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NEW SYNTHESIS OF 3-ARYL-2,5-DIHYDROFURANS

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Abstract – We present a straightforward synthesis of 3-aryl-2,5-dihydrofurans by ring contraction of 4-aryl-3,6-dihydro-*2H*-pyrans with the repeated treatment of MCPBA and BF_3-OEt_2. The building block 3-aryltetrahydrofuran-3-carboxylic acid with potential biological activities was also prepared.

1. INTRODUCTION

Many natural products and biological active compounds contain five-membered oxygen heterocyclic system.[1-2] Molecules incorporating either mono-, di-, or poly-substituted furans, dihydrofurans, tetrahydrofurans and other related analogs are well documented in the literature and these often served as key building blocks. A novel and facile preparation of a variety type of substituted furans, dihydrofurans, and tetrahydrofurans remains a current challenge in the organic synthesis. Development of a general and novel procedure for differently substituted five-membered oxygen heterocyclic system provides an expedient entry as shown in Figure 1.

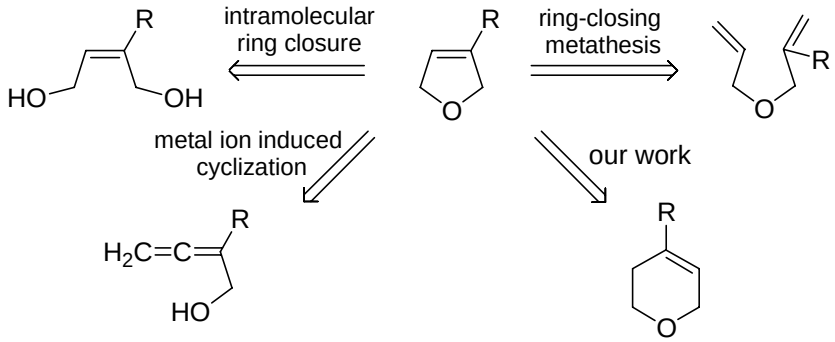


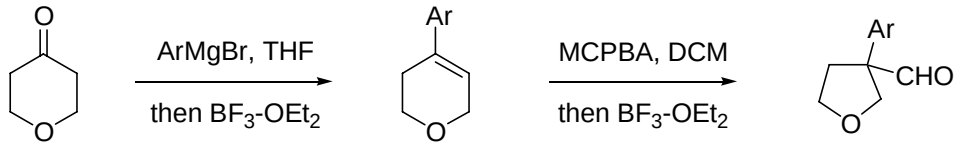
Figure 1. Some synthetic methods of 3-substituted dihydrofurans

Basically, the synthetic methods of 3-substituted dihydrofurans and its related analogs can be summarized in transition metal-promoted ring-closing cyclization and cycloisomerization or metathesis e.g.

palladium,[3] silver,[4] rhodium,[5] gold,[6] copper,[7] ruthenium,[8] mercury,[9] and zirconium.[10] Here we describe a straightforward strategy to 3-aryldihydrofurans by ring contraction of 4-aryl-3,6-dihydro-*2H*-pyrans with *m*-chloroperoxybenzoic acid (MCPBA) and boron trifluoride etherate (BF_3-OEt_2).

2. RESULTS AND DISCUSSION

Commercially available tetrahydro-*4H*-pyran-4-one (**1**) was chosen as the starting material for the preparation of 3-aryl-2,5-dihydrofurans. Some representative results are shown in Scheme 1 and Scheme 2. 3-Aryltetrahydrofuran-3-carbaldehydes (**3a**-**3e**) were prepared by two one-pot transformations. The first one is the easy access to produce 4-aryl-3,6-dihydro-*2H*-pyrans (**2a**-**2e**) by the Grignard addition of compound (**1**) with arylmagnesium bromides (a, Ar=C_6H_5; b, Ar=3-$MeOC_6H_4$; c, Ar=4-$MeOC_6H_4$; d, Ar=3,4-$CH_2O_2C_6H_3$; e, Ar=4-$C_6H_5C_6H_4$) in tetrahydrofuran at -78 ^oC for 2 h and subsequent dehydration of the resulting tertiary alcohols with boron trifluoride etherate for 15 min. The second step is a ring contraction from 4-aryl-3,6-dihydro-*2H*-pyrans (**2a**-**2e**) to 3-aryltetrahydrofuran-3-carbaldehydes (**3a**-**3e**) by epoxidation with MCPBA at rt for 3 h followed by rearrangement reaction of the resulting epoxides with BF_3-OEt_2 for 15 min. Thus, 3-aryltetrahydrofuran-3-carbaldehyde (**3**) could be obtained as a sole product in good yield via these two one-pot reactions, that is, Grignard reaction/dehydration and epoxidation/ring contraction.



1

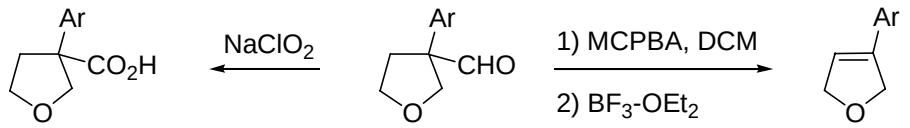
2a, Ar=C_6H_5(78%)
2b, Ar=3-$MeOC_6H_4$ (82%)
2c, Ar=4-$MeOC_6H_4$ (76%)
2d, Ar=3,4-$CH_2O_2C_6H_3$ (80%)
2e, Ar=4-$C_6H_5C_6H_4$ (83%)

3a (85%)
3b (88%)
3c (87%)
3d (82%)
3e (90%)

Scheme 1. Synthesis of 3-aryltetrahydrofuran-3-carbaldehydes (**3a**-**3e**)

Lewis acid-mediated ring contraction of six-membered ring framework was already investigated from the literature reports.[11-13] There are some different results between 4-aryl-3,4-epoxypiperidine and 1-aryl-1,2-epoxycyclohexane. According to Nagai's[11a] and Lyle's reports,[11b] different *N*-substitutents could affect the distribution of several products in the reaction of 4-aryl-3,4-epoxypiperidine derivatives. For the rearrangement reaction of 1-aryl-1,2-epoxycyclohexane, Schiketanz[12a] and Macchia[12b-d] reported totally different results in the reactivity and the structures of products. These interesting differences triggered our attention to examine the rearrangement of 4-aryl-3,4-epoxydihydropyran skeleton.[13] With enough amounts of compounds (**3a**-**3e**) in hand, synthesis of 3-aryl-2,5-dihydrofurans (**4a**-**4e**) and

3-aryltetrahydrofuran-3-carboxylic acids (**5a**-**5e**) was further studied. Conversion of compounds (**3a**-**3e**) into **4a**-**4e** was achieved in good yield by the repeated combination of MCPBA and BF_3-OEt_2 via Baeyer-Villiger oxidation and formic acid elimination. We also tried to prepare 3-methyl-2,5-dihydrofuran by repeated treatment of 4-methyl-3,6-dihydro-*2H*-pyran with the combination of MCPBA and BF_3-OEt_2, but complex products were provided. Although the synthetic application is decreased, the present work is complementary to existing methodology. While poring out the related literature of tetrahydrofuran-3-carboxylic acid, we found that it was a useful building block in the synthesis of various potential biological compounds.[14] Compounds (**5a**-**5e**) were afforded in nearly quantitative yield by oxidation of compounds (**3a**-**3e**) with sodium chlorite ($NaClO_2$).[15]



5a (98%)
5b (98%)
5c (97%)
5d (99%)
5e (99%)

3

4a (70%)
4b (75%)
4c (78%)
4d (76%)
4e (80%)

Scheme 2. Synthesis of 3-aryl 2,5-dihydrofurans (**4a**-**4e**) and tetrahydrofuran-3-carboxylic acids (**5a**-**5e**)

3. CONCLUSION

In summary, we have developed an easy and straightforward synthesis of 3-aryl-2,5-dihydrofurans (**4a**-**4e**) and 3-aryltetrahydrofuran-3-carboxylic acids (**5a**-**5e**) via the reaction of 4-aryl-3,6-dihydro-*2H*-pyrans (**2a**-**2e**) with the repeated treatment of MCPBA and BF_3-OEt_2.

4. EXPERIMENTAL

4.1. General. Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodium-benzophenone ketyl. All other reagents were obtained from commercial sources and used without further purification. Reaction was routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Extract was dried with anhydrous $MgSO_4$ before concentration *in vacuo*. Crude product was purified using column chromatography on SiO_2 (MN Kieselgel 60, 70~230 mesh).

4.2. A representative procedure for 4-aryl-3,6-dihydro-*2H*-pyrans (2a-2e) is as follows: A solution of arylmagnesium bromide (0.5 M in THF, 0.6 mL, 1.2 mmol) was added to a stirred solution of tetrahydro-*4H*-pyran-4-one (**1**) (100 mg, 1.0 mmol) in THF (10 mL) at -78 ^{o}C. The reaction mixture was stirred at rt for 2 h. The total procedure was monitored by TLC until the reaction was completed. Without

further purification, BF_3-OEt_2 (1 mL) was added to a stirred solution of the resulting reaction mixture at 0 ^oC. The reaction mixture was stirred at rt for 15 min. Saturated aqueous $NaHCO_3$ solution (1 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. Water (2 mL) and AcOEt (10 mL) was added to the residue and the mixture was filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure. The residue was extracted with AcOEt (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO_2 (hexane/AcOEt = 6/1) afforded 4-aryl-3,6-dihydro-*2H*-pyrans (**2a**-**2e**). For **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.22 (m, 5H), 6.16 (br s, 1H), 4.18 (br s, 2H), 3.96 (t, *J* = 7.5 Hz, 2H), 2.52 (br s, 2H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}O$ (M^++1) 161.0966, found 161.0968; Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.60; H, 7.38. For **2b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 8.1 Hz, 1H), 6.96 (d, *J* = 8.1 Hz, 1H), 6.95 (br s, 1H), 6.82 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.18 (br s, 1H), 4.35 (br s, 2H), 3.91 (t, *J* = 7.5 Hz, 2H), 3.81 (s, 3H), 2.50 (br s, 2H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_2$ (M^++1) 191.1072, found 191.1076; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.61; H, 7.36. For **2c**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.02 (br s, 1H), 4.30 (br s, 2H), 3.93 (t, *J* = 7.5 Hz, 2H), 3.79 (s, 3H), 2.46 (br s, 2H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_2$ (M^++1) 191.1072, found 191.1078; Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.94; H, 7.66. For **2d**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 1.8, 8.1 Hz, 1H), 5.99 (br s, 1H), 5.95 (s, 2H), 4.31 (br s, 2H), 3.91 (br s, 2H), 2.44 (br s, 2H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}O_3$ (M^++1) 205.0865, found 205.0870; Anal. Calcd for $C_{12}H_{12}O_2$: C, 70.57; H, 5.92. Found: C, 70.21; H, 5.66. For **2e**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.58 (m, 4H), 7.50-7.39 (m, 4H), 7.36-7.32 (m, 1H), 6.10 (br s, 1H), 4.38 (br s, 2H), 3.97 (t, *J* = 7.2 Hz, 2H), 2.58 (br s, 2H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}O$ (M^++1) 237.1280, found 237.1283; Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.11; H, 6.47.

4.3. A representative procedure for 3-aryltetrahydrofuran-3-carbaldehydes (3a-3e) is as follows: MCPBA (255 mg, 75%, 1.1 mmol) was added to a mixture of 3-aryltetrahydrofuran-3-carbaldehydes (**2a**-**2e**) (0.5 mmol) and Na_2CO_3 (130 mg, 1.2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Saturated aqueous Na_2CO_3 solution (5 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, BF_3-OEt_2 (1 mL) was added to a stirred solution of crude product in CH_2Cl_2 (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with

AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO_2 (hexane/AcOEt = 6/1~4/1) afforded 3-aryltetrahydrofuran-3-carbaldehydes (**3a**-**3e**). For **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.32-7.23 (m, 3H), 7.18-7.10 (m, 2H), 4.59 (d, *J* = 8.4 Hz, 1H), 3.95-3.86 (m, 2H), 3.81 (d, *J* = 8.4 Hz, 1H), 2.83-2.75 (m, 1H), 2.21-2.10 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}O_2$ (M^++1) 177.0916, found 177.0915; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.11; H, 6.59. For **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.30 (t, *J* = 8.1 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.78 (dd, *J* = 2.1, 8.1 Hz, 1H), 6.71 (br s, 1H), 4.61 (d, *J* = 8.4 Hz, 1H), 3.96-3.83 (m, 3H), 3.83 (s, 3H), 2.88-2.80 (m, 1H), 2.28-2.09 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_3$ (M^++1) 207.1021, found 207.1023; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.03; H, 7.05. For **3c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.61 (d, *J* = 8.1 Hz, 1H), 3.96-3.84 (m, 3H), 3.85 (s, 3H), 2.86-2.78 (m, 1H), 2.24-2.06 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_3$ (M^++1) 207.1021, found 207.1025; Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.61; H, 6.59. For **3d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.43 (br s, 1H), 6.78 (d, *J* = 1.2 Hz, 1H), 6.62-6.45 (m, 2H), 5.98 (s, 2H), 4.59 (d, *J* = 8.4 Hz, 1H), 3.98-3.83 (m, 2H), 3.80 (d, *J* = 8.4 Hz, 1H), 2.84-2.74 (m, 1H), 2.23-2.08 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}O_4$ (M^++1) 221.0814, found 221.0816; Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.68; H, 5.28. For **3e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (s, 1H), 7.61-7.58 (m, 4H), 7.50-7.41 (m, 4H), 7.38-7.34 (m, 1H), 4.63 (d, *J* = 8.4 Hz, 1H), 4.03-3.96 (m, 2H), 3.92 (d, *J* = 8.4 Hz, 1H), 2.98-2.83 (m, 1H), 2.38-2.22 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}O_2$ (M^++1) 253.1229, found 253.1233; Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.25; H, 6.50.

4.4. A representative procedure for 3-aryl-2,5-dihydrofurans (4a-4e) is as follows: MCPBA (255 mg, 75%, 1.1 mmol) was added to a mixture of 3-aryltetrahydrofuran-3-carbaldehydes (**3a**-**3e**) (0.5 mmol) and Na_2CO_3 (130 mg, 1.2 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at rt for 3 h. The total procedure was monitored by TLC until the reaction was completed. Saturated aqueous Na_2CO_3 solution (5 mL) was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Without further purification, BF_3-OEt_2 (1 mL) was added to a stirred solution of crude product in CH_2Cl_2 (10 mL) at rt. The reaction mixture was stirred at rt for 15 min. Saturated aqueous $NaHCO_3$ solution (5 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO_2 (hexane/AcOEt = 10/1~8/1) afforded 3-aryl-2,5-dihydrofurans (**4a**-**4e**). For **4a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 6.24 (t, *J* = 2.0 Hz, 1H), 5.02 (dd, *J* = 2.0, 5.0

Hz, 2H), 4.86 (dd, *J* = 2.0, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.44, 132.46, 128.60 (2x), 127.99, 125.74 (2x), 120.43, 76.75, 75.35; HRMS (ESI) *m*/*z* calcd for $C_{10}H_{11}O$ (M^++1) 147.0810, found 147.0813; Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.44; H, 6.68. For **4b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.0 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.88 (br s, 1H), 6.85 (dd, *J* = 2.5, 8.0 Hz, 1H), 6.23 (t, *J* = 2.0 Hz, 1H), 5.00 (dd, *J* = 2.0, 5.0 Hz, 2H), 4.85 (dd, *J* = 2.0, 5.0 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.70, 138.37, 133.81, 129.60, 120.90, 118.32, 113.23, 111.58, 76.71, 75.38, 55.24; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}O_2$ (M^++1) 177.0916, found 177.0916; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.61; H, 6.70. For **4c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 8.5 Hz, 2H), 6.09 (t, *J* = 2.0 Hz, 1H), 4.98 (dd, *J* = 2.0, 5.0 Hz, 2H), 4.85 (dd, *J* = 2.0, 5.0 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.35, 137.84, 129.98 (2x), 125.27, 118.23, 113.99 (2x), 76.79, 75.43, 55.28; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}O_2$ (M^++1) 177.0916, found 177.0917; Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.73; H, 6.62. For **4d**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (d, *J* = 1.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.07 (t, *J* = 2.0 Hz, 1H), 5.97 (s, 2H), 4.95 (dd, *J* = 2.0, 5.0 Hz, 2H), 4.84 (dd, *J* = 2.0, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.94, 147.41, 137.96, 126.77, 119.49, 118.98, 108.27, 106.04, 101.13, 76.71, 75.44; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{11}O_3$ (M^++1) 191.0708, found 191.0709; Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.68; H, 4.98. For **4e**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62-7.59 (m, 4H), 7.48-7.41 (m, 4H), 7.38-7.35 (m, 1H), 6.28 (t, *J* = 2.0 Hz, 1H), 5.06 (dd, *J* = 2.0, 5.0 Hz, 2H), 4.89 (dd, *J* = 2.0, 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.73, 140.46, 138.07, 131.41, 128.82 (2x), 127.46, 127.26 (2x), 126.93 (2x), 125.17 (2x), 120.55, 76.81, 75.36; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{15}O$ (M^++1) 223.1123, found 223.1124; Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.68; H, 6.20.

4.5. A representative procedure for 3-aryltetrahydrofuran-3-carboxylic acids (5a-5e) is as follows: A solution of 3-aryl-2,5-dihydrofurans (**4a**-**4e**) (0.3 mmol) and 2-methyl-2-butene (chlorine scavenger) (0.5 mL) in *t*-BuOH (10 mL) was treated with a solution of $NaClO_2$ (80%, 110 mg, 1.0 mmol) and KH_2PO_4 (95 mg, 0.7 mmol) in water (5 mL) at rt. The mixture was stirred for an additional 30 min and the solvent was removed under reduced pressure. The residue was extracted with AcOEt (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification by column on SiO_2 (hexane/AcOEt = 1/1) afforded 3-aryltetrahydrofuran-3-carboxylic acids (**5a**-**5e**). For **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (m, 5H), 4.74 (d, *J* = 8.1 Hz, 1H), 4.02-3.97 (m, 2H), 3.89 (d, *J* = 8.1 Hz, 1H), 3.03-2.95 (m, 1H), 2.21-2.03 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{11}H_{13}O_2$ (M^++1) 193.0865, found 193.0868; Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.92; H, 6.51. For **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.92-6.90 (m, 4H), 4.70 (d, *J* = 8.1 Hz, 1H), 4.06-3.97 (m, 2H), 3.88 (d, *J* = 8.1 Hz, 1H), 3.83 (s, 3H), 3.03-2.94 (m, 1H), 2.31-2.06 (m, 1H); HRMS (ESI) *m*/*z* calcd

for $C_{12}H_{15}O_4$ (M^++1) 223.0970, found 233.0977; Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.02; H, 6.53. For **5c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.71 (d, *J* = 8.4 Hz, 1H), 4.02-3.99 (m, 2H), 3.86 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.02-2.94 (m, 1H), 2.29-2.19 (m, 1H), 1.92 (br s, 1H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{15}O_4$ (M^++1) 223.0970, found 233.0971. For **5d** (rotamer): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82-6.63 (m, 3H), 5.88 (br s, 2H), 4.60 (br s, 1H), 3.88-3.74 (m, 3H), 2.89-2.80 (m, 1H), 2.30-2.20 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{12}H_{13}O_5$ (M^++1) 237.0763, found 237.0765. For **5e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.60 (m, 4H), 7.52-7.30 (m, 5H), 4.79 (d, *J* = 8.1 Hz, 1H), 4.08-3.94 (m, 2H), 3.90 (d, *J* = 8.1 Hz, 1H), 3.11-2.95 (m, 1H), 2.19-2.11 (m, 1H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}O_3$ (M^++1) 269.1178, found 269.1180; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.31; H, 6.28.

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