C, 67.74; H, 6.23.

**4-[2-(3-Nitrobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4f**

Light yellow crystals, mp 104-105 ºC (AcOEt, petroleum ether). IR (KBr): 3401, 1702, 1592, 1526, 1356, 1287, 880, 731 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.10 (s, 3H, $CH_3$), 2.59 (t, *J* = 7.4 Hz, 2H, $CH_2$), 2.79 (t, *J* = 7.4 Hz, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.03 (s, 2H, Ar-$CH_2$-Ar), 5.56 (s, 1H, OH), 6.68 (s, 1H, aryl H), 6.71 (s, 1H, aryl H), 7.43-7.49 (m, 2H, aryl H), 7.97 (s, 1H, aryl H), 8.06 (d, *J* = 7.6 Hz, 1H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.4, 30.0, 37.8, 44.8, 56.0, 112.1, 116.6, 121.3, 123.4, 129.3, 129.4, 130.9, 134.8, 143.2, 144.1, 145.6, 148.5, 207.7. MS (EI, 70eV): *m*/*z*(%) = 329 ($M^+$, 6). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.61; H, 5.76; N, 4.46.

**4-[2-(3-Bromobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4g**

White crystals, mp 101-102 ºC (AcOEt, petroleum ether). IR (KBr): 3280, 1707, 1589, 1513, 1292, 1101, 890 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.07 (s, 3H, $CH_3$), 2.49 (t, *J* = 7.7 Hz, 2H, $CH_2$), 2.79 (t, *J* = 7.7 Hz, 2H, $CH_2$), 3.89 (s, 5H, $OCH_3$+Ar-$CH_2$-Ar), 5.50 (s, 1H, OH), 6.69 (s, 1H, aryl H), 6.72 (s, 1H, aryl H), 7.07 (d, *J* = 7.6 Hz, 1H, aryl H), 7.15 (t, *J* = 7.8 Hz, 1H, aryl H), 7.27 (s, 1H, aryl H), 7.33 (d, *J* = 7.8 Hz, 1H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.5, 30.0, 38.1, 44.8, 56.0, 112.1, 116.8, 122.6, 127.3, 129.2, 130.0, 130.3, 130.9, 131.6, 143.5, 143.9, 145.3, 207.9. MS (EI, 70eV): *m*/*z*(%) = 362 ($M^+$, 72). Anal. Calcd for $C_{18}H_{19}O_3Br$: C, 59.52; H, 5.27. Found: C, 59.38; H, 5.18.

**4-[2-(4-Bromobenzyl)-4-hydroxy-5-methoxyphenyl]butan-2-one 4h**

White crystals, mp 80-81 ºC (AcOEt, petroleum ether). IR (KBr): 3379, 1705, 1587, 1516, 1298, 1013, 790 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.07 (s, 3H, $CH_3$), 2.48 (t, *J* = 7.7 Hz, 2H, $CH_2$), 2.78 (t, *J* = 7.7 Hz, 2H), 3.87 (s, 2H, $CH_2$), 3.89 (s, 3H, $OCH_3$), 5.47 (s, 1H, OH), 6.68 (s, 1H, aryl H), 6.71 (s, 1H, aryl H), 7.01 (d, *J* = 8.2 Hz, 2H, aryl H), 7.39 (d, *J* = 8.3 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.5, 30.1, 37.9, 44.9, 56.0, 112.0, 116.7, 119.8, 130.4, 130.6, 130.8, 131.5, 140.1, 143.9, 145.3, 208.0. MS (EI, 70eV): *m*/*z*(%) = 362 ($M^+$, 63). Anal. Calcd for $C_{18}H_{19}O_3Br$: C, 59.52; H, 5.27. Found: C, 59.83; H, 5.49.

**4-[2-(2,6-Dichlorobenzyl)-4-hydroxy-5-methoxy-phenyl]butan-2-one 4i**

White crystals, mp 166-167 ºC (AcOEt, petroleum ether). IR (KBr): 3416, 1711, 1590, 1513, 1434, 1200, 782 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.21 (s, 3H, $CH_3$), 2.82 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.02 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.88 (s, 3H, $OCH_3$), 4.21 (s, 2H, Ar-$CH_2$-Ar), 5.40 (s, 1H, OH), 6.18 (s, 1H, aryl H), 6.74 (s, 1H, aryl H), 7.19 (t, $J$ = 8.0 Hz, 1H, aryl H), 7.37 (d, $J$ = 8.0 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.9, 30.2, 33.0, 44.4, 56.0, 112.0, 113.5, 128.3, 128.4, 129.0, 130.4, 136.2, 136.4, 143.9, 144.8, 208.1. MS (EI, 70eV): $m/z$(%) = 352 ($M^+$, 69). Anal. Calcd for $C_{18}H_{18}O_3Cl_2$: C, 61.20; H, 5.14. Found: C, 61.06; H, 5.21.

**3-[2-(4-Nitrobenzyl)-4-hydroxy-5-methoxyphenyl]-1-phenylpropan-1-one 4j**

Light yellow crystals, mp 116-117 ºC (AcOEt, petroleum ether). IR (KBr): 3550, 1680, 1512, 1341, 729 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.95 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.05 (t, $J$ = 7.7 Hz, 2H, $CH_2$), 3.90 (s, 3H, $OCH_3$), 4.07 (s, 2H, Ar-$CH_2$-Ar), 5.55 (s, 1H, OH), 6.74 (s, 1H, aryl H), 6.77 (s, 1H, aryl H), 7.31-7.59 (m, 5H, aryl H), 7.83 (d, $J$ = 7.8 Hz, 2H, aryl H), 8.09 (d, $J$ = 8.5 Hz, 2H, aryl H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.9, 38.4, 40.0, 56.0, 112.3, 116.8, 123.7, 127.9, 128.6, 129.3, 129.5, 131.2, 133.3, 136.6, 144.1, 145.6, 146.4, 149.0, 199.1. MS (EI, 70eV): $m/z$(%) = 391 ($M^+$, 21). Anal. Calcd for $C_{23}H_{21}NO_5$: C, 70.58; H, 5.41; N, 3.58. Found: C, 70.38; H, 5.70; N, 3.31.

**4-[2-(4-Chlorobenzyl)-4,5-dimethoxyphenyl]butan-2-one 4l**

White crystals, mp 109-110 ºC (AcOEt, petroleum ether). IR(KBr): 1707, 1519, 1227, 1101 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ = 2.07(s, 3H, $CH_3$), 2.49(t, $J$ = 7.5 Hz, 2H, $CH_2$), 2.78(t, $J$ = 8.1 Hz, 2H, $CH_2$), 3.84(s, 3H, $OCH_3$), 3.89(s, 3H, $OCH_3$), 3.90(s, 2H, $CH_2Ar$), 6.65(s, 1H, Aryl-H), 6.70(s, 1H, Aryl-H), 7.05(d, $J$ = 8.3 Hz, 2H, Aryl-H), 7.26(d, $J$ = 8.3 Hz, 2H, Aryl-H). $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ = 26.4, 29.9, 37.9, 44.7, 56.03, 56.01, 112.8, 114.0, 128.5, 129.85, 129.81, 131.5, 131.8, 139.6, 147.3, 207.8. MS (EI, 70eV): $m/z$(%) =332 ($M^+$, 84). Anal. Calcd For $C_{19}H_{21}ClO_3$, C, 68.57, H, 6.36, Found: C, 68.27, H, 6.52.

**Crystal Data of 3e**

$C_{18}H_{19}NO_5$, M = 329.34, monoclinic, space group $P2_1/c$, $a$ = 15.159(3), $b$ = 7.1359(14), $c$ = 15.059(3) Å, $\alpha$ = 90°, $\beta$ = 100.20(3) °, $\gamma$ = 90°, $V$ = 1603.2(5) $Å^3$, $Z$ = 4, $d_{cacl}$ = 1.364 g/$cm^3$, $F$(000) = 696, $\mu$(MoKa) = 0.100 $mm^{-1}$, crystal size 0.27 mm x 0.21 mm x 0.10 mm, 3601 independent reflections were collected. The structure was solved by direct methods and refined on $F^2$ to $R_1$ 0.044, $wR_2$ 0.115.

**Crystal Data of 4c**

$C_{18}H_{19}ClO_3$, M = 318.78, Monoclinic, space group $P2_1/n$, $a$ = 8.022(2), $b$ = 19.865(4), $c$ = 10.692(2) Å, $\alpha$ = 90°, $\beta$ = 108.27(3) °, $\gamma$ = 90°, $V$ = 1618.0(6) $Å^3$, $Z$ = 4, $d_{cacl}$ = 1.309 g/$cm^3$, $F$(000) = 672, $\mu$(MoKa) = 0.246 $mm^{-1}$, crystal size 0.67 mm x 0.51 mm x 0.46 mm, 3566 independent reflections were collected. The structure was solved by direct methods and refined on $F^2$ to $R_1$ 0.052, $wR_2$ 0.153.

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