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A novel strategy for the expeditious synthesis of aryl-tethered highly congested 2-hydroxybenzyl alcohols from 2-pyranones

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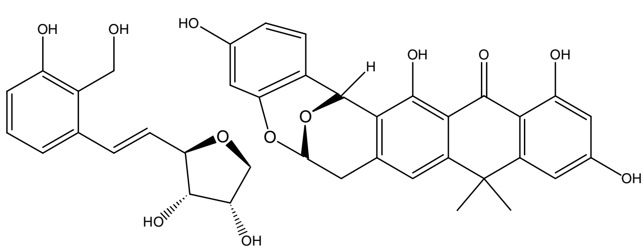
Abstract—An efficient and simple synthesis of highly congested 2-benzyloxy-3-benzyloxymethyl-5-*sec*-aminobiphenyl-4-carbonitriles **3a–e** has been delineated through base catalyzed ring transformation of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1** by 1,3-bisbenzyloxypropan-2-one **2**. Debenzylation of both the *O*-benzyl groups of **3a–e** with boron trichloride provided the corresponding diols, 2-hydroxy-3-hydroxymethyl -5-*sec*-aminobiphenyl-4-carbonitriles **4a–e** in very good yields.

The synthesis of highly functionalized and substituted benzene building blocks is of great significance due to their ubiquitous presence in various natural products, for example **I**, **II**. A frequently used subunit in natural product synthesis is 2-hydroxybenzyl alcohol. Additionally, these are useful precursors for the construction of anti-HIV agents[1] and positron emission tomography (PET) probes[2] for imaging amyloid plaques. The wide ranging therapeutic applications and their synthetic potential aroused our interest in developing a novel protocol for the construction of highly congested aryl-tethered 2-hydroxybenzyl alcohols with electron-donating and -attracting substituents.



I **II**

2-Hydroxybenzyl alcohols have generally been prepared[3] from phenols and paraformaldehyde under acidic or basic conditions. The catalytic reduction of salicylaldehyde[4] and salicylic acids[5] is an alternative route for the synthesis of substituted 2-hydroxybenzyl alcohols. They can also be obtained by the oxidation of 2-cresol.[6] The reduction of benzoxazine[7] by lithium borohydride in THF also furnished 2-hydroxybenzyl alcohols. Recently, 2,2-dimethyl-1,3-dibenzodioxan-4-ones have been identified as versatile precursors for the construction of congested 2-hydroxybenzyl alcohols through their reduction using various reducing agents. Thus, the reduction of 2,2-dimethyl-1,3-dibenzodioxan-4-ones with the excess of LAH[8] at room temperature readily provided the corresponding diols. Even halo-substituted 2,2-dimethyl-1,3-dibenzodioxan-4-ones can be conveniently reduced[1,9,10] by LAH to the respective 2-hydroxybenzyl alcohols without affecting the halo substituent. Similarly, reduction with excess of $LiBH_4$ (4 equiv) at room temperature furnished the desired compounds in very good yields. The stability of functional groups and orthogonally protected phenols direct the selection of reducing agents.[11] The various commonly used methodologies are summarized in Scheme 1.

Herein, we report an efficient and concise protocol for the construction of highly congested aryl-tethered 2-hydroxybenzyl alcohols in two steps. The first step is the synthesis of 2-benzyloxy-3-benzyloxymethyl-5-*sec*-aminobiphenyl-4-carbonitriles **3** through base catalyzed ring transformation of suitably functionalized 2-pyranones **1** by 1,3-dibenzyloxy-2-propanone **2**. The second step is *O*-debenzylation of both the benzyloxy groups by stirring with BCl_3 in methylene chloride at −78 °C to obtain the 2-hydroxy-3-hydroxymethyl-5-*sec*-amino

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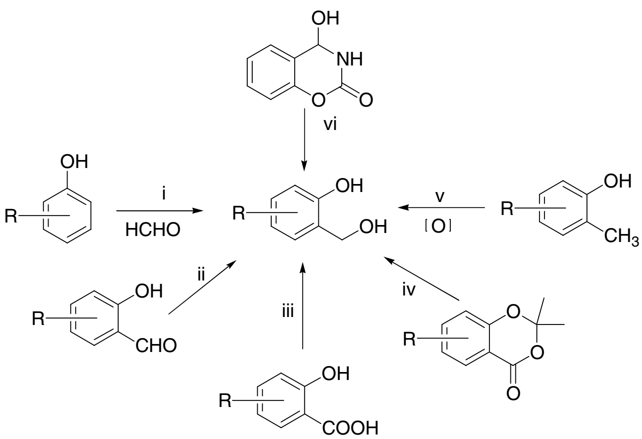


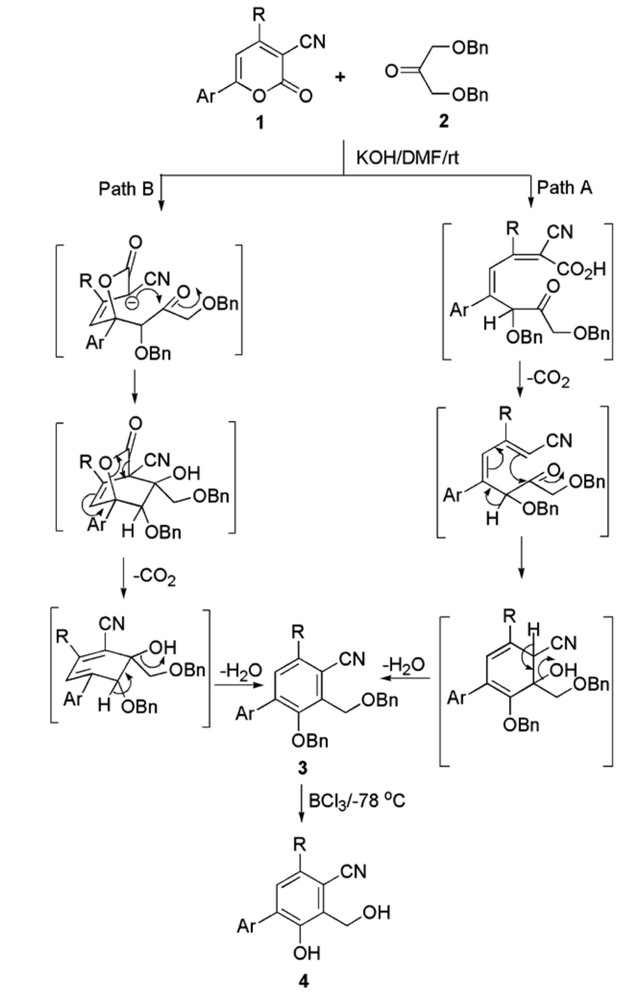
Scheme 1. Summary of the known synthetic procedures. Reagents: (i) HCl/AcOH or H_3BO_3/benzene or NaOH/D-glucose; (ii) $(CF_3CO)_2O$/TFA/LAH/THF or $NaBH_4/LiClO_3$ or $PyBH_3/CHCl_3$ or Bu_3SnH/MeOH; (iii) LAH/THF or $Zn(BH_4)_2$/cyclohexene or $Ca(BH_4)_2$; (iv) LAH or $LiBH_4$; (v) O_2/MeOH/pyridine; (vi) $LiBH_4/LiBH(Et)_3$.

biphenyl-4-carbonitriles. The various 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitriles **1a**–**e** used as precursors were prepared in two steps. The first step was the preparation of 6-aryl-4-methylsulfanyl-2*H*-pyran-2-one-3-carbonitriles from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate and aryl methyl ketones.[12] Amination[13] with a *sec*-amine in refluxing alcohol furnished **1a**–**e**. Ketone 1,3-dibenzyloxy-2-propanone **2** used as a source of carbanion for the ring transformation reactions was prepared by Swern oxidation of 1,3-bis-(benzyloxy)-2-hydroxypropane, obtained from glycerol by the literature procedure.[14]

Thus, stirring an equimolar mixture of **1**, 1,3-dibenzyloxy-2-propanone **2** in the presence of powdered KOH in DMF at room temperature for 2–4 h afforded 2-benzyloxy-3-benzyloxymethyl-5-*sec*-aminobiphenyl-4-carbonitriles **3a**–**e**. *O*-Debenzylation of **3a**–**e** with BCl_3 gave 2-hydroxy-3-hydroxymethyl-5-*sec*-aminobiphenyl-4-carbonitriles **4a**–**e**.

It is evident from the topography of 6-aryl-4-*sec*-amino-2*H*-pyran-2-one-3-carbonitrile **1** that it possesses three electrophilic centres C-2, C-4 and C-6 in which the latter is highly prone to nucleophilic attack due to extended conjugation and the presence of the electron-withdrawing CN substituent at position 3 of the 2-pyranone ring. This reaction may follow either of the two paths A and B to produce **3**. If the reaction follows the path A the carbanion generated from **2** in situ in the presence of a base, attacks at C-6 of the pyran ring **1** with ring opening followed by ring closure with concomitant loss of carbon dioxide and water to yield **3**. If the reaction follows the path B, the first step is the formation of a Michael adduct in situ followed by cyclization involving C-3 of 2-pyranone **1** and carbonyl function of adduct intermediate with the liberation of carbon dioxide and water to produce **3**, as shown in Scheme 2.

All the synthesized compounds listed in Table 1 were characterized by spectroscopic and elemental analyses.[15]



Scheme 2. Plausible mechanisms for the formation of **4a**–**e**.

Table 1. List of the synthesized compounds **3** and **4**

1, **3**, **4**	Ar	R	Yield (%) **3**	Yield (%) **4**
a	4-Br–C_6H_4	Pyrrolidin-1-yl	74	82
b	2-Naphthyl	Pyrrolidin-1-yl	72	84
c	2-Naphthyl	4-Methylpiperidin-1-yl	70	78
d	2-Naphthyl	4-Phenylpiperazin-1-yl	68	80
e	4-Br–C_6H_4	4-Phenylpiperazin-1-yl	71	85

In summary, this protocol provides a novel route for the synthesis of highly congested aryl-tethered 2-hydroxybenzyl alcohols with electron-withdrawing and -donating substituents through base catalyzed ring transformation of suitably functionalized 2-pyranones by 1,3-dibenzyloxy-2-propanone in very good yields without a catalyst. This is an efficient way to synthesize congested biphenyl diols not easily obtainable by other reported literature procedures.

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15. *General procedure for the synthesis of 2-benzyloxy-3-benzyloxymethyl-5-sec-aminobiphenyl-4-carbonitriles* **3a–e**: An equimolar mixture of **1a** (344 mg, 1.0 mmol) and **2** (270 mg, 1.0 mmol) was stirred in a suspension of powdered KOH (207 mg, 1.5 mmol) in DMF (10 mL) for 2 h at room temperature. The reaction mixture was diluted with distilled water and the precipitate was filtered. The crude product was purified on a silica gel column using DCM as eluent. Compound **3a**: white solid; mp 134–135 °C; IR (KBr) ν 2206 cm^{-1} (CN); MS (FAB): m/z 553 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.97–2.01 (m, 4H, pyrrolidinyl), 3.59–3.63 (m, 4H, pyrrolidinyl), 4.37 (s, 2H, CH$_2$), 4.69 (s, 2H, CH$_2$), 4.73 (s, 2H, CH$_2$), 6.58 (s, 1H, ArH), 6.94–6.97 (m, 2H, ArH), 7.16–7.33 (m, 6H, ArH), 7.39–7.43 (m, 4H, ArH), 7.51–7.54 (m, 2H, ArH); Anal. Calcd for $C_{32}H_{29}BrN_2O_2$: C, 69.44; H, 5.28; N, 5.06. Found: C, 69.55; H, 5.40; N, 5.20. Compound **3b**: white solid; mp 142–143 °C; IR (KBr) ν 2206 cm^{-1} (CN); MS (FAB): m/z 525 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99–2.03 (m, 4H, pyrrolidinyl), 3.63–3.67 (m, 4H, pyrrolidinyl), 4.36 (s, 2H, CH$_2$), 4.71 (s, 2H, CH$_2$), 4.77 (s, 2H, CH$_2$), 6.76 (s, 1H, ArH), 6.86–6.88 (m, 2H, ArH), 7.11–7.22 (m, 3H, ArH), 7.26–7.34 (m, 3H, ArH), 7.41–7.44 (m, 2H, ArH), 7.50–7.54 (m, 2H, ArH), 7.71–7.74 (m, 1H, ArH), 7.84–7.90 (m, 3H, ArH), 8.02 (s, 1H, ArH); Anal. Calcd for $C_{36}H_{32}N_2O_2$: C, 82.41; H, 6.15; N, 5.34. Found: C, 82.54; H, 6.23; N, 5.46. Compound **3c**: white solid; mp 132–133 °C; IR (KBr) ν 2218 cm^{-1} (CN); MS (FAB): m/z 553 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.15 (d, $J = 5.4$ Hz, 3H, CH$_3$), 1.52–1.55 (m, 3H, piperidinyl), 1.76–1.79 (m, 2H, piperidinyl), 2.76–2.83 (m, 2H, piperidinyl), 3.54–3.57 (m, 2H, piperidinyl), 4.41 (s, 2H, CH$_2$), 4.70 (s, 2H, CH$_2$), 4.77 (s, 2H, CH$_2$), 6.89–6.92 (m, 2H, ArH), 7.09 (s, 1H, ArH), 7.12–7.34 (m, 6H, ArH), 7.39–7.42 (m, 2H, ArH), 7.50–7.56 (m, 2H, ArH), 7.70–7.74 (m, 1H, ArH), 7.84–7.91 (m, 3H, ArH), 8.03 (s, 1H, ArH); Anal. Calcd for $C_{38}H_{36}N_2O_2$: C, 82.58; H, 6.57; N, 5.07. Found: C, 82.44; H, 6.70; N, 5.15. Compound **3d**: white solid; mp 79–80 °C; IR (KBr) ν 2218 cm^{-1} (CN); MS (FAB): m/z 644 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.34–3.41 (m, 8H, piperazinyl), 4.44 (s, 2H, CH$_2$), 4.68 (s, 2H, CH$_2$), 4.74 (s, 2H, CH$_2$), 6.87–7.00 (m, 6H, ArH), 7.22–7.45 (m, 12H, ArH), 7.54–7.57 (m, 2H, ArH); Anal. Calcd for $C_{38}H_{34}BrN_3O_2$: C, 70.80; H, 5.32; N, 6.52. Found: C, 70:94; H, 5.40; N, 6.64. Compound **3e**: white solid; mp 109–110 °C; IR (KBr) ν 2219 cm^{-1} (CN); MS (FAB): m/z 616 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 3.38–3.44 (m, 8H, piperazinyl), 4.43 (s, 2H, CH$_2$), 4.70 (s, 2H, CH$_2$), 4.78 (s, 2H, CH$_2$), 6.87–6.92 (m, 3H, ArH), 6.98–7.00 (m, 2H, ArH), 7.13–7.35 (m, 9H, ArH), 7.39–7.43 (m, 2H, ArH), 7.52–7.55 (m, 2H, ArH), 7.72–7.75 (m, 1H, ArH), 7.86–7.93 (m, 3H, ArH), 8.04 (s, 1H, ArH); Anal. Calcd for $C_{42}H_{37}N_3O_2$: C, 81.92; H, 6.06; N, 6.8. Found: C, 81.86; H, 6.20; N, 6.96. *General procedure for the synthesis of 2-hydroxy-3-hydroxymethyl-5-sec-aminobiphenyl-4-carbonitriles* **4a–e**: These compounds were prepared by stirring a mixture of **3** (0.5 mmol) and boron trichloride (1.0 mmol) in DCM (5 mL) at −78 °C for 2–3 h. The reaction mixture was allowed to warm to room temperature and diluted with methanol (3 mL). The solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography, using DCM as eluent. Compound **4a**: white solid; mp 172–174 °C; IR (KBr) ν 2207 (CN), 3362 cm^{-1} (OH); MS (FAB): m/z 373 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.95–2.00 (m, 4H, pyrrolidinyl), 2.78 (brs, 1H, OH), 3.48–3.52 (m, 4H, pyrrolidinyl), 5.13 (s, 2H, CH$_2$), 6.58 (s, 1H, ArH), 7.40 (d, $J = 8.4$ Hz, 2H, ArH), 7.55–7.58 (m, 3H, ArH and OH); Anal. Calcd for $C_{18}H_{17}BrN_2O_2$: C, 57.92; H, 4.59; N, 7.51. Found: C, 57.98; H, 4.70; N, 7.64. Compound **4b**: white solid; mp 190–191 °C; IR (KBr) ν 2206 (CN), 3463 cm^{-1} (OH); MS (FAB): m/z 345 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.99–2.03 (m, 4H, pyrrolidinyl), 2.56 (brs, 1H, OH), 3.55–3.66 (m, 4H, pyrrolidinyl), 5.14 (s, 2H, CH$_2$), 6.73 (s, 1H, ArH), 7.06 (brs, 1H, OH), 7.52–7.62 (m, 3H, ArH), 7.90–7.97 (m, 4H, ArH); Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.84; H, 5.96; N, 8.20. Compound **4c**: white solid; mp 225–226 °C; IR (KBr) ν 2206 (CN), 3394 cm^{-1} (OH); MS (FAB): m/z 373 (M+1); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.01 (d, $J = 5.4$ Hz, 3H, CH$_3$), 1.54–1.56 (m, 3H, piperidinyl), 1.73–1.76 (m, 2H, piperidinyl), 2.60 (brs, 1H, OH), 2.68–2.71 (m, 2H, piperidinyl), 3.61–3.64 (m, 2H, piperidinyl), 5.21 (s, 2H,

CH_2), 6.89 (s, 1H, ArH), 7.20 (brs, 1H, OH), 7.54–7.60 (m, 3H, ArH), 7.91–8.03 (m, 4H, ArH); Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.44; H, 6.40; N, 7.64. Compound **4d**: white solid; mp 170–172 °C; IR (KBr) ν 2206 (CN), 3396 cm^{-1} (OH); MS (FAB): m/z 464 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.68 (brs, 1H, OH), 3.20–3.23 (m, 4H, piperazinyl), 3.35–3.38 (m, 4H, piperazinyl), 5.16 (s, 2H, CH_2), 6.86–6.99 (m, 4H, ArH), 7.28–7.37 (m, 2H, ArH), 7.42 (d, $J = 8.7$ Hz, 2H, ArH), 7.68 (d, $J = 8.7$ Hz, 2H, ArH), 8.05 (brs, 1H, OH); Anal. Calcd for $C_{24}H_{22}BrN_3O_2$: C, 62.08; H, 4.78; N, 9.05. Found: C, 62.18; H, 4.88; N, 9.14. Compound **4e**: white solid; mp 182–184 °C; IR (KBr) ν 2206 (CN), 3430 cm^{-1} (OH); MS (FAB): m/z 436 (M+1); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.66 (brs, 1H, OH), 3.27–3.30 (m, 4H, piperazinyl), 3.39–3.42 (m, 4H, piperazinyl), 5.17 (s, 2H, CH_2), 6.86–6.99 (m, 2H, ArH), 7.28–7.36 (m, 8H, ArH, OH), 7.48–7.66 (m, 2H, ArH), 7.91–8.01 (m, 2H, ArH); Anal. Calcd for $C_{28}H_{25}N_3O_2$: C, 77.22; H, 5.79; N, 9.65. Found: C, 77.34; H, 5.88; N, 9.76.