Direct conversion of \((R)-\)epichlorohydrin to \((S)-3\) -aminopropane-1,2-diol:  
An important chiral C-3 building block

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A new and effective method for the preparation of optically active \((S)-3\)-amino-1,2-propanediol \(1\) has been established starting from \((R)-\)epichlorohydrin \(2\). The synthetic approach involves the reaction of \((R)-\)epichlorohydrin \(2\) with acetone catalyzed by boron trifluoride etherate (BF\(_3\)·OEt\(_2\)) to give the \((R)-4\)-(chloromethyl)-2,2-dimethyl-1,3-dioxolane, \(5\). Replacing the chloro group in \((R)-5\) with amino group by azidation followed by reduction gives \((S)-2,2\)-dimethyl-1,3-dioxolan-4-yl)methanamine \(7\). Acetal deprotection of the obtained \((S)-7\) with MeOH·HCl gives \((S)-3\)-aminopropane-1,2-diol·HCl.

**Keywords**: \((S)-3\)-Aminopropane-1,2-diol, \((R)-\)epichlorohydrin, azidation, Rivaroxaban (Bay-59-7939), \(\beta\)-amino alcohol

Optically active 3-aminopropane-1,2-diol \(1\) (Figure 1) is a very important C-3 chiral building block for 2-oxazolidinone derivatives [Rivaroxaban (Bay-59-7939)]\textsuperscript{1} or derivatives of chiral 5-hydroxymethyl-2-oxazolidinone][2], an anti-depressant drug (e.g. Reboxetine)[3], \(\beta\)-adrenoceptor antagonists and/or cardioactive compounds (e.g. CGP 12177, Propranolol, Pindolol or Cyanopindolol)[4] and it has been established that the activity generally resides in the \((S)-\)isomers\textsuperscript{5}. Racemic 3-aminopropane-1,2-diol is also used in the synthesis of contrast agents (e.g. Visipaque, Iopentol and/or Iomeprol)[5]. Many pharmaceutical compounds contain three-carbon chiral substructures, the development of routes to which is often the most difficult aspect of the large scale synthesis of such compounds. Because of this, there is a constant ongoing effort to identify synthetic routes to these three-carbon chiral building blocks.

**Results and Discussion**

As a part of the ongoing research programme on synthesis of small chiral building blocks\textsuperscript{7}, it is wished to report herein the synthesis of \((S)-3\)-aminopropane-1,2-diol. \(1\) Initially, the feasibility for the synthesis of targeted \((S)-1\) was achieved by the reaction of \((S)-\)epichlorohydrin \(2\) with potassium cyanate (KOCN) under reported conditions\textsuperscript{8} gave the \((S)-5\)-(chloromethyl)oxazolidin-2-one \(3\). Since the reaction takes more than 15 hr, magnesium sulfate (MgSO\(_4\)) was introduced to reduce the reaction time. On the other hand, \((S)-\)epichlorohydrin \(2\) on reaction with KOCN using MgSO\(_4\) in water gave the required \((S)-3\). The reaction was completed within 4 hr and obtained \((S)-3\) in 70% yield. Compound \((S)-3\) was further treated with sodium benzoate in dimethylsulfoxide (DMSO) at 170°C to give benzoate ester \((S)-4\). Finally, the hydrolysis of benzoate ester and cyclic carbamate (2-oxazolidinone) groups in \((S)-4\) was achieved using aqueous basic conditions (LiOH, H\(_2\)O) at 80°C to give the targeted compound \((S)-1\)-HCl (Scheme I). The most important issue in Scheme I is that the specific optical rotation (SOR) value of \((S)-1\)-HCl does not match with the reported value (lit\textsuperscript{9}, \([\alpha]\textsuperscript{2}D = -23.3^\circ, c = 1, H_2O\)) indicating that the obtained \((S)-1\) is racemized to some extent.

Subsequently, efforts were focused to identify alternative synthetic strategies to make \((S)-1\). In Scheme I, initially the target was to build 1,2-aminoalcohol followed by introduction of C3-hydroxyl group. The viewpoint was altered to build

Figure 1

\[
\begin{align*}
\text{(S)-1} \\
\text{HO} & \text{OH} \\
& \text{NH}_2
\end{align*}
\]
2,3-diol initially followed by introduction of Cl-amino group. Accordingly, (R)-epichlorohydrin 2 on reaction with acetone catalyzed by boron trifluoride etherate at 40°C gave the corresponding chloro compound\textsuperscript{10}, (R)-5 which was further treated with sodium azide in \(N,N\)-dimethylformamide (DMF) at 110°C to give azide (S)-6 in good yield. The azide group in (S)-6 was reduced using Zn-NH\(_4\)Cl in EtOH-H\(_2\)O mixture to give the corresponding amine (S)-7. Deprotection of the 2,3-dimethyl acetal in (S)-7 was performed in acidic media (MeOH-HCl) to give the targeted (S)-1-HCl. However, it was not possible to obtain the (S)-1-HCl as a fine solid due to its low melting and hygroscopic nature.

The most important aspect is the specific optical rotation (SOR) value of (S)-1-HCl prepared using Scheme II matches with the reported value (lit. \([\alpha]\)\textsubscript{D} = -23.3°, c = 1, H\(_2\)O). (S)-1-HCl prepared using Scheme II was converted to its free-base by using basic resin amberlite IR-420. To establish the enantiomeric excess (ee) of (S)-1 (free base) by using chiral gas chromatography (GC), numerous experiments were performed with racemic 3-amino propane-1,2-diol which was prepared using Scheme II. However, it was not possible to resolve both the enantiomers by using chiral GC\textsuperscript{11}. Hence, efforts were extended to identify the enantiomeric excess of (S)-1 by converting it into the diastereomer. To achieve resolution, it was required to identify a suitable chiral acid to prepare the diastereomeric salt of (±)-1. (S)-Mandelic acid was found suitable for this purpose. The rationale behind selecting (S)-mandelic acid was to monitor the diastereomeric excess (de) of the obtained (2S)-2-hydroxy-N-((2S)-2,3-dihydroxypropyl)-2-phenylacetamide by the reaction of (S)-1 with (S)-mandelic acid using \(^1\)H NMR. However, it was not possible to identify both the diastereomers of (S,S)-8 and (S,R)-8 by \(^1\)H NMR. In contrast, it was possible to identify both the diastereomers of (S,S)-9 and (S,R)-9 by the reaction of racemic 7 with (S)-mandelic acid using \(^1\)H NMR. Accordingly, (2S)-2-hydroxy-\(N\)-((2S)-2,2-dimethyl-1,3-dioxolan-4-yl) methyl)-2-phenyl acetamide, (S,S)-9 was prepared by using (S)-7 with (S)-mandelic acid and no other diastereomer (S,R)-9 was found from the \(^1\)H NMR. The diastereomeric excess of (S,S)-9 indirectly confirms the enantiomeric excess of (S)-7 as well as (S)-1 (Scheme III).

**Experimental Section**

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR
spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One). \(^1\)H and \(^{13}\)C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-\(d_6\) and CDCl\(_3\) as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over anhydrous sodium sulfate after work-up. The dry reactions were carried out under dry nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column chromatography was carried out over silica gel (230-400 mesh) unless otherwise stated.

**Preparation of (S)-5-(chloromethyl)oxazolidin-2-one, 3.** To a stirred solution of (S)-(chloromethyl)oxirane (5.0 g, 0.054 mole) in water (50 mL), potassium cyanate (8.76 g, 0.108 mole) and magnesium sulfate (13.0 g, 0.108 mole) were added at 25°C. The reaction mass temperature was raised to 100°C and maintained at the same temperature for 5 hr. The reaction mass was then filtered and the filtrate was extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with saturated sodium chloride solution (25 mL), dried over anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure. The obtained solid was triturated with \(n\)-hexane and filtered to give (S)-3 as a white solid (5.3 g); yield 72%; m.p. 66-68°C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.5-3.8 (m, 4H), 4.8 (m, 1H), 5.8 (br s, 1H); \(^{13}\)C NMR (DMSO-\(d_6\)): \(\delta\) 42.5, 46.2, 73.9, 158.2; ESI-MS: \(m/z\) (\(M^+1\)) 135; IR (KBr): 3363, 1746 cm\(^{-1}\).

**Preparation of ((S)-2-oxooxazolidin-5-yl)methyl benzoate, 4.** To a stirred solution of (S)-3 (5.0 g, 0.036 mole) and DMSO (50 mL), sodium benzoate (10.6 g, 0.073 mole) was added at 25°C. The reaction mass temperature was raised to 170°C and maintained at the same temperature for 4 hr. The progress of reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was cooled to RT, diluted with water (75 mL) and extracted with ethyl acetate (2 × 50 mL). The combined organic layer was washed with saturated sodium carbonate solution (50 mL) and water (50 mL), dried over anhydrous sodium sulfate and the solvent was removed by evaporation under reduced pressure. The obtained crude compound was purified by column chromatography over silica gel eluting with ethyl acetate:hexane (4:1) to give (S)-4 as an off-white coloured solid (4.0 g); yield 50%; m.p. 90-92°C; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.5 (dd, \(J = 12.3\) Hz, 3.7 Hz, 1H), 3.8 (dd, \(J = 12.3\) Hz, 5.0 Hz, 1H), 4.5 (m, 2H), 5.0 (m, 1H), 6.0 (br s, 1H), 7.5 (m, 2H), 7.6 (m, 1H), 8.0 (d, 2H); ESI-MS: \(m/z\) (\(M^+1\)) 222; IR (KBr): 3347, 1757 cm\(^{-1}\).

**Preparation of (S)-3-aminopropane-1,2-diol hydrochloride, (S)-1·HCl.** To a stirred solution of LiOH (3.8 g) in H\(_2\)O (38 mL), (S)-4 (3.8 g, 0.017 mole) was added at 25°C. The reaction mixture was heated to 80°C and maintained at the same

![Scheme III](image-url)
temperature for 1 hr. The progress of reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was allowed to cool to RT, acidified using 1.0N HCl and extracted with ethyl acetate (2 × 20 mL) to remove by-products. The aqueous layer was completely distilled out to give (S)-1-HCl (traces of water was removed by azeotropic distillation with toluene) as an off-white coloured semi-solid (1.65 g); yield 75%; [α]D 25 = −5.0° (c = 1, H2O) (lit. [α]D 25 = −23.3°, c = 1, H2O).

Preparation of (R)-4-(chloromethyl)-2,2-dimethyl-1,3-dioxolane, 5. To a solution of (R)-epichlorohydrin 2 (50.0 g, 0.540 mol) and acetone (500 mL), BF3.OEt2 (0.5 mL) was added at 0°C (ice bath). After stirring for 1 hr, the reaction mixture was heated to 40°C and again stirred for 5 hr. Concentration under reduced pressure gave compound (R)-5 as a colourless oil (65.12 g); yield 80%; [α]D 25 = +35.9° (c = 5.3, Bz); 1H NMR (CDCl3): δ 1.37 (s, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 1.38-3.91 (m, 1H), 4.10-4.15 (m, 1H), 4.3-4.34 (m, 1H); 13C NMR (CDCl3): δ 25.1, 26.6, 44.3, 67.2, 75.2, 109.8; ESI-MS: m/z (M+1) 151.0; IR (neat): 2988, 1066, 845 cm−1.

Preparation of (S)-4-(azidomethyl)-2,2-dimethyl-1,3-dioxolane, 6. To a stirred solution of (R)-5 (50.0 g, 0.33 mole) in DMF (200 mL), sodium azide (86.66 g, 1.33 mole) and TBAB (0.5 g, 0.033 mole) were added at 25°C. The reaction mixture was stirred at 5°C for 1 hr. After completion of reaction, the reaction mixture was basified with NH4OH (50 mL) and extracted with ethyl acetate (3 × 60 mL). The combined organic layer was washed with water (200 mL), dried over anhydrous Na2SO4 and the solvent removed under reduced pressure at below 25°C (low boiling liquid) to give (S)-7 as a pale yellow coloured liquid (12.0 g; yield 72%; 1H NMR (CDCl3): δ 1.4 (s, 3H), 1.43 (s, 3H), 2.8 (m, 2H), 3.6 (m, 2H), 4.1 (m, 1H); ESI-MS: m/z (M+1) 132; IR (neat): 3364, 1026 cm−1.

Preparation of (S)-3-aminopropane-1,2-diol hydrochloride, (S)-1-HCl. A stirred solution of (S)-7 (10.0 g) in 10% HCl in methanol (50 mL) was stirred at RT for 1 hr. The progress of reaction was monitored by TLC. After complete consumption of starting material, the solvent was removed completely under reduced pressure to dryness and triturated with ethyl acetate to give (S)-1-HCl as an off-white coloured semi-solid (7.3 g); yield 75%; [α]D 25 = −23.8° (c = 1, H2O) (lit. [α]D 25 = −23.3°, c = 1, H2O); 1H NMR (CD2OD): δ 2.9 (m, 1H), 3.1 (m, 1H), 3.6 (m, 2H), 3.8 (m, 1H); 13C NMR (CD2OD): δ 43.5, 64.8, 69.1; ESI-MS: m/z (M+1) 92 (free base); IR (neat): 3372, 2987 cm−1.

Preparation of (2S)-2-hydroxy-N-((S)-2,3-dihydroxypropyl)-2-phenylacetamide, (S,S)-8. To a stirred solution of (S)-1 (hydrochloride salt was liberated using amberlite IR-400) (2.0 g, 0.022 mole) and THF (10 mL), HOBt (3.2 g, 0.024 mole), DCC (5.0 g, 0.024 mole) and (S)-mandelic acid (3.3 g, 0.022 mole) were added at RT. The reaction mixture was heated to reflux temperature and maintained at the same temperature for 4 hr. The progress of reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was filtered and the solvent completely removed from the filtrate under reduced pressure to dryness. The obtained crude compound was purified by column chromatography over silica gel to give (S,S)-8 as an off-white coloured semi-solid (2.1 g); yield 60%; 1H NMR (CD2OD): δ 3.3 (m, 2H), 3.4 (m, 2H), 3.7 (m, 1H), 5.0 (s, 1H), 7.3 (m, 3H), 7.4 (d, J = 14.1 Hz 2H); ESI-MS: m/z (M+1) 226; IR (neat): 3327, 1626 cm−1.

Preparation of (2S)-2-hydroxy-N-(((S)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2-phenyl acetate-
to a stirred solution of (S)-7 (1.5 g, 0.011 mole) and THF (8 mL), HOBt (1.7 g, 0.012 mole), DCC (2.6 g, 0.012 mole) and (S)-mandelic acid (1.74 g, 0.011 mole) were added at RT. The reaction mixture was heated to reflux temperature and maintained at the same temperature for 4 hr. The progress of reaction was monitored by TLC. After complete consumption of starting material, the reaction mixture was filtered and the solvent completely removed from the filtrate under reduced pressure to dryness. The obtained crude compound was purified by column chromatography over silica gel to give (S,S)-9 as an off-white coloured semi-solid (1.9 g); yield 62%; 1H NMR (CDCl3): δ 1.2 (s, 3H), 1.25 (s, 3H), 3.4 (m, J = 4.2 Hz, 5.4 Hz, 2H), 3.6 (dd, J = 6.3 Hz, 2.4 Hz, 1H), 4.0 (dd, J = 6.6 Hz, 1.8 Hz, 1H), 4.2 (m, 1H), 5.1 (s, 1H), 7.4 (m, 5H); ESI-MS: m/z (M+H) 264; IR (neat): 3399, 2986, 1658, 1055 cm−1.

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References