A convenient synthesis of d-Sotalol

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Synthesis of d-Nifenalol and d-Sotalol has been achieved in high enantiomeric purity via Sharpless asymmetric dihydroxylation of 4-nitrostyrene followed by the regiospecific opening of chiral cyclic sulfate with isopropylamine.

Reentrant ventricular arrythmia is a major factor for most cases of sudden cardiac death.1 Class III antiarrhythmia compounds2 such as d-Sotalol [4'-[2-(isopropylamino)-1-hydroxyethyl]methanesulfonamide], 1a, effectively control such arrhythmia. This molecule exists in the zwitterionic form due to low pKa value (8.3) of the sulfonamide, thus diminishing the possibility of hydrogen bond donation. As a result of this ionisation, Sotalol is an extremely hydrophilic compound. It is the only commercially successful β-antagonist to emerge from the aryl ethanolamine series. There are a few reports on the synthesis of d-Sotalol involving resolution3, chiral homogeneous hydrogenation4, CBS reduction5 etc.

Another effective antiarrhythmic drug is Nifenalol 1b, which is less studied so far. There are two reports available for the synthesis of d-Nifenalol in the literature. While the first one deals with the synthesis of racemic Nifenalol 1b via ring opening of epoxide with primary amine,6 the other concerns with the resolution of racemic Nifenalol to get the optically pure compound.7 However, the existing synthetic routes suffer from limitations such as lower optical purity, use of resolving agents, use of toxic reagents, etc. Thus, it is essential to find a more convenient route for the synthesis of these important β-adrenergic blockers.

With the new synthetic developments of the enantiomerically enriched diols, their stereoselective transformations are of contemporary interest and are widely used for the total synthesis of a variety of naturally occurring and biologically active compounds. Herein, we report a new synthetic route for the synthesis of both d-Sotalol and d-Nifenalol using Sharpless asymmetric dihydroxylation as the key step followed by the regiospecific opening of the chiral cyclic sulfate with isopropylamine (Scheme I).

The present strategy for the synthesis of Nifenalol and Sotalol is depicted in the Scheme I. 4-Nitrostyrene 2, prepared by following the reported procedure8, was subjected to asymmetric
dihydroxylation using DHQ-PHAL as chiral ligand to furnish the chiral diol 3. The diol 3 was first transformed into cyclic sulfite using SOCl₂ in pyridine. The crude cyclic sulfite was subsequently oxidized with NaOCl in the presence of a catalytic amount of RuCl₂ to produce the cyclic sulfate 4. It was then refluxed with isopropyl amine in THF. After completion of reaction, the reaction mixture was first acidified with 20% sulfuric acid and then treated with 20% NaOH to get the required compound Nifenalol 1b in 61% yield. Interestingly, isopropylamine reacts with the cyclic sulfate at the less hindered terminal carbon selectively in a 2:2 pathway to furnish the chiral β-hydroxypropylamine 1b in good yield. The enantiomeric purity of Nifenalol 1b was determined by comparing the optical rotation of the same reported in the literature and found to be 96%.

Nifenalol 1b was further reduced with H₂/Pd-C in ethanol at 50 psi pressure to furnish the amino compound 5. The crude product was then treated with methanesulfonyl chloride to produce the final compound d-Sotalol 1a. The yield of this step is low (40%) and a mixture of products was formed due to simultaneous mesylation of hydroxyl group. However, d-Sotalol was easily separated by column chromatography. Optical purity of the final compound d-Sotalol was determined by comparing the optical rotation for the same reported in the literature and found to be 94%.

In conclusion, a simple method is developed for the synthesis of two antiarrythmia agents (d-Nifenalol and d-Sotalol) using Sharpless asymmetric dihydroxylation as the key step.

**Experimental Section**

All solvents were distilled before use. Compounds were purified by flash chromatography over silica gel. IR spectra were recorded on a Perkin-Elmer 137 E spectrometer. ¹H and ¹³C NMR spectra on 200 MHz and 300 MHz instruments using TMS as internal standard and the mass spectra (MS) on automated Finnigan MAT 1020C mass spectrometer using an ionization energy of 70 eV. The optical rotations were carried out on JASCO-181 digital polarimeter at 25°C using sodium D light. DHQ-PHAL ligand was procured from Aldrich chemicals, USA.

**Synthesis of 4-nitrobenzyl bromide.** The stirred solution of 4-nitrotoluene (10g, 73 mmoles), NBS (15g, 84 mmoles) in CCl₄ (300 mL) and benzoyl peroxide (1.8g, 7.4 mmoles) was heated under reflux for 5hr. The reaction mixture was filtered and washed with water, brine solution and dried over Na₂SO₄. Removal of solvent and column chromatography over silica gel (60-120 mesh) using pet. ether as eluent afforded 4-nitrobenzyl bromide, yield 13.9g (88%), mp 97-98°C [lit. mp 98-100°C]; IR (Nujol): 1600, 1460, 1360, 1230, 1100 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.5 (s, 2H), 7.55 (d, J=8 Hz, 2H), 8.2 (d, J=8 Hz, 2H).

**Preparation of 4-nitrobenzyltriphenylphosphonium bromide.** 4-Nitrobenzyl bromide (4g, 18.5 mmoles) and triphenyl phosphine (4.86g, 18.5 mmoles) were taken in 30 mL benzene and the mixture stirred at 50°C for 2 hr. White precipitate formed was filtered and dried to get the triphenyl phosphonium salt, yield 8.6 g (97%); mp 295-97°C.

**Preparation of 4-nitrostyrene.** 4-Nitrobenzylphosphonium bromide (8.5g, 17.8 mmoles) was added slowly to a stirred aqueous 20% K₂CO₃ (200 mL) solution and stirring was continued for 1hr. The purple coloured phosphorane precipitated was filtered off and washed with water to make it free from base. Phosphorane was then treated with 100 mL of 30% formalin solution till colour of phosphorane disappeared (15 minutes). The solution was extracted thrice with 30 mL portions of chloroform. Combined organic extract was washed with brine, dried over Na₂SO₄ and evaporated to get crude 4-nitrostyrene. The crude styrene was purified by passing through a column of alumina using pet. ether as eluent, yield 2.1g (79%); IR (Nujol): 2942, 1654, 1598, 1514, 1494, 1344, 1320, 1110 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz): δ 5.5 (d, J=10.8 Hz, 1H), 5.9 (d, J=16.7 Hz, 1H), 6.7-6.9 (dd, J=10.8 Hz and 6.7 Hz, 1H), 7.55 (d, J=8.1 Hz, 2H), 8.2 (d, J=8.1 Hz, 2H).

**Synthesis of 4-nitrobenzyl diol 3.** A 250 mL round bottom flask was charged with K₂Fe(CN)₆ (8.28g, 25 mmoles), K₂CO₃ (3.47g, 25 mmoles), (DHQ)₂PHAL (0.13g, 0.17 mmoles) and t-BuOH:H₂O (1:1) mixture (80 mL) and stirred for 5 minutes at room temperature. The flask was cooled to 0°C and a solution of OsO₄ (0.4 mL of 0.2 molar solution in toluene; 0.084 mmoles) was added, followed by 4-nitrostyrene (1.25g, 8.4 mmoles). The reaction mixture was stirred for 40 hr at room temperature. Ethyl acetate (50 mL) and sodium metabisulfite (1g) was then added to the mixture and stirred for 1hr. Organic layer was separated and aqueous layer extracted with EtOAc (3x20 mL). Combined organic layer was washed with brine, dried over sodium...
sulfate and evaporated to dryness. The crude product was purified by flash column chromatography using EtOAc : pet ether (1:1) to yield the diol 3 as a white solid, yield 1.26g (82%); mp 101.0-2°C; [α]D +25° (c 0.8, MeOH); IR (Nujol) 3500-3200, 2920, 1600, 1510, 1460, 1375, 1340, 1275, 1095 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz); δ 2.6(bs, 1H), 3.5(d, J = 5.4 Hz, 1H), 3.7(d, J = 5.4 Hz, 1H), 4.4(bs, 1H), 4.8(m, 1H), 7.5(d, J = 6.8 Hz, 2H), 8.8(d, J = 6.8 Hz, 2H); ¹³C NMR (Acetone-d₆, 50 MHz) δ 68.46, 74.65, 124.01, 128.38, 148.31, 151.52, (Found: C, 52.46; H, 4.92, N, 7.65 %).

**Synthesis of ethyl(4S)-4-(4-nitrophenoxy)-1,3,2-dioxathiolane-2,2-dioxide 4.** The diol 3 (0.7 g, 3.8 mmoles) was dissolved in dry pyridine (3 mL) and cooled to 0°C in an ice-bath under argon atmosphere. Freshly distilled thionyl chloride (0.47 g, 0.34 mL, 3.9 mmoles) was added dropwise and the reaction mixture was stirred for 3 hr. Ice cold water was then added to the reaction mixture and extracted with ether. The ethereal layer was washed with dil. HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was evaporated. Ethyl acetate was added to the crude product with 95% EtOAc and 0.59g of the crude product. 'HNMR (CDCl₃): 8 1.15(d, J = 7.7 Hz, 2H), 1.7(bs, 1H), 2.35(b, 1H), 2.95(bs, 1H), 3.65(dd, J = 7.7 Hz and 3.8 Hz, 1H), 3.85(dd, J = 7.7 Hz and 3.8Hz, 1H), 4.05(m, 1H), 4.95(dd, J = 5.8 Hz and 3.8 Hz, 1H, CH), 7.6(d, J = 7.7 Hz, 2H), 8.25(d, J = 7.7 Hz, 2H) (Found: C, 58.58, H, 7.06; N, 12.40. C₇H₆NO₃ requires C, 58.93, H, 7.14, N, 12.5%).

**Reduction of Nifenanol 1b to produce 1-(4-Aminophenyl)-2-isopropylaminoethanol 5.** A par bottle is charged with 150 mg of Nifenanol (150 mg, 0.67 mmoles), 10mg of 5% Pd/C and 10 mL of 95% ethanol. The mixture was stirred with H₂ under 50 psi for 2hr. The catalyst was filtered and solvent evaporated. Ethyl acetate was added to the crude product, dried over sodium sulfate and evaporated to dryness. Flash column of the crude product with EtOAc: pet ether (1:6) gave 4 as white solid, yield 0.59g (86%); mp 139°C; [α]D +51.5° (c 0.4, MeOH); IR (CHCl₃): 1600, 1530, 1355, 1310, 1230 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.55(t, J = 4.9 Hz, 1H), 5.05(dd, J = 6.4 Hz, 1H), 6.0(dd, J = 5.4 Hz, 1H), 7.65(d, J = 8.1 Hz, 2H, Ar-H), 8.35(d, J = 8.1 Hz, 2H, Ar-H); ¹³C NMR (50 MHz, CDCl₃): δ 73.82, 81.92, 124.54, 127.66, 139.72, 149.10; MS (m/z, % rel. intensity) 165(14), 153(27), 150(5), 135(24), 105(100), 77(50) (Found: C, 39.13, H, 2.96, N, 5.75, S, 13.11. C₆H₇NO₃S requires C, 39.18, H, 2.86, N, 5.71, S, 13.0%).

**Reaction of cyclic sulfate with isopropyl amine to produce Nifenanol 1b.** A 25 mL RB flask was charged with cyclic sulfate (300 mg, 1.2 mmoles) in dry THF (10 mL) and freshly distilled isopropyl amine in excess (6 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 10 hr (monitored by TLC). The solvent was evaporated under reduced pressure to get a thick red viscous residue. This residue was treated with 5 mL 20% H₂SO₄ and 10 mL ether for 12 hr. White precipitate was observed. The reaction mixture (as such) was further treated with 20% NaOH solution up to pH 10 and stirred for 0.5 hr. The white precipitate disappeared. There after reaction mixture was extracted with ether (3x20 mL) and then with ethyl acetate. The ether layer was discarded and ethyl acetate layer was washed with brine and dried over Na₂SO₄. Removal of ethyl acetate gave almost pure product, which was recrystallized to afford 168 mg of R-Nifenanol 1b, yield 0.168g (61%); mp 139°C; IR (Nujol): 3350, 3245, 2920, 1595, 1530, 1460, 1370, 1340, 1260 cm⁻¹; [α]D +41.5° (c 0.4, 1N HCl) (lit.8 +43° (c 2, H₂O) for Nifenalol hydrochloride); ¹H NMR (200 MHz, CDCl₃): δ 1.15(d, J = 7.7 Hz, 6H), 1.7(bs, 1H), 2.35(b, 1H), 2.95(bs, 1H), 3.65(dd, J = 7.7 Hz and 3.8 Hz, 1H), 3.85(dd, J = 7.7 Hz and 3.8 Hz, 1H), 4.05(m, 1H), 4.95(dd, J = 5.8 Hz and 3.8 Hz, 1H, CH), 7.6(d, J = 7.7 Hz, 2H), 8.25(d, J = 7.7 Hz, 2H) (Found: C, 58.58, H, 7.06; N, 12.40. C₇H₆NO₃ requires C, 58.93, H, 7.14, N, 12.5%).

**Reduction of Nifenalol 1b to produce d-Soitalol 1a.** 1-(4-Aminophenyl)-2-isopropylaminoethanol was dissolved in 3 mL of pyridine, cooled at -20°C (with iced-salt bath), treated dropwise with a solution of mesyl chloride (0.07g, 0.62 mmoles) in pyridine (2 mL) and stirred at the same temperature for 1hr. The ice-water was added and the mixture was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na₂SO₄ and flash column chromatography with EtOAc: pet ether (95:5) as eluent furnished d-Soitalol. The resulting product was treated with 1 equiv. of 5% HCl get d-Soitalol hydrochloride, yield (67 mg) 40%; mp 199-201°C.
(lit. mp, 204–05 °C); IR (CHCl₃): 3350, 3260, 2960, 2850, 1495, 1210, 1125, 1040 cm⁻¹; [α]₀ +34.6° (c 0.7, H₂O) [lit. +36° (H₂O)]; ¹HNMR (200 MHz, CDCl₃): δ 1.1(d, J=6.5 Hz, 6H), 1.9(bs, 1H), 2.3(bs), 3.65(m, 1H), 3.0(s, 3H), 3.8(m, 1H), 4.0(m, 1H), 4.95(m, 1H), 7.1(m, 4H); ¹³CNMR(50 MHz, CDCl₃): δ 24.84, 38.57, 63.93, 67.48, 74.48, 121.45, 129.70, 134.18, 134.85.

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