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An Expedient Approach to (2R,3S)-3-Azido-1,2-epoxy-4-phenyl butane : A key intermediate for HIV protease Inhibitors

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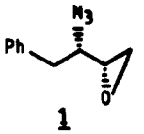
Abstract : A facile synthesis of the title product (**1**) starting from cis-butene-1,4-diol (**2**) has been described. The isomerised 3-butene-1,2-diol derivative **3** on Sharpless kinetic resolution with (+) DIPT as a chiral auxiliary provided the enantiomerically pure epoxyalcohol (**4**). Successive opening of the epoxide (**5**) with PhMgBr, replacement of OH group with azide and derivatisation of the oxirane ring provided the requisite product **1**.

The aquired immune deficiency syndrom (AIDS) has attained status symbol of a major health hazard. Our present understanding of the molecular events during HIV replication, have given us tremendous impetus to develop innovative strategies for combating the AIDS disease[1]. For example, compounds that can antagonise HIV proteases, responsible for the processing of gag and gag-pol polyprotein, have received significant attention as viable therapeutical alternatives[2]. In fact, synthesis of novel protease inhibitors formed the basic objective of many laboratories[3]. In conjunction with these studies, enantiomerically pure 3-azido-1,2-epoxy-4-phenylbutane derivatives, as versatile chiral building blocks, were reported[4]. We now describe starting from cis-butene-1,4-diol (**2**) a facile protocol to prepare the title product **1**.



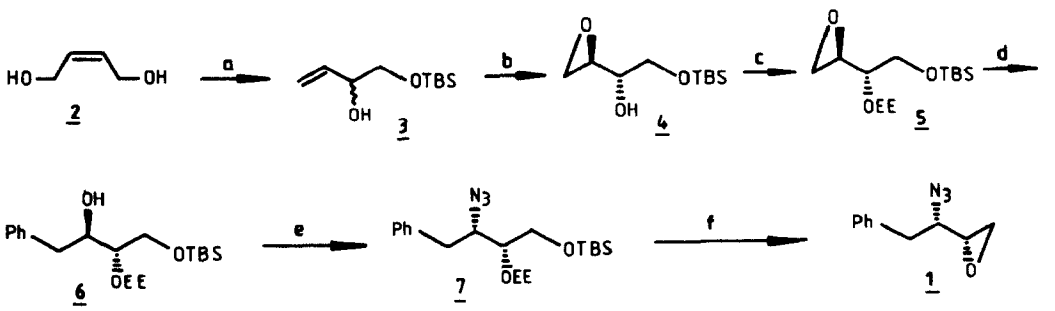
1

Isomerisation[5] of **2** in the presence of $HgSO_4$-H_2SO_4-H_2O followed by distillation with a long vigreux column provided 3-buten-1,2-diol (60%), the primary OH group of which was protected selectively by using 1.05 eq of tert.butyldimethylsilyl (TBS) chloride and imidazole to afford compound **3** in 91% yield. The Sharpless asymmetric epoxidation[6] of **3** under kinetic resolution conditions with (+) diisopropyltartrate (DIPT) as a chiral auxiliary provided **4** (60% theoretical yield) whose enantiomeric excess was determined by chemical transformations to the known and enantiomerically pure derivative **1**. At this stage the protection of free OH in **4** was carried out using ethyl vinyl ether and PPTS as a catalyst to afford **5**.

The ring opening reaction of **5** with 1M solution of phenylmagnesium bromide in tetrahydrofuran occurred smoothly at 0°C to give rise to **6** in 53% yield. The Mitsunobu reaction of **6** with HN_3-triphenylphosphine (TPP) diethylazidocarboxylate (DEAD) in THF at -78°C gave **7** (47%) along with 20% of the eliminated product . The ethoxyethyl and TBS ethers present

in **6** were deprotected by treatment with 1N HCl at room temperature to give the azidodiol derivative which was converted into the monotosylate derivative by employing 1.2 eq. tosyl-chloride in pyridine. Consequent reaction with sodium methoxide in chloroform at -20°C gave the target molecule **1** (52% overall yield) $[\alpha]_D$ + 20.9 ($CHCl_3$), lit.[4] $[\alpha]_D$ +20.1 ($CHCl_3$). The ^{1}H-NMR spectrum of **1** was identical with the reported data[4].

Scheme



Reagents : a) i) $HgSO_4$, H_2SO_4, H_2O, 80°C, 1.5 h; ii) TBDMSCl (1.05 eq.), imidazole (2.5 eq.), CH_2Cl_2, 0°C, 1.5 h, 91%; b) $Ti(iOPr)_4$ (1.0 eq.), (+)DIPT (1.2 eq.), TBHP (0.5 eq.), CH_2Cl_2, -20°C, 18 h; c) $EtOCH{=}CH_2$ (2.0 eq.), PPTS, CH_2Cl_2, 1.5 h, 94%; d) PhMgBr (2.0 eq.), THF, -20°C to RT, 12 h, 53%; e) Ph_3P (1.0 eq.), DEAD (1.1 eq.), HN_3 (2.0 eq.), THF, -78°C to RT, 12 h, 47%; f) i) 5% methanolic-HCl, RT, 0.5 hr, 97%; ii) Pyridine (1.5 eq.), pTsCl (1.2 eq.), RT, 12 h; iii) $NaOCH_3$, $CHCl_3$, -20°C, 1 h, 52%.

EXPERIMENTAL

General - Infrared spectra were recorded on a Shimatzu IR-470 spectrophotometer. ^{1}H NMR spectra were recorded on a Gemini Varian 200 MHz spectrometer with TMS as an internal standard. Specific rotations were measured on Jasco DIP 370 polarimeter. Solvents were distilled before use. Light petroleum refers to the fraction b.p. 60-80°. THF was dried and distilled from sodium benzophenone ketyl.

1-tert-Butyldimethylsilyl-3-butene-1,2-diol (3). A solution of 3-butene-1,2-diol[5] (**1**) (5.75 g, 65.3 mmol), tert.butyldimethylsilyl chloride (10.5 g, 69.7 mmol) imidazole (11.2 g) in CH_2Cl_2 (100 ml) was stirred at room temperature for 1.5 h. The reaction mixture was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel with light petroleum-ethyl acetate (95:5) as eluent to afford **3** (12.0 g, 91%) as an oil, ^{1}H-NMR ($CDCl_3$) data: δ 0.81 (s, 9H), 2.37 (d, 1H, J=3.3 Hz), 3.33 (dd, 1H, J=8.3, 9.6 Hz), 3.56 (dd, 1H, J=4.1, 9.6 Hz), 4.3 (m, 1H), 5.2-5.6 (m, 2H), 5.9 (m, 1H) Anal. Calcd for $C_{10}H_{22}O_3Si$: C, 59.4; H, 10.9. Found: C, 60.5; H, 10.0.

(2S,3R)-1-tert-Butyldimethylsilyl-3,4-epoxybutane-1,2-diol (4). To a stirred solution of titaniumtetraisopropoxide (5.6 g, 19.7 mmol) and (+)DIPT (5.6 g, 23.9 mmol) in CH_2Cl_2 at -20°C was added compound **3** (4.0 g, 19.8 mmol) followed by after 10 min. with tert.butylhydro-peroxide (2.73 ml, 3.62M in toluene). The resulting solution was stirred at -20°C for 18 h and then worked up by conventional procedure. The residue was purified by column chromatography

on silica gel by eluting with ethyl acetate-light petroleum (1:12) as eluent to afford **4** (1.3 g, 60%) as a syrup. $[\alpha]_D$ +13° (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) data : δ 0.82 (s, 9H), 2.36 (d, 1H, J=4.0 Hz), 2.76 (*m*, 2H), 3.00 (*m*, 1H), 3.52 (*m*, 1H), 3.74 (d, 2H, J=4.4 Hz); Anal Calcd for $C_{10}H_{22}O_3Si$: C, 55.0; H, 10.1. Found: C, 54.5; H, 10.0.

(2S,3R)-1-tert-Butyldimethylsilyl-2-(RS)ethoxyethyl-4-phenylbutane-1,2,3-diol (6). Compound **4** (1.2 g, 5.5 mmol) ethyl vinyl ether (1 ml) and PPTS (10 mg) in CH_2Cl_2 (10 ml) were stirred 1.5 h at room temperature. Triethylamine (0.1 ml) was added and the solution was concentrated. The residue was purified on silica gel column by eluting with ethyl acetate-light petorleum (1:9) to give **5** (1.5 g, 94%).

To the above product **5** (1.5 g, 5.2 mmol) in dry THF (5 ml) under nitrogen at -20°C was added 1M solution of PhMgBr in THF (10 ml). After 12 h the reaction was quenched with ammonium chloride solution and then extracted with ethyl acetate. The ethyl acetate layer was washed with water dried and concentrated. The residue was chromatographed on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **6** (1.0 g, 53%) as an oil, ^1H NMR ($CDCl_3$) data : δ 0.82 (s, 9H), 1.12 (2t, 3H, J=6.5 Hz), 1.26 (2d, 3H, J=6.0 Hz), 2.6-3.1 (m, 3H), 3.4-4.1 (m, 6H), 3.75 (m, 1H), 7.25 (m, 5H).

(2R,3S)-3-Azido-1-tert-butyldimethylsilyl-2(RS)-ethoxyethyl-4-phenylbutane-1,2-diol (7). To a solution of Ph_3P (0.37 g, 1.4 mmol) in dry THF at -78°C was added DEAD (0.24 ml, 1.5 mmol) and hydrazoic acid (10 ml, prepared from 5.2 g NaN_3 and 1.3 ml of H_2SO_4 in 20 ml benzene and 20 ml water) followed by **6** (0.4 g, 1.1 mmol) in THF. Then the reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue chromatographed on silica gel by eluting with ethyl acetate-light petroleum to afford **7** (0.2 g, 47%) as an oil; IR: 3440-3300, 2100 cm^{-1}; ^1H NMR ($CDCl_3$) data: δ 2.45 (bs), 2.93 (dd, 1H, J=8.5, 13.1 Hz), 3.08 (dd, 1H, J=6.3, 13.1 Hz), 3.5-3.8 (m, 4H) Anal. Calcd for $C_{20}H_{35}N_3O_3Si$: C, 61.1; H, 8.9. Found: C, 61.0; H, 8.8.

(2R,3S)-3-Azido-1,2-epoxy-4-phenylbutane (1). Compound **7** (0.8 g, 2.1 mmol) and 5% methanolic-HCl (0.5 ml) in MeOH (5 ml) were stirred at room temperature for 30 min., and neutralized with ammonium hydroxide solution. The reaction mixture was concentrated and chromatographed on silica gel to afford **7** (0.42 g, 97%) which was stirred with pyridine (2 ml) and $CHCl_3$ (20 ml) and cooled to 0°C. Freshly crystallized p-toluenesulphonyl chloride (0.46 g, 2.4 mmol) was added. After 12 h at room temperature, the reaction mixture was concentrated and codistilled with toluene to remove traces of pyridine. The residue was dissolved in $CHCl_3$ (10 ml) and $NaOCH_3$ (30 mg) was added at -20°C. After 1 h the reaction mixture was washed with water, dried and concentrated. The residue was purified by column chromatography on silica gel by eluting with ethyl acetate light petroleum to give **1** (0.2 g, 52%); $[\alpha]_D$ +20.9 (c 0.52, $CHCl_3$), lit $[\alpha]_D$ +20.1 ($CHCl_3$). IR: 3300-3400, 2100 cm^{-1}; ^1H NMR ($CDCl_3$) data: δ 2.55 (m, 1H), 2.76 (t, 1H, J=3.9 Hz), 3.94 (d, 2H, J=7.9 Hz), 4.08 (m, 1H), 4.37 (dd, J=5.2, 13.1 Hz), 7.3 (m, 5H).

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