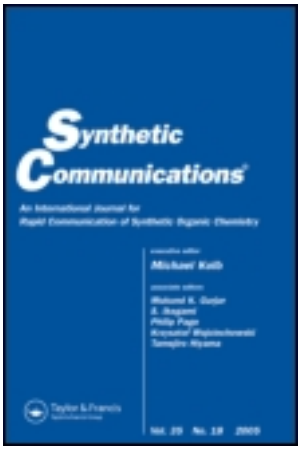

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A Novel Synthesis of 2-Hydroxymethyl-3-Phenyl-1, 4-Benzodioxanes

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A NOVEL SYNTHESIS OF 2-HYDROXYMETHYL-3-PHENYL-1, 4-BENZODIOXANES

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Abstract: The reaction of 3,4-dihydroxybenzaldehyde (4a), methyl-(3,4-dihydroxy) benzoate (4b), ethyl-(3,4-dihydroxy) benzoate (4c), 3,4-dihydroxybenzonitrile (4d), 2,3-dihydroxynitrobenzene (4e) with 2-bromomethyl-3-phenyl oxirane (3) in acetone-K_2CO_3 medium gave six membered heterocycles, 2-hydroxymethyl-3-phenyl-1,4-benzodioxanes (5a-e) regioselectively.

The 1,4-benzodioxane ring system occupies prominent place among α-adrenoreceptor antagonists, β-adrenergic blocking agents and antihypertensive agents[1-4]. Natural 1,4-benzodioxanes americanin A, isoamericanin A, americanol A, isoamericanol A have neurotropic and choline acetyltransferase enhancing acti-

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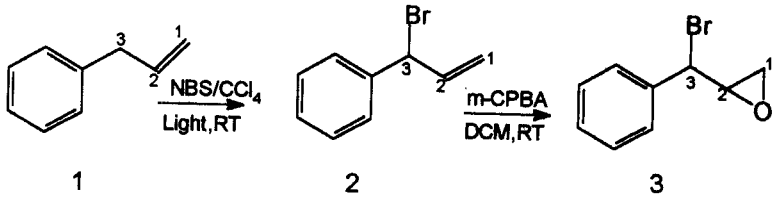
vity[5,6]. Silybin, a flavanolignan, is used in indigenous medicine as hepatoprotective agent[7], and several coumarins with fused 1,4-benzodioxane ring systems are reported[8]. Three methods were reported for the synthesis of 2-hydroxymethyl-3-aryl-1,4-benzodioxanes, These are i) reaction of catechol with 2,3-dibromodihydroethylcinnamate in basic medium gave 2-carboethoxy-3-phenyl-1,4-benzodioxane, which on reduction gave 2-hydroxymethyl-3-phenyl-1,4-benzodioxane[9]. ii) oxidative coupling of catechol with isoeugenol or coniferylalcohol in the presence of silver oxide[10]. iii) reaction of epoxyconiferylalcohol with 3,4-dihydroxybenzaldehyde in the presence of alkali[11]. We now report a new synthesis of 2-hydroxymethyl-3-phenyl-1,4-benzodioxanes by the reaction of substituted catechols (4a-e) with 2-bromomethyl-3-phenyl oxirane (3). The catechols used here have electron withdrawing groups at ortho or para to the catechol hydroxyls.

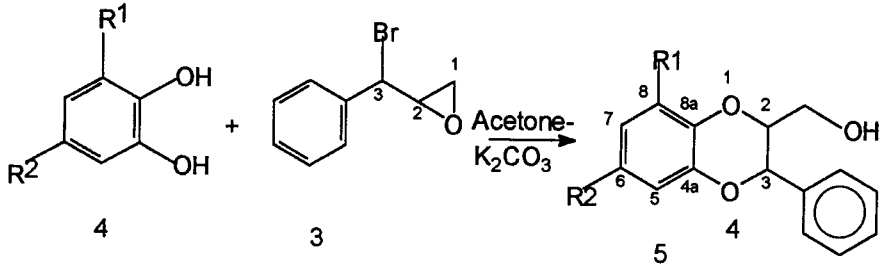
2-Bromomethyl-3-phenyloxirane (3) is synthesized as follows. NBS/CCl_4 bromination of allylbenzene (1) gave 3-bromo-3-phenyl-1-propene (2), which on epoxidation with m-CPBA gave (3)[12] (Scheme1). Earlier Yoshida et al.,[13]reported oxirane 3 as a minor product formed by the reaction of 2,3-dibromo-3-phenyl-propanol-1 in alkali.

The typical procedure for the synthesis of 2-hydroxymethyl-3-phenyl-6-formyl-1,4-benzodioxane (5a) is described here. 3,4-Dihydroxybenzaldehyde (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3) (10 mmoles), K_2CO_3 (5g) in acetone (40 mL) were refluxed for 24h, acetone decanted , evaporated and residue

Scheme 1



Scheme 2



a. R^1=H, R^2=CHO
b. R^1=H, R^2=COOEt
c. R^1=H, R^2=COOMe
d. R^1=H, R^2=CN
e. R^1=NO_2, R^2=H

a. R^1=H, R^2=CHO
b. R^1=H, R^2=COOEt
c. R^1=H, R^2=COOMe
d. R^1=H, R^2=CN
e. R^1=NO_2, R^2=H

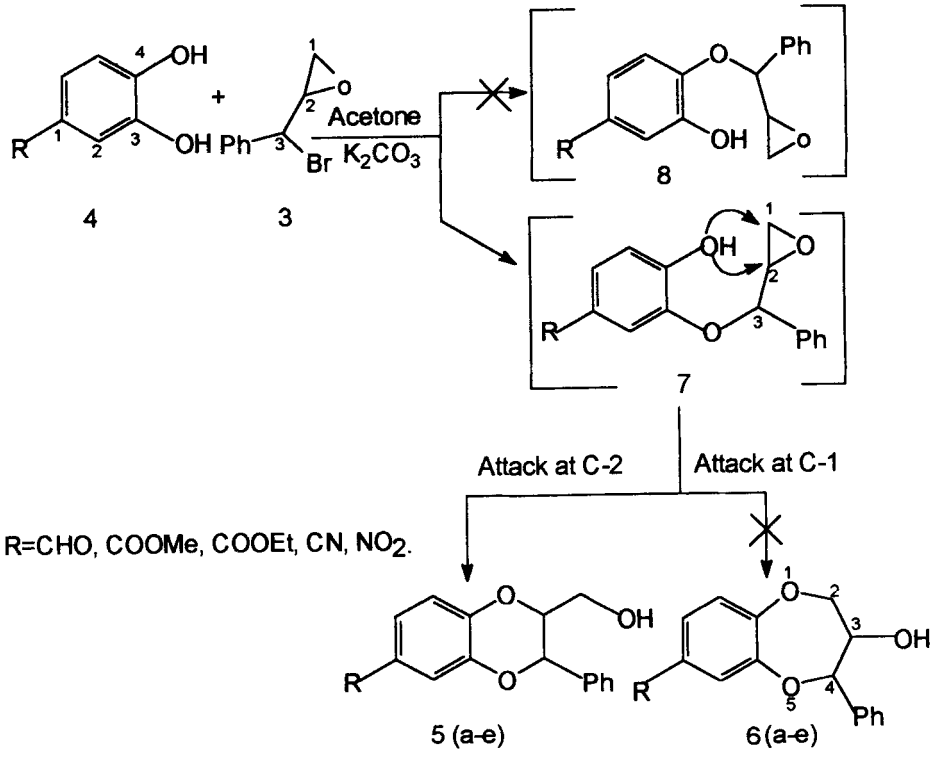
extracted with ether (100 mL) and washed with aq KOH (2%). Ether layer was concentrated and chromatographed to give 2-hydroxymethyl-3-phenyl-6-formyl-1,4-benzodioxane 5a (Scheme 2). The structure of 5a is established by its spectral data. In the ^{1}H NMR the H-3 resonated at δ 5.15 as a doublet (J=9 Hz) indicating the C-3 phenyl and C-2 hydroxymethyl groups are trans . The H-2 resonated at δ 4.05 as multiplet . The diastereotopic hydroxymethyl methylene protons exhibited

the ABq x 2 pattern with one proton resonating at δ 3.40 (J=13, 2 Hz) and the other at δ 3.70 (J=13, 2 Hz). The H-8 appeared as doublet at δ 7.10 (J=9 Hz), and remaining seven aromatic protons (H-5,7, and H-2',3',4',5',6') resonated as a multiplet at δ 7.40. The formyl proton resonated as singlet at δ 9. 85. In ^{13}C NMR of 5a the dioxane ring carbons resonated at δ 62.00 (CH_2OH), 77.50 (C-2) 73.00 (C-3) In MS the $M^{+\bullet}$ peak appeared at m/z 270 the other intense ions are at 252 (28), 149 (78), 133 (53),115 (42), 105 (50), 91 (78), 77 (42) in agreement with assigned structure.

The formation of 5a involve two levels of regioselectivity. Due to electron withdrawing nature of formyl group in dihydroxybenzaldehyde (4a), the C-3 OH is more nucleophilic than C-4 OH. Thus in the first step C-3 OH in its potassium salt form selectively displaces the bromide of the oxirane(3) to give an intermediate 7 which could not be isolated. The nucleophilic displacement of bromide by C-4 OH is not preferred, this attack if it takes place should generate regioisomer 8. In the second step of reaction the C-4 OH opens the oxirane. There are two possibilities for oxirane opening. Attack at C-2 of oxirane leads to the formation of six membered 1,4-benzodioxanes (5a-e), while attack at C-1 leads to seven membered 1,5-benzodioxapines (6a-e). C-2 attack is preferred because the trantition state in this opening involves the incipient secondary carbocation and the resulting compound is a thermodynamically stable six membered ring (Scheme-3).

The proof for the formation of six membered rings (5a-e) is from ^{1}H, ^{13}C and acetylation studies. In the ^{1}H NMR the chemical shifts and the signal pattern of protons in 5a and 6a are similar and hence cannot differentiate the ring size.

Scheme 3



However the ^{13}C NMR chemical shifts of oxygenated ring carbons are different for 6 and 7 membered systems. Several natural compounds are based on six membered 2-hydroxymethyl-3-aryl-1,4-benzodioxane skeleton. In these the chemical shifts for the ring carbons are at δ 60.17 ($\underline{C}H_2OH$) 78.3 (C-2) 75.6 (C-3)[6,14,15]. In seven membered benzodioxapines the chemical shifts of ring carbons at δ 85.3 (C-2) 75.0 (C-3) 74.9 (C-4)[12]. In 5 a-e the chemical shifts of these carbons are in agreement with six membered systems.

Acetylation experiment helps in differentiating CH_2OAc (5a) CH-OAc (6a) type systems. In the case of CH_2OAc the methylene protons undergo small downfield shifts upon acetylation (δ 0.1–0.4 ppm) while in the latter case the methine proton undergoes a larger downfield shift (upto δ 1.5 ppm). In 5a the hydroxymethylene protons appeared centered at δ 3.72 (ABq x 2) while in its acetate derivative these methylene protons appeared centered at δ 4.10 that is downfield by δ 0.38 ppm. This indicates that the reaction product is 5a rather than 6a.

Similarly, reaction of methyl-(3,4-dihydroxy) benzoate (4b), ethyl-(3,4-dihydroxy) benzoate (4c), 3,4-dihydroxybenzonitrile (4d) and 2,3-dihydroxy-nitrobenzene (4e) with 2-bromomethyl-3-phenyl oxirane (3) in acetone-K_2CO_3, gave six membered 2-hydroxymethyl-3-phenyl-6-carbomethoxy-1,4-benzodioxane (5b), 2-hydroxymethyl-3-phenyl-6-carboethoxy-1,4-benzodioxane(5c), 2-hydroxy-methyl-3-phenyl-6-nitrile-1,4-ben-zodioxane (5d) and 2-hydroxymethyl-3-phenyl-8-nitro-1,4-benzodioxane (5e). Its regioisomers (6 a-e) are not formed in the reaction. Thus in this reaction, 5a-e are formed in single step in good yield by regioselective oxirane ring opening.

EXPERIMENTAL:

^1H NMR (200 MHz) and ^{13}C NMR (50.3 MHz) are recorded on Varian Gemini 200 spectrometer in $CDCl_3$ and chemical shifts are given in δ ppm downfield from TMS. Mass spectra were recorded on a UG micro mass 7070 H instrument.

3-Bromo-3-phenyl-1-propene (2). Allylbenzene (1) (10 mmoles) NBS (15 mmoles) in CCl_4 (60 mL) refluxed vigorously under light (200 Watts bulb) for 24h. The succinimide filtered off, filtrate concentrated, chromatographed over silica gel and eluted with pet-ether to give (2) (75% yield). mp. 97^{0}C. ^{1}H NMR ($CDCl_3$): δ 3.90 (dd, J=13, 5Hz, H-1), 4.24 (dd, J-13, 4Hz , H-1) 4.70 (m, H-2), 5.30 (d, J=10, H-3), 7.40 (m, arom, 5H). found : C, 55.10; H, 4.60 : C_9H_9Br requires C, 55.10; H, 4.59%.

2-Bromomethyl-3-phenyl oxirane (3) 3-Bromo-3-phenyl-1-propene (2) (10 mmoles) m-CPBA (12 mmoles) dichloromethane(30 mL) stirred for 4h. Compound extracted with chloroform and washed with $NaHCO_3$ (2%) dried, concentrated , chromatographed over silicagel and eluted with pet-ether: chloroform (20:1) to give 2-bromomethyl-3-phenyl oxirane(3). (70%yield).^{1}H NMR ($CDCl_3$): δ 2.72 (dd, J=5, 4Hz, H-1), 2.95 (dd, J=4, 2Hz ,H-1), 3.55 (ddd, J=7, 4, 2, Hz, H-2), 4.62 (d, J=8Hz, H-3), 7.40 (m, arom, 5H). ^{13}C NMR (DMSO-d_6): δ 47.4 (C-1), 57.1 (C-2), 53.9 (C-3), 127.1 (C-2', 6'), 127.2 (C-3', 5') 127.5 (C-4'), 136.5 (C-1'). MS m/z 212 ($M^{+\bullet}$) (5), 194 (15), 168 (13), 132 (100), 114 (55), 104 (67),102 (89), 91 (61),77 (68).

2-Hydroxymethyl-3-phenyl-6-formyl-1,4-benzodioxane (5a) 3,4-Dihydroxy-benzaldehyde (4a) (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3) (10 mmoles) K_2CO_3 (5g) acetone (40 mL) refluxed for 24h. Acetone decanted and evaporated the product was extracted with solvent ether, washed with chilled aq. KOH (2%), dried, concentrated and chromatographed over silicagel eluted with pet ether:

ethylacetate (9:1) to give 5a (70%yield) mp.104^{0}C ^{1}H NMR ($CDCl_3$): δ 3.56 (ABq, J=13, 2 Hz, C$\underline{H}_2$0H), 3.88 (ABq, J=13, 2 Hz, C$\underline{H}_2$0H), 4.08 (m, H-2,) 5.15 (d, J=9Hz, H-3), 7.10 (d, J=9Hz, H-8), 7.48 (m, H-5,7, 2', 3', 4', 5', 6', 7H) 9.85 (s, C$\underline{H}$O) ^{13}C NMR ($CDCl_3$): δ 62.0 (C$\underline{H}_2$OH) 78.0 (C-2), 74.5 (C-3), 118.0 (C-5), 122.0 (C-6), 125.0 (C-7), 125.9 (C-1'), 127.0 (C- 2', 6'), 128.5 (C-4'), 129.0 (C-3', 5'), 136.5 (C-8), 138.0 (C-8a), 144.5 (C-4a), 191.0 (C=O). MS m/z 270 (M^+) (100), 252 (28), 149 (78), 133 (53), 115 (42), 105 (50), 91 (78), 77 (42). Anal cacld for $C_{16}H_{14}O_4$: C,71.10; H, 5.22%; found C, 71.00; H, 5.24%

2-Hydroxymethyl-3-phenyl-6-carbomethoxy-1, 4-benzodioxane (5b). Methyl-(3,4-dihydroxy) benzoate (4b) (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3) (10 mmoles) K_2CO_3 (5g) acetone (40 mL) refluxed for 24h. Reaction worked up as in 5a to give 5b (75%yield). Semisolid ^{1}H NMR ($CDCl_3$): δ 3.55 (ABq, J=13, 2Hz, C$\underline{H}_2$OH), 3.85 (ABq, J=13 , 2 Hz, C$\underline{H}_2$OH), 4.60 (m, H-2), 5.15 (d, J=9Hz, H-3), 7.00 (d, J=8Hz, H-8), 7.40-7.70 (m, H-5,7, 2', 3', 4', 5', 6', 7H). ^{13}C NMR ($CDCl_3$): δ 52.0 (OCH_3), 61.9 (C$\underline{H}_2$OH), 76.0 (C-2), 74.5 (C-3), 118.5 (C-5), 121.0 (C-6), 125.0 (C-7), 125.9 (C-1'), 127.5 (C-2', 6'), 128.5 (C-4'), 129.0 (C-3', 5'), 136.0 (C-8), 139.0 (C-8a), 143.5 (C-4a), 167.0 (C=O). MS: m/z 300 ($M^{+\bullet}$) (25), 282 (10), 269 (15), 255 (15), 179 (35), 133 (50),115 (40), 105 (68), 91 (68), 77 (78). Anal cacld for $C_{17}H_{16}O_5$: C,67.99; H,5.37%; found C, 67.98; H, 5.37%.

2-Hydroxymethyl-3-phenyl-6-carboethoxy-1,4-benzodioxane (5c). Ethyl-(3,4-dihydroxy) benzoate (4c) (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3) (10 mmoles) K_2CO_3 (5g) acetone (40mL) refluxed for 24h, reaction worked up as in

5a to give 5c (75%yield) semisolid ^{1}H NMR ($CDCl_3$): δ 1.45 (t, CH_3), 2.30 (s, OH), 3.50 (ABq, J=13, 2 Hz, C$\underline{H_2}$OH), 3.80 (ABq, J=13, 2Hz, C$\underline{H_2}$OH), 4.30 (q, OC$\underline{H_2}$), 4.60 (m, H-2), 5.05 (d, J=9Hz, H-3), 6.95 (d, J=8Hz, H-8), 7.40-7.55 (m, H-5,7, 2', 3', 4', 5', 6',7H). ^{13}C NMR ($CDCl_3$): δ 14.0 (CH_3), 61.0 (OCH_2), 61.5 ($\underline{C}H_2OH$), 76.0 (C-2), 75.0 (C-3), 117.5 (C-5), 121.0 (C-6), 125.5 (C-7), 125.9 (C-1'), 128.0 (C-2', 6'), 128.5 (C- 4'), 129.5 (C-3', 5'), 136.0 (C-8), 138.5 (C-8a), 143.0 (C-4a),167.0 (C=O). MS: m/z 314 ($M^{+\bullet}$) (30), 296 (15), 269 (20), 223 (15), 193 (20), 179 (15), 165 (15), 149 (20), 133 (100), 107 (45), 9I (80), 79 (60). Anal cacld for $C_{18}H_{18}O_5$: C,68.78; H,5.77%; found C,68. 79; H, 5.78%.

2-Hydroxymethyl-3-phenyl-6-nitrile-1,4-benzodioxane (5d) 3, 4-Dihydroxy-benzonitrile (4d) (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3) (10 mmoles) K_2CO_3 (5g) acetone (40 mL) refluxed for 24h, reaction worked up as in 5a, to give 5d (70%yield). Semisolid ^{1}H NMR ($CDCl_3$): δ 3.56 (ABq, J=13, 2Hz, C$\underline{H_2}$OH), 3.80 (ABq, J=13, 2Hz, C$\underline{H_2}$OH), 4.00 (m, H-2), 5.05 (d, J=9Hz, H-3), 7.95 (d, J=9Hz, H-8), 7.15-7.40 (m, H-5,7, 2', 3',4', 5', 6',7H). ^{13}C NMR ($CDCl_3$): δ 61.5 ($\underline{C}H_2OH$), 78.5 (C-2), 74.5 (C-3), 118.5 (C-5), 121.5 (C-6), 126.0 (C-7), 126.1 (C-1'), 128.0 (C-2', 6'), 128.5 (C-4'), 129.5 (C-3', 5'), 135.9 (C-8), 142.1 (C-8a), 148.0 (C-4a). MS: m/z 267 ($M^{+\bullet}$) (60), 249 (35), 222 (10), 176 (10), 146 (65), 133 (50), 115 (55), 105 (45), 91(100), 77 (70) Anal cacld for $C_{16}H_{13}NO_3$: C,71.90; H,4.90; N,5.24%; found C, 71.89; H,4.91; N, 5.24%.

2-Hydroxymethyl-3-phenyl-8-nitro-1,4-benzodioxane (5e). 2,3-Dihydroxy-nitrobenzene (4e) (10 mmoles) 2-bromomethyl-3-phenyl oxirane (3)(10 mmoles) K_2CO_3 (5g) acetone (40mL) refluxed for 24h, reaction worked up as in 5a,to give 5e (70%yield) yellow semisolid, ^1H NMR ($CDCl_3$): δ 3.10 (bs, OH), 3.55 (ABq, J=13, 2Hz, $C\underline{H}_2OH$), 3.80 (ABq J=13, 2Hz, $C\underline{H}_2OH$), 4.20 (m, H-2), 5.15 (d, J=9Hz, H-3), 6.85 (d, J=9Hz, H-5), 7.00 (m, H-6), 7.20-7.40 (m, H-7, 2', 3', 4', 5', 6', 6H). ^{13}C NMR ($CDCl_3$): δ 61.5 ($\underline{C}H_2OH$), 77.5 (C-2), 72.0 (C-3), 118.0 (C-5), 120.0 (C-6), 122.0 (C-7), 126.0 (C-1'), 126.5 (C-2', 6'), 128.0 (C-4'), 128.5 (C-3', 5'), 138.0 (C-8), 138.5 (C-8a), 144.0 (C-4a). MS: m/z 287 ($M^{+\bullet}$)(2), 270 (80), 181 (40), 107 (85), 105 (20), 91 (15), 79 (100), 77 (50). Anal cacld for $C_{16}H_{13}NO_5$: C,64.21; H,4.38; N 4.68%; found C, 64.20; H, 4.39; N 4.68%.

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