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SYNTHESIS OF 2-HYDROXYMETHYL-2,3-DIHYDROBENZOFURANS

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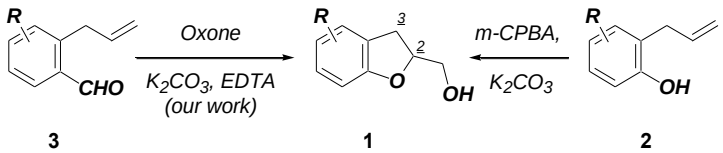
Abstract – A one-pot protocol toward 2-hydroxymethyl-2,3-dihydrobenzofurans (**1**) starting with oxygenated *o*-allylbenzaldehydes (**3**) was described. The facile one-pot process was carried out by the oxidation of *o*-allylbenzaldehydes (**3**) with Oxone in the co-solvent of acetone and DMF in the presence of aqueous EDTA solution and then intramolecular ring-closure of the resulting *o*-allylphenols (**2**) in acceptable yields.

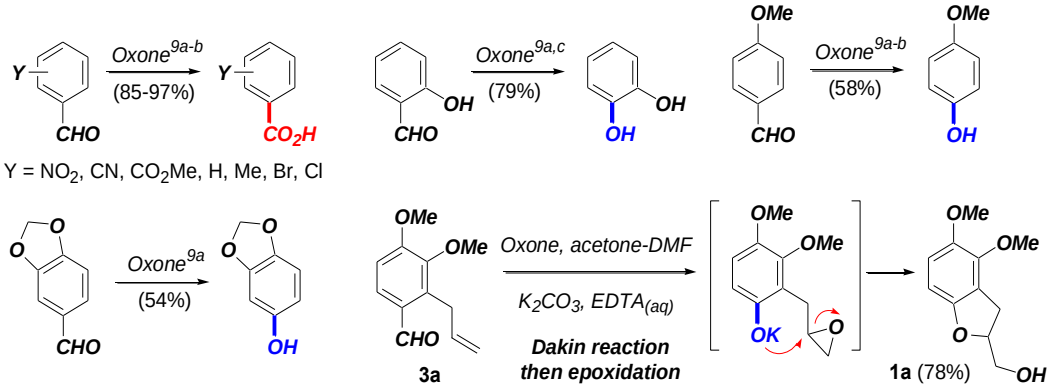
Functionalized 2,3-dihydrobenzofurans (coumaran) have been studied extensively since this ring system possesses various potential biological and pharmaceutical activities.[1-3] Substituted 2-hydroxymethyl-2,3-dihydrobenzofuran (**1**) is an important core structure of naturally occurring oxygen heterocycles.[4] Thus, some synthetic routes to access this scaffold have been developed.[5] Among these methods, *m*-CPBA/K_2CO_3 system-mediated intramolecular cyclization of *o*-allylphenol (**2**) is the most frequently employed method for generating the skeleton of 2,3-dihydrobenzofuran with a C2-hydroxymethyl group (Scheme 1). In the course of our efforts with the application of *o*-allylbenzaldehyde (**3**),[6] the Oxone-mediated synthesis of skeleton (**1**) with oxygenated groups on the benzene ring position was chosen as the key focus.



Scheme 1. Route toward skeleton (**1**)

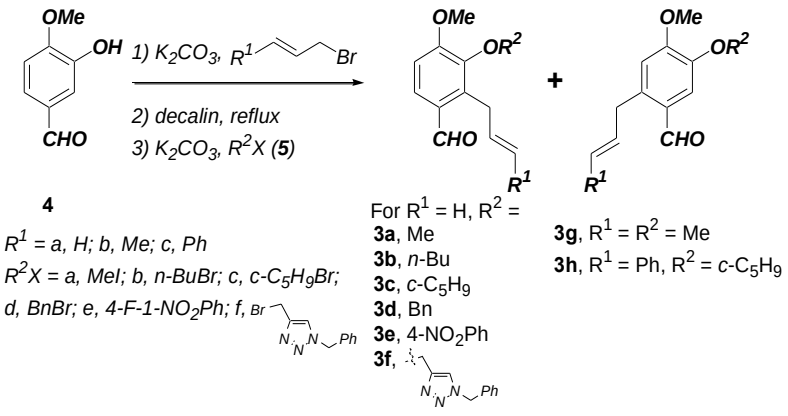
Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is a mild, stable, non-toxic, inexpensive, easy-operation, and environmentally benign oxidation regent.[7] It has largely been employed as the co-oxidant in the presence of a metal catalyst for a variety of oxidation transformations.[8,9] Webb and Ruszkay reported that treatment of electron-withdrawing and electron-neutral aromatic aldehydes with Oxone afforded

carboxylic acids. However, when electron-donating substrates, such as *p*-anisaldehyde, salicylaldehyde or piperonal, were reacted with Oxone, *p*-methoxyphenol, catechol or sesamol were isolated.[9a] This observation was noted by Borhan[9b] and Chang,[9c] as shown in Scheme 2. The majority of electron-rich benzaldehydes was converted to Dakin products.[10] For Oxone-mediated oxidation of non-aromatic ketones, Baeyer-Villiger esterification was a major route.[11] With this idea in mind, treatment of *o*-allylbenzaldehyde **3a** with the 3,4-dimethoxy group was examined.



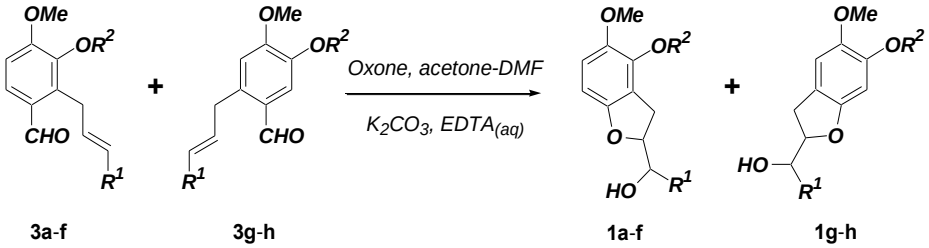
Scheme 2. Oxone-mediated reaction of aromatic aldehydes

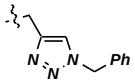
Under the EDTA aqueous solution (0.4 mM, 8 mL), treatment of compound (**3a**) with Oxone and K_2CO_3 in the co-solvent of acetone and DMF (8 mL, v/v = 1:1) produced compound (**1a**) (78%) via a Dakin reaction of compound (**3a**) followed by intramolecular ring-closure of the resulting intermediate of potassium *o*-allylphenoxide.[12] The present Oxone-mediated oxidation reaction of model substrate (**3a**) with the dimethoxy group is consistent with previous reports. Although this work was not originally intended, a facile route for the present synthesis of skeleton (**1**) was achieved. The three-step known approach was employed to create this skeleton (**3**), starting with isovanillin (**4**) via (1) *O*-allylation of compound (**4**) with allyl, *trans*-crotyl or *trans*-cinnamyl bromides (R^1 = H, Me, Ph) in acetone, (2) Claisen rearrangement of allyl phenyl ether in decalin and (3) *O*-substitution of the resulting compounds with halides (**5**) in acetone (Scheme 3).[6]



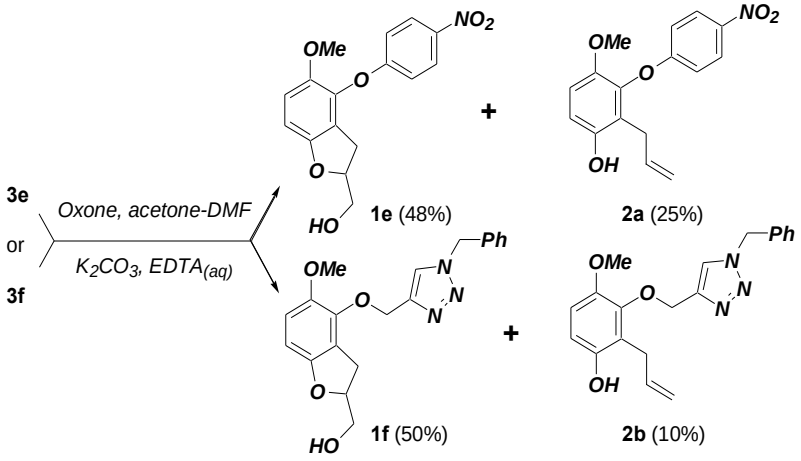
Scheme 3. Three-step synthesis of skeleton (**3**)[6]

Table 1. Synthesis of skeleton (**1**)[a]



entry	skeleton **3**	skeleton **1**, yield[b]
1	**3a**, R^1 = H, R^2 = Me	**1a**, 78%
2	**3b**, R^1= H, R^2 = *n*-Bu	**1b**, 65%
3	**3c**, R^1 = H, R^2 = *c*-C_5H_9	**1c**, 62%
4	**3d**, R^1 = H, R^2 = Bn	**1d**, 68%
5	**3e**, R^1 = H, R^2 = 4-NO_2Ph	**1e**, 48%[c]
6	**3f**, R^1 = H, R^2 = 	**1f**, 50%,[d] (64%)[e]
7	**3g**, R^1 = Me, R^2 = Me	**1g**, 70%
8	**3h**, R^1 = Ph, R^2 = *c*-C_5H_9	**1h**, 73%

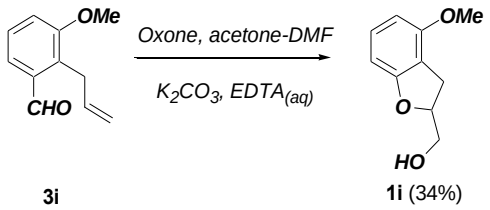
[a]The reaction was run on a 1.0 mmol scale with scale with skeleton (**3**), Oxone (1.8 g, 3.0 mmol, in 8 mL of 4 mM EDTA), K_2CO_3 (550 mg, 4.0 mmol), in the co-solvent of acetone and DMF (v/v = 1/1, 8 mL), rt. [b]The product was >95% pure as determined by ^{1}H-NMR analysis. [c]Product (**2a**) was isolated in 25% yield. [d]Product (**2b**) was isolated in 10% yield. [e]5 equiv of Oxone was added.



Scheme 4. Reaction of compounds (**3e**-**f**)

As shown in Table 1, compounds (**3a**-**h**) were efficiently constructed in moderate yields (48-78%) by the facile protocol. Different substituents (R^1, R^2), with aliphatic or aromatic groups, were performed. By exchanging different substituents (R^2 = Me, *n*-Bu, *c*-C_5H_9, Bn), the modest yields of compounds (**1a**-**d**) were isolated (entries 1-4). Entry 5 shows that *o*-allylphenol (**2a**) with a 4-nitrophenyl R^2 group was separated in a 25% yield. Compared with epoxidation (terminal olefin → epoxide), a reasonable

explanation could be that the Dakin reaction (formyl → hydroxyl group) is preferred to proceed. For the isolated yield of compound (**2b**) with the triazoyl group (~10%), similar results were observed, as shown in entry 6 and Scheme 4. The structure of *o*-allylphenol (**2b**) was determined by single-crystal X-ray crystallography.[12] When the amounts of Oxone were increased to 5.0 equiv., the yield of compound (**1f**) was improved. By the above reaction conditions, reaction of compound (**3g**) or (**3h**) provided a pair of enantiomer (**1g**) or (**1h**) (entries 7-8) via the stereospecific cyclization.



3i **1i** (34%)

Scheme 5. Reaction of compound (**1i**)

To examine the limitation of this route, the 4-methoxy group of compound (**3a**) was removed. Under a similar process, treatment of compound (**3i**) with a C3-methoxy substituent afforded a 34% yield of compound (**1i**) along with some unknown products (Scheme 5). Based on the observation, we believe that two methoxy groups could increase the yield of the desired skeleton (**1**) and inhibit the formation of the unknown products by one-pot methodology. For the one-pot reactions of compounds (**3e**-**f**) and (**3i**), the reactivity should be affected by the electronic character of the phenol moieties in the intermediates. A facile synthetic methodology for producing several oxygenated 2-hydroxymethyl-2,3-dihydrobenzofurans (**1**) has been successfully presented using Oxone-mediated Dakin reaction of *o*-allylbenzaldehydes (**3**) with acceptable yields. Further investigation regarding one-pot cascade synthesis of functionalized heterocycles will be conducted and published in due course.

EXPERIMENTAL

General. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a SMP3 melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and at 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are given in Hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-Ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

A representative procedure of skeleton (**1**) is as follows: K_2CO_3 (550 mg, 4.0 mmol) was added to a

solution of skeleton (**3**) (1.0 mmol) in the co-solvent of acetone and DMF (8 mL, v / v = 1 : 1) at rt. Oxone (1.8 g, 3.0 mmol) in an aqueous EDTA (4 mM, 8 mL) solution was added to the stirred reaction mixture solution at rt. The reaction mixture was stirred at rt for 6 h. $NaHSO_{3\,(aq)}$ (50%, 10 mL) was added to the reaction mixture and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 10/1~2/1) afforded skeleton (**1**).

*Compound (**1a**).* Yield = 78% (164 mg); Colorless solid; mp 52-53 ^{o}C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{11}H_{15}O_4$ 211.0970, found 211.0977; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 4.89-4.83 (m, 1H), 3.87 (s, 3H), 3.81 (dd, *J* = 2.8, 12.4 Hz, 1H), 3.78 (s, 3H), 3.71 (dd, *J* = 6.4, 12.4 Hz, 1H), 3.28 (dd, *J* = 9.2, 16.0 Hz, 1H), 3.05 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.37 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 146.3, 146.2, 118.7, 112.6, 103.0, 83.5, 64.7, 59.8, 56.9, 29.7.

*Compound (**1b**).* Yield = 65% (164 mg); Colorless oil; HRMS (ESI, M^{+}+1) calcd for $C_{14}H_{21}O_4$ 253.1440, found 253.1435; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H), 4.87-4.81 (m, 1H), 4.01 (t, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.79-3.66 (m, 2H), 3.22 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.98 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.70 (br s, 1H), 1.71-1.64 (m, 2H), 1.50-1.41 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 146.7, 145.4, 119.5, 112.8, 103.0, 83.5, 72.2, 64.6, 56.9, 32.2, 29.7, 19.0, 13.7.

*Compound (**1c**).* Yield = 62% (164 mg); Colorless oil; HRMS (ESI, M^{+}+1) calcd for $C_{15}H_{21}O_4$ 265.1440, found 265.1442; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (d, *J* = 8.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 4.87-4.78 (m, 2H), 3.75 (dd, *J* = 2.8, 12.4 Hz, 1H), 3.73 (s, 3H), 3.67 (dd, *J* = 6.4, 12.4 Hz, 1H), 3.18 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.94 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.85 (br s, 1H), 2.01-1.52 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 146.9, 144.1, 120.2, 112.8, 102.8, 83.5, 83.4, 64.5, 56.8, 32.8, 32.7, 29.9, 23.3 (2x).

*Compound (**1d**).* Yield = 68% (195 mg); Colorless oil; HRMS (ESI, M^{+}+1) calcd for $C_{17}H_{19}O_4$ 287.1283, found 287.1285; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.29 (m, 5H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.44 (d, *J* = 8.8 Hz, 1H), 5.09 (s, 2H), 4.80-4.74 (m, 1H), 3.82 (s, 3H), 3.68-3.57 (m, 2H), 3.02 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.73 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.52 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.8, 146.8, 144.6, 137.5, 128.2 (4x), 127.9, 120.4, 112.7, 103.5, 83.5, 74.2, 64.6, 56.8, 29.5.

*Compound (**1e**).* Yield = 48% (152 mg); Colorless solid; mp 85-86 ^{o}C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{16}H_{16}NO_6$ 318.09778, found 318.0979; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 8.4 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 4.94-4.87 (m, 1H), 3.81 (dd, *J* = 3.2, 9.2 Hz, 1H), 3.70 (s, 3H), 3.69 (dd, *J* = 6.0, 9.2 Hz, 1H), 3.07 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.88 (dd, *J* = 7.2, 16.0 Hz, 1H), 2.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):

δ 162.5, 154.5, 146.1, 142.4, 139.0, 125.9 (2x), 121.0, 115.3 (2x), 112.9, 106.2, 83.9, 64.5, 56.8, 29.2.

*Compound (**1f**).* Yield = 50% (184 mg); Colorless solid; mp 61-62 ^{o}C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{20}H_{22}N_3O_4$ 368.1610, found 368.1615; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.38-7.33 (m, 3H), 7.23-7.18 (m, 2H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.41 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 15.2 Hz, 1H), 5.47 (d, *J* = 14.8 Hz, 1H), 5.20 (s, 2H), 4.79-4.72 (m, 1H), 3.74 (s, 3H), 3.70 (dd, *J* = 3.2, 12.0 Hz, 1H), 3.60 (dd, *J* = 6.0, 12.0 Hz, 1H), 3.04 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.81 (dd, *J* = 6.8, 16.0 Hz, 1H), 2.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 146.7, 144.9, 144.0, 134.5, 129.1 (2x), 128.7, 127.9 (2x), 123.0, 120.5, 112.4, 103.8, 83.6, 65.2, 64.6, 56.7, 54.0, 29.6.

*Compound (**1g**).* Yield = 70% (157 mg); Colorless gum; HRMS (ESI, M^{+}+1) calcd for $C_{12}H_{17}O_4$ 225.1127, found 225.1128; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.40 (s, 1H), 4.66 (dt, *J* = 3.6, 8.4 Hz, 1H), 4.10-4.08 (m, 1H), 3.79 (s, 6H), 3.15 (dd, *J* = 8.4, 15.2 Hz, 1H), 3.03 (dd, *J* = 9.6, 15.2 Hz, 1H), 2.18 (br s, 1H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.5, 149.1, 143.3, 116.5, 109.2, 94.6, 87.0, 68.2, 56.8, 56.0, 29.5, 17.6.

*Compound (**1h**).* Yield = 73% (248 mg); Colorless gum; HRMS (ESI, M^{+}+1) calcd for $C_{21}H_{25}O_4$ 341.1753, found 341.1758; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.34 (m, 5H), 6.58 (s, 1H), 6.51 (s, 1H), 4.75 (d, *J* = 8.0 Hz, 1H), 4.71-4.67 (m, 1H), 4.15-4.10 (m, 1H), 3.80 (s, 3H), 3.00 (dd, *J* = 5.2, 15.6 Hz, 1H), 2.84 (dd, *J* = 8.8, 15.6 Hz, 1H), 1.96-1.53 (m, 8H), 1.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.8, 147.4, 144.5, 138.1, 128.8 (2x), 128.7, 127.2 (2x), 113.3, 110.3, 103.4, 81.8, 80.3, 68.4, 56.8, 32.8, 32.7, 32.4, 24.0 (2x).

*Compound (**1i**).* Yield = 34% (61 mg); Colorless oil; HRMS (ESI, M^{+}+1) calcd for $C_{10}H_{13}O_3$ 181.0865, found 181.0851; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (t, *J* = 8.0 Hz, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.95-4.89 (m, 1H), 3.82 (s, 3H), 3.82-3.69 (m, 2H), 3.18 (dd, *J* = 9.2, 16.0 Hz, 1H), 2.90 (dd, *J* = 7.6, 16.0 Hz, 1H), 2.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 156.5, 129.0, 113.4, 103.0, 102.7, 83.6, 64.9, 55.2, 28.7.

*Compound (**2a**).* Yield = 25% (19 mg); Colorless gum; HRMS (ESI, M^{+}+1) calcd for $C_{16}H_{16}NO_5$ 302.1029, found 302.1032; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.2 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 5.88-5.79 (m, 1H), 5.11 (br s, 1H), 5.04-4.99 (m, 2H), 3.68 (s, 3H), 3.35 (dt, *J* = 1.2, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 148.9, 146.0, 142.2, 140.7, 134.9, 126.8 (2x), 120.9, 116.5, 115.2 (2x), 113.1, 111.5, 56.3, 28.5.

*Compound (**2b**).* Yield = 10% (35 mg); Colorless solid; mp 61-62 ^{o}C (recrystallized from hexanes and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{20}H_{22}N_3O_3$ 352.1661, found 352.1667; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.40-7.34 (m, 3H), 7.26-7.23 (m, 2H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.91-5.81 (m, 1H), 5.52 (s, 2H), 5.41 (br s, 1H), 5.13 (s, 2H), 5.02-4.97 (m, 2H), 3.76 (s, 3H), 3.37 (dt, *J* = 1.6, 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.9, 146.7, 145.8, 145.1, 136.2, 134.5,

129.1 (2x), 128.7, 128.0 (2x), 122.9, 120.6, 115.6, 111.1, 110.9, 66.2, 56.2, 54.1, 28.5. Single-crystal X-ray diagram: crystal of compound **2b** was grown by slow diffusion of EtOAc into a solution of compound **2b** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P C 2/c, a = 30.00(4) Å, b = 6.608(8) Å, c = 18.39(2) Å, V = 3643(8) Å^3, Z = 8, d_{calcd} = 1.281 g/cm^3, F(000) = 1488, 2θ range 1.358~27.376^o, R indices (all data) R1 = 0.2467, wR2 = 0.3585.

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12. CCDC 996277 (**2b**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

SUPPLEMENTARY MATERIAL

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