A concise and simple synthesis of 1-hydroxy-phenethylamine derivatives: Formal synthesis of naturally occurring norephedrine, virolin and 3-hydroxy-2-phosphonylmethoxypropyl adenine

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MS received 25 November 2013; revised 2 January 2014; accepted 11 January 2014

Abstract. A concise and simple synthesis of 1-hydroxy-phenethylamine derivatives has been achieved following classical organic transformations using commercially available chiral pools. The said derivatives were explored for the synthesis of naturally occurring bio-active small molecules. Formal synthesis of norephedrine, virolin and 3-hydroxy-2-phosphonylmethoxypropyl adenine has been demonstrated.

Keywords. Synthesis; 1-hydroxy-phenethylamine derivatives; intermediates; bio-active; small molecules.

1. Introduction

It is well-documented in the literature¹ that 1-hydroxyphenethylamine derivatives with a core structure (I) are good synthons for a wide range of biologically active naturally occurring small molecules.



 α -Hydroxy- β -amino esters and the vicinal amino diols are major contributing class with such core structure. Both of these structural moieties are significant not only for their own biological activity but also being a part of complex natural products such as vancomycin, chloramphenicol, GE2270 thiopeptide family, and Ustiloxin.^{1a,1d} Similarly, norephedrine, norpseudoephedrin, and cathionone are well-known naturally occurring biologically active alkaloids which act as stimulants, entactogens, and hallucinogens.^{2a} Moreover, said structural moiety is widely used as useful starting material for the preparation of chiral 2oxazoline, piperidines, aziridines, and imidazolines.² It is known^{2c} that the production cost of chemically synthesized ephedrine was sixty percent lower with better quality compared to extracted naturally occurring ephedrine. So, a good synthetic procedure is always desirable, and that is reflected in several recent publications.^{2c,3} We were interested in designing a general synthetic strategy for the stereoselective synthesis of 1-hydroxy-phenethylamine derivatives using commercially available or easily accessible chiral pools involving simple classical organic transformations. Carbohydrates and amino acids are well-known wealth of naturally occurring chiral pools with proper stereochemical dimension. Resemblance in chirality between the target and stock starting material is the necessary condition for the chiron approach.⁴ Most of the reported synthesis of ephedrine and related compounds dealt with recemic products although only a few are stereoselective but suffer from lack of generality.³ We report here a mild and concise synthesis of optically active 1-hydroxy-phenethylamine derivatives, the advanced intermediates for the synthesis of bio-active natural products. Formal synthesis of norephedrine, virolin and 3-hydroxy-2-phosphonylmethoxypropyl adenine has been demonstrated.

2. Experimental

Melting points were determined in open capillary tubes and are uncorrected. ¹HNMR and ¹³C NMR spectra were recorded in CDCl₃ 300 and 500 MHz

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spectrometer using tetramethyl silane as the internal standard. IR spectra were recorded on FT IR-8300 instrument. Column chromatography was performed on silica gel (60–120 mesh) and preparative TLC was performed using pre-coated silica 60 F 254 plates (0.2 mm). High-resolution mass spectra were obtained using a Qtof Micro YA263 instrument. GC was performed at 130°C using BP1 column on Perichrom PR 2100 machine. Diethyl ether and tetrahydrofuran were freshly distilled from sodium. Methylene chloride was freshly distilled over calcium hydride. Light petroleum of boiling range 60–80°C was used for chromatography.

X-ray single crystal data were collected using MoK α ($\lambda = 0.7107$ Å) radiation on a SMART APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, structure solution/refinement were carried out using the software package of SMART APEX. The structure was solved by direct method and refined in a routine manner. Non-hydrogen atoms were treated anisotropically. The hydrogen atoms were geometrically fixed. CCDC 862357 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac. uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ ccdc.cam.ac.uk).

2.1 Synthesis of (S)-tert-butyl 4-(hydroxy(phenyl) methyl-2,2-dimethyloxazolidine-3-carboxylate (**1a** and **1a**¹)

Freshlyprepared Grignard reagent at 0°C [prepared from bromobenzene (3 g, 0.02 mol) and Mg (550 mg, 0.02 mol) in THF (20 mL)] was added to the Garner's aldehyde **A** (4.8 g, 0.02 mol) in THF (30 mL) over a period of 1 h. The mixture was stirred for 3 h at room temperature. Saturated aqueous NH₄Cl was added to the reaction mixture, extracted with diethyl ether (3 × 70 mL). The combined organic layer was washed successively with water (3 × 10 mL) and brine (5 mL), and finally dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography over silica gel to afford an inseparable mixture of alcohols **1a** and **1a**¹ (4.5 g, 70%) in almost equal ratio [GC (R_t = 6.12 and 6.15 min)].

2.1a *IR* (*neat*): 3300, 3009, 2980, 1691, 1448, 1396, 1367, 1170 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.09 (s, 3H), 1.21 (s, 3H), 1.27–1.46 (m, 9H), 3.65–3.99 (m, 1H), 4.02–4.07 (m, 1H), 4.17–4.22 (m, 1H),

4.74–4.75 (m, 1H), 7.24–7.35 (m, 5H) ¹³C NMR (125 MHz, CDCl₃): δ 23.1, 23.2, 25.9, 26.4, 28.0, 48.7, 49.0, 62.9, 64.0, 74.4, 94.5, 125.9, 127.1, 127.9, 128.2, 141.2. HRMS: calcd for C₁₇H₂₅NO₄Na [M+Na]⁺ 330.1681; found 330.1681. The ¹H NMR spectrum was very complicated due to mixture of rotamers of both the isomers and there was no distinguishable signal for identifying the ratio of the isomers.

2.2 Synthesis of (S)-tert-butyl 4-(yl(phenyl) methanone-2,2-dimethyloxazolidine-3-carboxylate (**2a**)

To a stirred solution of compound 1 (3.0 g, 9.8 mmol) and an excess of molecular sieves (4 Å) in CH_2Cl_2 (20 mL), pyridinium chlorochromate (PCC) (3.2 g, 14.7 mmol) was added in one portion. The stirring was continued for another 30 min for the complete conversion (monitored by TLC). Diethyl ether (40 mL) was added to the reaction mixture and the solids were filtered off. The filtrate was successively washed with aqueous 10% HCl (10 mL), water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄. The crude product was purified by column chromatography (10%) ethyl acetate in light petroleum) to afford the pure keto compound 2a (2.4 g, 80%, mixture of two rotamers) as crystalline solid, mp 102-105°C). IR (KBr): 2982, 2857, 1703, 1651, 1396, 1361, 1246, 1172 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.28-1.76 (6s, 15H, Boc, $2 \times CH_3$, 3.92-3.96 (m, 1H, OCH), 4.28-4.33 (m, 1H, OCH), 5.36 (dd, J = 3.5, 7.5 Hz, $\frac{1}{2}$ H, NCH), 5.46 (dd, $J = 2.5, 7 Hz, \frac{1}{2} H NCH), 7.44-7.51 (m, 2H), 7.55-$ 7.60 (m, 1H), 7.90–7.93 (m, 2H); ¹³C NMR (125 MHz, $CDCl_3$): δ 24.8, 25.5, 26.0, 28.3, 28.5, 61.8, 62.0, 65.8, 66.2, 80.4, 80.9, 95.7, 95.4, 128.3, 128.5, 128.9, 129.0, 133.5, 133.6, 135.3, 151.4, 152.2, 195.3, 196.0; HRMS: calcd for $C_{17}H_{23}NO_4Na \ [M+Na]^+$ 328.1525; found 328.1527. The ¹H NMR spectrum was complex due to the rotamers of 2a.

2.3 Synthesis of (S)-tert-butyl 4-((S)-hydroxy(phenyl) methyl-2,2-dimethyloxazolidine-3-carboxylate (**1a**)

A suspension of LiAlH₄ LiAlH₄ (890 mg, 23 mmol) in THF (20 mL) was added drop-wise to a stirred solution of the keto compound **2a** (2.3 g, 7.8 mmol) in THF (10 mL) at -78° C under N₂. The reaction was further stirred for 30 min at that temperature followed by the addition of 1 mL of MeOH and the temperature was gradually increased to 0°C. A saturated aqueous solution of sodium potassium tartrate (10 mL) and excess of diethyl ether (50 mL) was added. The stirring was continued until complete precipitation. The solids were

filtered off and the filtrate was washed successively with dilute aqueous 10% HCl (10 mL), water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄. The organic solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (15% ethyl acetate in light petroleum) to afford the alcohol 1a (mixture of two rotamers) (2.1 g, 90%) as a viscous mass. $[\alpha]_{D}^{24.0} = +13.7$ (c, 2.01 in CHCl₃); IR (neat): 3444, 2978, 2879, 1699, 1670, 1456, 1395, 1367, 1255 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.41 (s, 6H), 1.47 (s, 9H), 3.60–3.61 (m, 1H), 3.68–3.69 (m, 1H), 4.05 (brs, 1H), 4.19–4.21 (m, 1H), 4.74 (d, J = 8.5 Hz, 1H), 7.19–7.31 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): δ 24.4, 27.0, 27.3, 28.5, 63.8, 64.9, 78.2, 81.9, 94.8, 127.4, 127.5, 128.2, 128.6; HRMS: calcd for C₁₇H₂₅NO₄Na [M+Na]⁺ 330.1681; found 330.1682. The ¹H NMR spectrum was complex due to the rotamers of 1a.

2.4 Synthesis of tert-butyl (1S,2S)-1,3-dihydroxy-1phenylpropan-2ylcarbamate (**3a**)

To a solution of **1a** (2.0 g, 6.5 mmol) in AcOH–H₂O (10:1, 5 mL) was added LiCl (540 mg, 13.0 mmol) at room temperature. The reaction mixture was stirred for 2 h at that temperature. Then, it was concentrated and co-evaporated with hexane (50 mL). The residue obtained was purified by column chromatography (40% ethyl acetate in light petroleum) to afford the diol **3a** (mixture of two rotamers) (1.2 g, 70%) as an oil. $[\alpha]_D^{25.5} = +35.5$ (c, 2.07 in CHCl₃); IR (neat): 3406, 2978, 2933, 1693, 1504, 1454, 1367, 1168 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.30 (brs, 9H), 3.76–3.81 (m, 3H), 4.98 (d, J = 2.5 Hz, 1H), 7.27–7.38 (m, 5H); ¹³C NMR (125 MHz, CDCl₃): 20.6, 28.2, 57.3, 62.0, 74.2, 80.1, 126.2, 127.9, 128.9, 141.4; HRMS: calcd for C₁₄H₂₁NO₄Na [M+Na]⁺ 290.1368; found 290.1367.

2.5 Synthesis of tert-butyl (1S,2S)-1-hydroxy-3tosyloxy-1-phenylpropan-2ylcarbamate (**4a**)

To a stirred solution of **3a** (1.0 g, 3.74 mmol) and triethyl amine (5.6 mmol, 0.8 mL) in dry CH₂Cl₂ (20 mL) at 0°C was added *p*-toluenesulphonyl chloride (850 mg, 4.49 mmol) in portions during 30 min. After stirring for an additional 3 h at room temperature, the mixture was poured into ice-water. The organic layer was separated and the aqueous portion was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts was washed successively with aqueous 10% HCl (5 mL), water (5 mL) and brine (5 mL), and finally dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by column chromatography of the residue obtained over silica gel (20% ethyl acetate in light petroleum) afforded the monotosylated derivative **4a** (mixture of two rotamers) (1.25 g, 80%) as crystalline solid, mp 132–135°C). $[\alpha]_D^{25.0} = +26.3$ (c, 3.09 in CHCl₃); IR (KBr): 3323, 3250, 3088, 1732, 1599, 1512, 1371, 1188 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.22 (s, 9H), 2.38 (s, 3H), 2.85 (brs, 1H), 3.85–3.87 (m, 2H), 4.09 (dd, J = 6.5, 10.0 Hz, 1H), 4.81 (d, J = 4.0 Hz, 1H), 7.17–7.22 (m, 4H), 7.23–7.29 (m, 3H), 7.71 (d, J = 8.0 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 21.8, 28.3, 68.7, 126.1, 126.2, 128.0, 128.1, 128.2, 128.5, 128.8, 130.1, 145.2; HRMS: calcd for C₂₁H₂₇NO₆SNa [M+Na]⁺ 444.1457; found 444.1455.

2.6 Synthesis of tert-butyl (1S,2S)-1-hydroxy-1phenylpropan-2ylcarbamate (5a)

A suspension of LiAlH₄(270 mg, 7.3 mmol in THF (5 mL) was added to a stirred solution of compound 4a (1.0 g, 2.4 mmol) in THF (10 mL) at 0°C. The reaction mixture was stirred additionally for 45 min at 0°C. Then, 0.5 mL of MeOH was added to the reaction mixture followed by the addition of a saturated aqueous solution of sodium potassium tartrate (10 mL) and excess of diethyl ether (40 mL). The stirring was continued until complete precipitation at room temperature. The solids were filtered off and the filtrate was washed successively with aqueous 10% HCl (10 mL), water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄. The organic solvent was evaporated under reduced pressure to afford the N-Boc protected amino alcohol 5a (360 mg, 60%) as white crystalline solid, mp $85-87^{\circ}$ C. $[\alpha]_{D}^{25.5} = +24.9$ (c, 2.81 in CHCl₃); IR (neat): 3403, 3375, 2980, 1684 cm⁻¹; ¹H NMR (500 MHz, CDCl_3): δ 1.07 (d, J = 6.5 Hz, 3H), 1.40 (s, 9H), 3.84– 3.86 (m, 1H), 4.54 (d, J = 6.0 Hz, 1H), 4.68-4.72 (m,1H), 7.32–7.37 (m, 5H); ¹³NMR (125 MHz, CDCl₃): δ 17.0, 28.5, 55.0, 79.9, 126.8, 127.9, 128.4, 141.8; HRMS: calcd for $C_{14}H_{21}NO_3Na [M+Na]^+ 274.1419;$ found 274.1417.

2.7 Synthesis of (3,4-dimethoxyphenyl)((R)-2,2cyclohexylidene-1,3-dioxolan-4-yl)methanol (**1b** and **1b**¹)

To a stirred solution of Grignard reagent at 0° C [prepared from 4-bromoveratrole (3 g, 14.0 mmol) with Mg (400 mg, 17.0 mmol) in THF (20 mL)] under N₂ was added (R)-2,3-O-cyclohexylideneglyceraldehyde (**B**) (2.9 g, 17 mmol) in THF (30 mL) over a period of 1 h. The mixture was stirred for 3 h at room

temperature. Saturated aqueous NH₄Cl (10 mL) was added to the reaction mixture followed by extraction with ether (3 \times 70 mL). The combined organic layer was washed with water (3 \times 10 mL) and brine (5 mL), and finally dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (15% ethyl acetate in light petroleum) over silica gel to afford an inseparable mixture of alcohols **1b** and **1b**¹ (2.5 g, 60%) in almost equal ratio.

2.7a *IR* (*neat*): 2920, 2810, 1690, 1595, 1420, 1260, 1163 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.36–1.38 (m, 2H), 1.55–1.65 (m, 8H), 3.64–3.66 (m, 1H), 3.71–3.75 (m, 1H), 3.82 (s, 3H), 3.84 (s, 3H), 3.90–3.95 (m, 1/2H), 4.16–4.19 (m, 1H), 4.21–4.28 (m, 1/2H), 4.43 (d, *J* = 7.9 Hz, 1/2H), 4.78 (d, *J* = 4.2 Hz, 1/2H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 6.84 (s, 1H); ¹³C (75 MHz, CDCl₃): δ 23.8, 24.0, 25.1, 34.7, 34.9, 36.3, 36.4, 36.7, 55.9, 56.2, 63.1, 64.3, 65.4, 65.7, 72.5, 75.8, 79.2, 79.9, 109.1, 110.1, 118.3, 119.4, 132.5, 148.5, 149.1; HRMS: calcd for C₁₇H₂₄O₅Na [M+Na]⁺ 331.1521, found 331.1520.

2.8 Synthesis of (3,4-dimethoxyphenyl)((R)-2,2cyclohexylidene-1,3-dioxolan-4-yl)methanone (**2b**)

To a stirred solution of the crude mixture of alcohols **1b** and **1b**¹ (2.5 g, 8.1 mmol) in CH₂Cl₂, pyridinium chlorochromate (2.4 g, 11.3 mmol) was added in the presence of excess of molecular sieves (4 Å) in one portion. The reaction mixture was stirred for another 30 min for complete conversion. Excess diethyl ether (40 mL) was added to the reaction mixture followed by filtration. The filtrate was washed successively with aqueous 10% HCl (10 mL), water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄. The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (10% ethyl acetate in light petroleum) to afford pure keto compound **2b** (2.1 g, 85%) as a viscous liquid.

2.8a *IR* (*neat*): 2936, 2806, 1693, 1595, 1514, 1446, 1263, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.40–1.43 (m, 2H), 1.54-1.72 (m, 8H), 3.95 (s, 3H), 3.96 (s, 3H), 4.25–4.31 (m, 2H), 5.22 (m, 1H), 6.90–6.94 (m, 2H), 7.06–7.10 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 24.0, 252, 35.3, 35.6, 56.2, 66.2, 77.5, 110.2, 110.7, 111.7, 119.3, 124.1, 134.4, 148.5, 153.8, 195.5; HRMS: calcd for C₁₇H₂₂O₅Na [M+Na]⁺ 329.1365, found 329.1364.

2.9 Synthesis of (R)-(3,4-dimethoxyphenyl)((R)-2,2cyclohexylidene-1,3-dioxolan-4-yl)methanol(**1b**)

A suspension of LiAlH₄ (740 mg, 19.5 mmol) in THF (10 mL) was added drop-wise to a stirred solution of the keto compound **2b** (2.0 g, 6.5 mmol) in THF (10 mL) at -78° C. The reaction mixture was stirred at this temperature for another 30 min. MeOH (1 mL) was added to the reaction mixture and the temperature was gradually raised to 0°C. At this temperature a saturated aqueous solution of sodium potassium tartrate (10 mL) and excess of diethyl ether (50 mL) was added. The stirring was continued until complete precipitation. It was filtered and the filtrate was successively washed with aqueous 10% HCl (10 mL), water (10 mL) and brine (10 mL), and finally dried over Na_2SO_4 . The organic solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (10% ethyl acetate in light petroleum) to afford the syn isomer **1b** (1.6 g, 80%) as a viscous liquid. $[\alpha]_{D}^{26.8} =$ -17.2 (c, 8.1 in CHCl₃); IR (neat): 3485, 2997, 2935, 1593, 1514, 1263, 1161 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.38–1.41 (m, 2H), 1.54–1.68 (m, 8H), 3.67 (dd, J = 5.5, 8.5 Hz, 1H), 3.76-3.78 (m, 1H), 3.76 (s, 1H))3H), 3.78 (s, 3H), 4.17 (dd, J = 6.5, 13.5 Hz, 1H), 4.45 (d, J = 8.0 Hz, 2H), 6.80–6.83 (m, 2H), 6.86– 6.91 (m, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 23.9, 24.3, 25.3, 35.1, 36.5, 36.9, 56.09, 65.9, 76.2, 80.1, 110.2, 110.9, 111.3, 119.6, 132.5, 149.4; HRMS: calcd for C₁₇H₂₄O₅Na [M+Na]⁺ 331.1521, found 331.1520.

2.10 Synthesis of (R)-4-((R)-(4-methoxybenzyloxy) (3,4-dimethoxyphenyl)methyl)-2,2-cyclohexylidine-1,3dioxolane (**3b**)

To a stirred suspension of sodium hydride (350 mg, 60% dispersion in oil, 14.6 mmol) in dry THF (20 mL) was added drop-wise to a solution of the alcohol 1b (1.5 g, 4.9 mmol) in dry THF (10 mL) at 0° C under N₂. Then, a solution of *p*-methoxy benzyl bromide (1.2 g, 5.8 mmol) in dry THF (20 mL) was added drop-wise at 0°C over 30 min. The reaction was continued to stir at room temperature for 3 h. The reaction mixture was then carefully quenched with ice-water. After removal of most of THF under reduced pressure, the resulting residue was extracted with diethyl ether $(3 \times 50 \text{ mL})$. The combined ether extract was washed successively with water $(3 \times 10 \text{ mL})$ and brine (5 mL), and finally dried (Na₂SO₄). Removal of the solvent under reduced pressure afforded a viscous liquid, which was purified by column chromatography (5% ethyl acetate in light petroleum) over silica gel to afford *p*-methoxybenzyl protected ether 3b (1.4 g, 70%) as a viscous oil. IR (neat): 3009, 2935, 2862, 1612, 1514, 1464, 1249, 1163 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 1.30–1.34 (m, 2H), 1.40–1.56 (m, 8H), 3.45 (dd, J = 6.5, 8.5 Hz, 1H), 3.56–3.59 (m, 1H), 3.72 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.13–4.16 (m, 1H), 4.25 (dd, J = 6.5, 14 Hz, 1H), 4.44-4.52 (m, 2H), 6.76-6.84 (m, 5H), 7.16 (d, J = 8.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 23.9, 24.1, 25.3, 35.3, 36.4, 55.4, 55.9, 56.0, 65.8, 69.8, 78.8, 81.8, 110.6, 110.7, 111.0, 113.8, 113.9, 114.1, 128.7, 129.6, 130.4, 130.7, 149.1, 149.2, 159.3; HRMS: calcd for C₂₅H₃₂O₆Na [M+Na]⁺ 451.2097, found 451.2098.

2.11 Synthesis of (2R,3R)-3-(4-methoxybenzyloxy)-3-(3,4-dimethoxyphenyl)propane-1,2-diol(4b)

The compound **3b** (1.4 g, 3.27 mmol) was stirred with 80% aqueous acetic acid (5 mL) at 40°C for 2 h (monitored by TLC). Acetic acid was removed under reduced pressure and co-evaporated with toluene. The crude residue obtained was chromatographed (20%) ethyl acetate in light petroleum) over silica gel to afford the pure diol 4b (800 mg, 70%) as a viscous liquid. $[\alpha]_{D}^{25.6} = -63.4$ (c, 5.2 in CHCl₃); IR (neat): 3464, 2958, 2837, 1514, 1464, 1251, 1030 cm⁻¹; ¹H NMR $(500 \text{ MHz}, \text{CDCl}_3)$: δ 3.34 (dd, J = 5.0, 11.0 Hz, 1H),3.51 (dd, J = 3.5, 12.0 Hz, 1H), 3.73-3.78 (m, 1H),3.80 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.21 (d, J =11.0 Hz, 1H), 4.33 (d, J = 8.0 Hz, 1H), 4.41 (d, J =11.0 Hz, 1H), 6.86–6.91 (m, 5H), 7.19 (d, J = 8.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 55.4, 56.0, 56.1, 62.6, 70.3, 75.7, 81.7, 110.2, 111.2, 114.1, 120.5, 129.7, 129.8, 129.9, 130.5, 149.2, 149.4, 159.5; HRMS: calcd for $C_{19}H_{24}O_6$ [M+Na]⁺ 371.1471, found 371.1472.

2.12 Synthesis of (2R,3R)-3-(4-methoxybenzyloxy)-2hydroxy-3-(3,4-dimethoxyphenyl)propyl 4-methylbenzenesulphonate (**5b**)

To a stirred solution of **4b** (800 mg, 2.3 mmol) and excess of pyridine (3 mL) in dry CH₂Cl₂ (20 mL) at 0°C was added *p*-toluenesulphonyl chloride (530 mg, 2.75 mmol) in portions during 30 min under N₂. After stirring for another 12 h at room temperature, the mixture was poured into ice-water. The organic layer was separated and the aqueous portion was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extract was washed successively with aqueous 10% HCl (5 mL), water (5 mL) and brine (5 mL), and finally dried (Na₂SO₄). Removal of the solvent under reduced pressure followed by column chromatography of the residue (10% ethyl acetate in light petroleum) over silica gel afforded the monotosylated derivative **5b** (810 mg, 70%) as an oil. $[\alpha]_{D}^{25.8} = -37.4$ (c, 3.0 in CHCl₃); IR (neat): 3520, 2955, 2935, 2837, 1612, 1514, 1454, 1359, 1249, 1176 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 2.43 (s, 3H), 3.80 (s, 3H), 3.83–3.86 (m, 2H), 3.88 (s, 3H), 3.90 (s, 3H), 3.97 (dd, J = 2.5, 9.5 Hz, 1H), 4.20 (d, J = 11.0 Hz, 1H), 4.36–4.40 (m, 2H), 6.84–6.87 (m, 5H), 7.16 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 21.8, 55.4, 56.0, 56.1, 69.9, 70.6, 73.5, 80.6, 110.3, 111.4, 114.0, 114.1, 120.2, 128.0, 128.1, 129.7, 129.8, 129.9, 130.0, 132.9, 144.9, 149.4, 149.5, 159.6; HRMS: calcd for C₂₆H₃₀O₈SNa [M+Na]⁺ 525.1559, found 525.1559.

2.13 Synthesis of (1R,2R)-1-(4-methoxybenzyloxy)-1-(3,4-dimethoxyphenyl)propan-2-ol(**6b**)

A suspension of LiAlH₄(5.0 mmol) in THF (5 mL) was added drop-wise to the stirred solution of compound **5b** (800 mg, 1.6 mmol) in THF (5 mL) at 0°C under N₂. Then the reaction mixture was stirred for 45 min at room temperature. Then, 0.5 mL of MeOH was added to the reaction mixture followed by the addition of a saturated aqueous solution of sodium potassium tartrate (10 mL) and excess of diethyl ether (40 mL). The stirring was continued until complete precipitation at room temperature. The solids were filtered off and the filtrate was washed successively with aqueous 10% HCl, water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄. The organic solvent was evaporated under reduced pressure to afford the alcohol **6b** (420 mg, 80%) as an oil.

2.13a $[\alpha]_{D}^{25.8} = 68.7$ (c, 2.2 in CHCl₃); IR (neat): 3550, 2935, 2837, 1519, 1467, 1248 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 0.95 (d, J = 6.5 Hz, 3H), 3.80 (s, 3H), 3.83–3.87 (m, 1H), 3.89(s, 3H), 3.90 (s, 3H), 3.98 (d, J = 8.5 Hz, 1H), 4.20 (d, J = 11.0 Hz, 1H), 4.38 (d, J = 11.5 Hz, 1H), 6.86–6.90 (m, 5H), 7.20 (d, J =8.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃): δ 18.2, 29.8, 55.4, 56.0, 56.1, 70.3, 71.5, 86.8, 110.3, 111.1, 114.0, 114.1, 120.7, 129.8, 130.2, 131.3, 149.2, 149.4, 159.5; HRMS: calcd for C₁₉H₂₅O₅ [M+H]⁺ 333.1702, found 333.1693.

2.14 Synthesis of ((R)-2,2-cyclohexylidine-1, 3-dioxolan-4-yl)methyl 4-methylbenzenesulphonate (2c)

To a stirred solution of (R)-2,3-O-cyclohexylideneglyceraldehyde (**B**) (850 mg, 5 mmol) in MeOH (8 mL) NaBH₄ (290 mg, 7.5 mmol) was added portion-wise at 0°C. The reaction mixture was stirred for another 30 min (monitored by TLC). Water (1 mL) was added to the reaction mixture and MeOH was evaporated under reduced pressure. The remaining residue was extracted with diethyl ether (3 × 40 mL) and combined organic layer was washed successively with water (10 mL) and brine (10 mL), and finally dried over Na₂SO₄ to afford the known alcohol **1c** (80%, 680 mg). The crude alcohol was sufficient pure to use in the next step.

2.14a Compound **2c** (920 mg, 75%) was prepared form the alcohol 1c (650 mg, 3.8 mmol) following the similar procedure as described for **5b**. IR (neat): 2937, 2862, 1599, 1450, 1365, 1178 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.34–1.39 (m, 2H), 1.49–1.51 (m, 8H), 2.42 (s, 3H), 3.73 (dd, J = 5.0 Hz, 8.7 Hz, 1H), 3.92–3.97 (m, 2H), 3.98-4.02 (m, 1H), 4.23-4.27 (m, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.1 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 21.7, 23.97, 23.9, 25.1, 34.7, 36.4, 65.9, 69.8, 72.6, 110.7, 128.0, 129.9, 132.7, 145.1; HRMS: calcd for C₁₆H₂₂O₅S [M+Na]⁺ 349.1086, found 349.1086.

2.15 Synthesis of 9-(((R)-2,2-cyclohexylidine-1,3dioxolan-4-yl)methyl-9H-purin-6-amine (**3***c*)

A mixture of adenine (400 mg, 3.0 mmol), powdered anhydrous K₂CO₃ (550 mg, 4.0 mmol) and 18-crown-6 (1.0 g, 4.0 mmol) in dry DMF (3 mL) was stirred for 15 min at 80°C under argon. Then, a solution of the tosylate 2c (650 mg, 2.0 mmol) in dry DMF (2.0 mL) was added drop-wise and the reaction mixture was heated at 80°C for 4 h. The mixture was allowed to come to the room temperature and concentrated to dryness under reduced pressure. The residue obtained was purified by column chromatography (CH₂Cl₂-MeOH, 15:1) over silica gel to give the pure compound 3c (370 mg, 65%) as crystalline solid, mp 210-212°C. IR (KBr): 3346, 3290, 2937, 2887, 1604, 1475, 1419, 1309, 1107 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.38– 1.40 (m, 2H), 1.55–1.59 (m, 8H), 3.67 (dd, J = 5.9, 8.6 Hz, 1H), 4.10 (dd, J = 6.4, 8.7 Hz, 1H), 4.25 (dd, J = 5.9, 14.2 Hz, 1H), 4.44–4.50 (m, 2H), 5.64 (brs, 2H), 7.94 (s, 1H), 8.35 (s, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 23.7, 24.0, 25.1, 34.7, 36.5, 45.7, 66.1, 70.5, 73.7, 110.8, 141.6, 153.1.

2.16 Synthesis of (R)-3-(6-amono-9H-purin-9-yl) propane-1,2-diol (**4c**)

To the stirred solution of the compound 3c (580 mg, 2 mmol) in MeOH (3 mL), 0.2 mL conc. HCl was

added. The reaction mixture was stirred for 0.5 h. Then the solvent was removed under reduced pressure and CH₂Cl₂ (8 mL) was added to it. The reaction mixture was kept aside for one hour for complete precipitation of the compound **4c**. The solids were filtered off and was washed carefully with CH₂Cl₂ (~10 mL) to get the pure diol **4c** (330 mg, 80%) as a white crystalline solid, mp 215–217°C. IR 3379, 3300, 2733, 1668, 1510, 1354, 1041 cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ 3.33 (dd, J = 6.5, 11.0 Hz, 1H), 3.42 (dd, J = 5.0, 11.0 Hz, 1H), 3.82 (dd, J = 9.0, 14.0 Hz, 1H), 4.09–4.14 (m, 1H), 4.38 (dd, J = 2.5, 14.0 Hz, 1H), 8.42 (s, 1H), 8.49 (s, 1H); ¹³C NMR (125 MHz, DMSO-d₆): δ 63.8, 70.1, 70.3, 145.1, 145.3, 149.2, 150.5.

2.17 X-ray crystallographic data of 3c

A yellowish plate shaped crystal (0.16 × 0.14 × 0.10 mm) of **3c** was analysed. Empirical formula $C_{14}H_{22}N_5O_2$, Chemical formula weight = 292.37, monoclinic, space group *P2(1)*, *a* = 10.7820(17), *b* = 8.5518(14), *c* = 15.817(3) Å. *V* = 1418.7(4) Å³, *T* = 298 K, *Z* = 4. ρ_{cal} = 1.369 gcm⁻³. *F* (000) = 628, λ (Mo-K α) = 0.71073 Å, μ MoK α /mm⁻¹ = 0.095, 2θ max = 43.92°, 10226 total reflections, 3461 unique reflections, 3461 observed [(I > 2 σ (I)]; 382 parameters; R_{int} = 0.0476, w R_2 = 0.1247 [I > 2 σ (I)]; R_1 = 0.0419; w R_2 = 0.1164 (all data) with GOF = 0.962.

3. Results and discussion

Our synthetic strategy was initiated with nucleophilic addition of phenyl magnesium bromide to commercially available Garner's aldehyde (**A**) to produce an inseparable mixture of two isomeric alcohols **1a** and **1a**¹ in a ratio of 1:1 (scheme 1). Each isomer shows two rotamers which made the ¹H NMR spectrum very complicated. Ratio was determined by GC. The crude alcohol was subjected to PCC oxidation to furnish the ketone **2a** in 80% yield. Compound **2a** was also a mixture of two rotamers. Reduction of **2a** with LiAlH₄ in THF furnished the *syn* alcohol **1a** exclusively without a trace of any *anti* isomer **1a**¹ (scheme 1).⁵ Due to the presence of rotamers the NMR spectra of the compounds described showed complicated patterns which has already been explained by Nishida *et al.*⁵ in details.

The high selectivity of the nucleophilic addition of hydride to carbonyl moiety⁶ in **2a** may be explained with the analogy as reported by Chikasita.^{6a} The nucleophilic addition depends not only on the nucleophile or the chiral environment around but also on the metal ion used. In general, the strong chelating effect of



Scheme 1. Synthesis of 1-hydroxy-phenethylamine derivative.

the counter ion lithium favours the β -chelation transition state **C** over the α -chelation transition state **D** (figure 1). In case of **2a** the α -chelation transition state **F** is totally disfavoured due to the presence of the bulky N-Boc group resulting in only the *syn* alcohol **1a** through the β -chelation transition state **E**.

However, a recent report by Hajra *et al.*^{7a} revealed during the asymmetric synthesis of a dopamine D1 agonist that 1-hydroxy-phenethylamine derivative **1a** could be prepared in one step using CuI.DMS complex. *syn*-Selective addition to Garner aldehyde has been reported by Ganem *et al.*^{7b} during the synthesis of a potent glucosylceramide synthase inhibitor. In the comprehensive review by Mengel and Reiser,^{7c} the necleophilic addition to Garner aldehyde has been discussed in details.

Compound **1a** was then deprotected using aqueous acetic acid in the presence of LiCl to afford **3a** in good yield. The diol **3a** was selectively monotosylated⁸ using tosyl chloride in the presence of excess triethylamine in dichloromethane to afford **4a** in 80% yield. The compound **4a** was reduced with LiAlH₄ in THF to produce the substituted N-Boc protected 1-phenyl 2-amino alcohol **5a** in good yield (scheme 2). The compound **5a** has already been transformed to norephedrine

(6a) and ephedrine (7a).^{2c,9} So, a formal synthesis of norephedrine has been achieved.

The important N-protected amino alcohol **3a** has also been used by Baruwa *et al.*¹⁰ for the synthesis of different biologically active natural products such as chloramphenicol A. Stereoselective synthesis of chiral β hydroxy- α -amidoester from **1a** could easily be obtained as reported by Rao *et al.* through simple chemical transformations.¹¹

Our next target was the synthesis of virolin (7b), a biologically active neolignan¹² or its advanced intermediate starting from easily accessible (R)-2,3-Ocyclohexylidine glyceraldehydes (B) as a source of chiral pool. Thus, freshly prepared Grignard reagent (ArMgBr) from 4-bromo veratrole was added to the aldehyde **B** to derive an inseparable mixture of two isomeric alcohols 1b and $1b^1$ in a ratio of 1:1 (scheme 3). The crude alcohol was subjected to PCC oxidation to produce the ketone 2b. The ketone 2b was reduced by LiAlH₄ in THF to afford an inseparable mixture of alcohols (syn:anti = 95:5) which was directly treated with the *p*-methoxybenzyl bromide in the presence of NaH and a catalytic amount of HMPA to afford the PMB-protected aryl ether **3b** after column chromatography (10% ethyl acetate in light petroleum).



Figure 1. Transition states in nucleophilic addition.



Scheme 2. Formal synthesis of norephedrine and ephedrine.

In this case, the slightly lower selectivity in nucleophilic addition was observed due to the probability of α -chelation (X = O, figure 1) involving counter ion lithium in transition state **D** although the major product was formed through the transition state **C**.^{6a} The aryl ether **3b** on treatment with 80% aqueous acetic acid at 40°C afforded the diol **4b**. The primary hydroxy group of the diol **4b** was selectively monotosylated using tosyl chloride with excess of pyridine in DCM furnishing the monotosylated alcohol **5b**. The alcohol **5b** was treated with LiAlH₄ in THF at room temperature to afford the alcohol **6b** in 80% yield.

Here, it is noteworthy to mention that a class of 4hydroxy-7,8-diol **8b** could easily be synthesized from the intermediate **6b**. These diols themselves are naturally occurring compounds and have considerable medicinal applications such as treatment of disease due to malnutrition in children.¹³ Now, the monoprotected diol **6b** could be converted into the *threo* isomer of Virolin (**7b**) as reported by Zanardi^{12b} and Xia^{12d} with the inversion of the stereochemistry at C-8. We extended the synthetic strategy towards the



Scheme 3. Formal synthesis of virolin.



Scheme 4. Formal synthesis of HPMPA.

synthesis of optically active acyclic nucleoside and nucleotide analogues.¹⁴ These compounds are used as antiviral drugs such as inhibitors of viral DNA polymerases.^{14a} Thus, (R)-2,3-O-cyclohexylidine glyceraldehydes (**B**) was treated with NaBH₄ in MeOH for 1 h to afford the alcohol **1c** in excellent yield (scheme 4). The primary alcohol **1c** was then tosylated with TsCl in pyridine to get **2c** in 75% yield. Now, the tosylate group in **2c** was substituted by adenine in the presence of K₂CO₃ and 18-Crown-6 in DMF¹⁵ at 80°C to furnish **3c** in 65% yield. Structure of **3c** was confirmed by X-ray crystallographic study (figure 2).

Compound **3c** was treated with HCl in MeOH to get the highly polar diol **4c** in 80% yield as a crystalline solid. Since, compound **4c** has already been converted^{14a} to the 3-hydroxy-2-phosphonylmethoxypropyl adenine (HPMPA) (**5c**), an anti-pox agent, we may claim the formal synthesis of HPMPA. Our strategy for the synthesis of 9-(2,3-dihydroxypropyl) adenine (DHPA) (**4c**) is found to be much superior compared to the reported procedure by Zakirova *et al* from D-ribose.^{14a} Although



Figure 2. ORTEP diagram of compound 3c.

Holý *et al.*¹⁶ followed the similar strategy, our strategy is better with respect to the reaction time, purification procedure and yield of the products. Following the present method, few grams of pure **4c** could easily be prepared within a day or so. We believe that the compound **4c** could be an advanced intermediate for the synthesis of tenofovir (**6c**), an anti-HIV drug.

4. Conclusion

In conclusion, we have designed a generalized strategy for the synthesis of some advanced optically active intermediates which have broad spectrum of application in the synthesis of a variety of biologically active molecules involving simple chemistry and easily accessible starting materials without using any expensive chiral catalyst. These features of the strategy are expected to contribute sufficiently to scientific literature and arrogate industrial applications.

Acknowledgements

We sincerely thank the Department of Science and Technology (DST), New Delhi for financial support. SS thanks the council of Scientific and Industrial Research (CSIR), New Delhi, for awarding the fellowship. We express our sincere thanks to S Ray and N Chakraborty, Summer Project Fellows, for their help in preparing some of the starting materials. We also express our sincere thanks to Dr. S Paira, Inorganic Chemistry Department of this Institute for analysing X-Ray data.

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