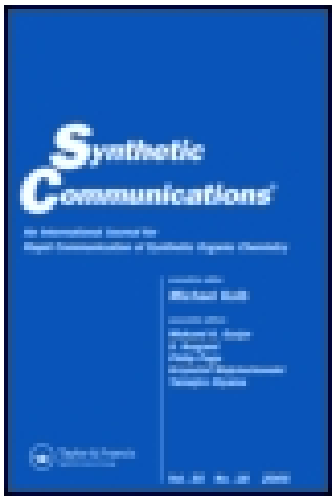

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An Enantioselective Synthesis of ((1R,2R)-Cyclohexane-1,2-diyl)bis(methylene)dimethanesulfonate, a Lurasidone Hydrochloride Intermediate

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An Enantioselective Synthesis of ((1*R*,2*R*)-Cyclohexane-1,2-diyl)bis(methylene)dimethanesulfonate, a Lurasidone Hydrochloride Intermediate

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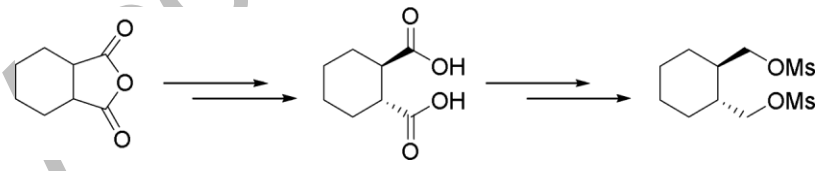
Abstract

A concise, economical and highly enantioselective synthesis of bis mesylate intermediate of Lurasidone HCl, an antipsychotic has been developed. The key steps involved in the synthesis are, thionyl chloride catalyzed esterification of tetrahydro phthalic anhydride in MeOH, epimerization of cis to trans isomer, hydrolysis of the di ester, resolution of the di acid, reduction with Red-Al and finally bis mesylation of the corresponding diol provided the desired intermediate ((1R,2R)-cyclohexane-1,2-diyl)bis(methylene) dimethanesulfonate in overall good yield.



KEYWORDS: Esterification, Epimerization, Hydrolysis, Resolution, Reduction and Bis-mesylation.

INTRODUCTION

Natural products often inspire synthetic organic chemists, because of their biological properties and complex structural design. Development of shorter routes to the known and bioactive natural products *via* newly established methodologies is of high demand in modern organic synthesis. Indeed, these strategies allow quicker and economical access to these compounds for medicinal and other uses. Chiral structures such as 1,2 substituted cyclo hexane subunits are an integral part of many biologically active compounds including alkaloids, pharmaceuticals and research probes. The development of synthetic routes to these structures is often challenging. Considerable efforts have been made in the recent past both in academia as well as industry for the development of small molecule based drug discovery program

Trans-1,2-substituted cyclohexane subunit gained the attention of synthetic organic chemists, as it is the key precursor for the synthesis of various pharmaceutically important drug substances. Lurasidone. HCl (**1**) used for the treatment of schizophrenia and bipolar disorder. The trans-((1*R*,2*R*)-cyclohexane-1,2-diyl)dimethanol (**2**) is the key intermediate used in the synthesis of Lurasidone. Lurasidone (1), an antipsychotic was developed by the Japanese firm Dainippon Sumitomo and approved by the U.S. FDA for the treatment of schizophrenia. The compound showed significant antagonist effects on D2, 5-HT2A, and 5-HT7 receptors which are linked to learning and cognition.[1] In contrast to available antipsychotics, lurasidone. HCl (1) lacks anticholinergic side effects, giving it an improved safety profile against existing treatments.[2]

Lurasidone HCl (1) chemically divided into three components: a piperazine benzothiazole, a [2.2.1]-bicycloheptane fused succinimide, and a C_2-symmetric *trans*-1,2 disubstituted cyclohexane (Fig.1). As per the literature reported methods, the large scale preparation of lurasidone involved an interesting ring-opening alkylation reaction of a spirocyclic quaternary ammonium derivative (**5**) . The synthesis commenced with the bis mesylation of commercially available dimethanol **2**, which proceeded in high yield to give dimethane sulfonate **3**.[3, 7] This bis-electrophile **3** underwent dialkylation with commercially available piperazine **4** under base catalyzed reaction conditions, giving to quaternary ammonium species **5** [4], isolated in 80% yield as the mono-mesylate salt. Thus the obtained compound **5** was immediately subjected to alkylative conditions with commercially available succinimide **6** to provide lurasidone in 94% yield from **5**, [5] and lurasidone hydrochloride (**1**) was achieved by subsequent salt formation using hydrochloric acid.[6] Therefore the key intermediate required for the syntheses of Lurasidone HCl (**1**) is *trans*-1,2-substituted cyclohexane subunit (**2**) and which is further mesylated to its dimethane sulfonate (**3**) derivative (Scheme 1).

RESULTS & DISCUSSION

We have been in the development of new strategies and methodologies for various natural products, API's and their key intermediates.[8-11] After the literature scouting for the synthesis of dimethanol (**2**), we have developed an efficient scalable process with the commercially available and economically benign raw materials. Based on the literature precedence following methods are utilized for the synthesis of **8**, the esterification has been carried out using catalytic amount of H_2SO_4[12] or trimethyl orthoformate and

alcohol. In general the meso bis ester (**8**) is subjected to epimerization followed by hydrolysis to provide the racemic diacid. Then the resolution[13] of racemic diacid using α-methyl benzyl amine provide the trans-diacid with high optical purity. Reduction of *trans*-diacid using DIBAL-H or $LiAlH_4$ provide the bis alcohol.[14] According to Jakovac and co-authors the meso alochol was converted to its corresponding chiral γ-lactone using horse liver alcohol dehydrogenase catalyzed oxidation conditions. Subsequently the lactone was converted to chiral acid alcohol derivative and finally reduction using LAH provided the bis alcohol **3**. [15]

Our synthesis of **3** began with thinoyl chloride catalyzed esterification of tetrahydro phthalic anhydride (**7**) in presence of MeOH. The obtained meso diester (**8**) was subjected to epimerization using catalytic NaOMe in MeOH as solvent to afford the *trans*- diester. The diester was subjected to *in-situ* hydrolysis using NaOH. This telescopic process helped us in improving the overall yield of **9** & **10** to 87%**,** over three steps and obtained the *trans*-diacid consisting of *R,S* and *R,R* isomers (9,10). The resolution of **9** & **10** was carried out as per the literature methods using a suitable isomer of α-methyl benzyl amine and obtained the desired *R,R* isomer of *trans*-diacid (**10**) was purified in MeOH and obtained 25% of yield. Subsequently the optically pure *trans*-diacid **10** with *R,R* configuration was reduced to *trans*-dimethanol under Red-Al reaction conditions using toluene as solvent. The dimethanol **2** was purified using DCM and *n*-hexane and obtained as an off-white color solid in 82% yield. The obtained *trans*-bis alcohol **2** was then converted to dimethane sulfonate **3** under the reported conditions using TEA and MsCl and obtained the product **3** in 92% yield and 99.4% *ee* (Scheme 2).

In Summary, we have established a simple, convenient and economically benign process for **3** and achieved overall good yield and high *ee*. Also developed the analytical methods for this non UV active intermediates using RI detector in both chemical and chiral methods.

EXPERIMENTAL

General methods: All reactions were carried out in oven dried glassware under an atmosphere of N_2. ^1H & ^{13}C NMR spectra were recorded in $CDCl_3$ & DMSO-d_6 on *Varian Gemini 400 MHz FT* spectrometers. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet). Coupling constants (*J*) are given in Hertz. Mass spectra were obtained on a HP-5989A Mass Spectrometer. Thin layer chromatography was performed on silica gel plates (SRL 230-400 mesh). All solvents used are commercially available and were distilled before use.

Synthesis Of (1*R*,2*R*)-Cyclohexane-1,2-Dicarboxylic Acid And (1*R*,2*S*)-Cyclohexane-1,2-Dicarboxylic Acid (9 & 10)

$SOCl_2$ (15.45 g, 129.8 mmol) was added to a mixture of *cis*-1, 2-cyclohexanedicarboxylic anhydride (200 g, 1298 mmol) and methanol (1400 mL) at 20 °C. The reaction mass was refluxed for 3 - 4 h. Methanol was concentrated completely and residue was diluted with MTBE 1000 mL and sodium bicarbonate solution was added to it. Organic layer was separated and was washed with water and brine solution.

Organic layer was distilled completely to furnish **8**. The residue was dissolved in fresh methanol (1040 mL) and added sodium methoxide (28 g, 519.4 mmol). The reaction mass was refluxed for 4 h and methanol was distilled completely under reduced pressure. To the residue 13% aq. NaOH solution (2000 mL) was added. Reaction mass was maintained for 3 - 4 h at 75 °C and cooled the reaction mass to 0-5 °C. The reaction mass pH was adjusted to 2.0 at 0 - 5 °C with concentrated HCl (900 mL). The obtained solid was filtered and wet cake was washed with excess water (1500 mL) and dried under reduced pressure to give a white solid. Yield: 87%. HRMS (ESI TOFMS): calcd. for $C_8H_{12}O_4Na$, 173.0814; found, 173.0821; HPLC Conditions: Chemical: Column: Zorbax SB CN (150 * 4.6 mm) * (3.5µ), Mobile phase: A: 0.1% H_3PO_4 in H_2O, M.P. B: ACN, Purity by HPLC (Area under curve): 94.3% (*trans*) retention time: 6.98 and 2.1% (*cis*) retention time: 7.579; Chiral: Column: Chiral PAK IC (250 x 4.6 mm) 5.0 µm, Mobile phase: *n*-Hexane: IPA : TFA (950 : 50l : 1), Diluent : Methanol :mp (1:1), Flow rate: 1.0mL/min, Column temp: 25°C, Inj. vol: 10 µl. Wave length: 210 nm. Purity by HPLC (area under curve) 40.35% (*R*,*S* Isomer) retention time 16.065 and 56.18% (*R*,*S* Isomer) retention time 20.269.

Synthesis Of (1*R*,2*R*)-Cyclohexane-1,2-Dicarboxylic Acid (10)

R-(+)-Phenyl ethyl amine (**11**) (35.25 g, mL 290.69 mmol) was added to a solution of *trans* racemic mixture of trans diacid (**9** & **10**) (50.0 g, 290.69 mmol) in methanol (150.0 mL) at 0 °C. Mixture was stirred about 30 mins. and then stirred for 3 h at 25 – 35 °C. Reaction mixture was cooled to -5 to 0 °C and stirred for 1 h then filtered. Dried the solid under suction and obtained 30 g of wet compound. The wet compound and MeOH (90.0

mL) charged in RBF and heated to 65 °C. Maintained under stirring at same temperature for 2h and mixture was cooled to -5 °C then it was stirred for 2h and filtered. The obtained compound was suspended in 1N HCl (345 mL) and extracted with ethyl acetate (2X 230 mL). Organic layer was separated and concentrated to dryness under reduced pressure to obtain white color solid. Yield: 25%. ^{1}H-NMR (DMSO d_6, 400MHz): δ 12.06 (s, 1H), 2.35 (s, 1H), 1.92 (s, 1H), 1.69 (s, 1H), 1.23 (s, 2H). ^{13}C-NMR (DMSO d_6, 400MHz): 175.1, 41.8, 26.1, 23.6. HRMS (ESI TOFMS): calcd. for $C_8H_{12}O_4Na$, 173.0814; found, 173.0821. HPLC Conditions: Chemical: Column: Zorbax XDB C8 (250* 4.6 mm)* (3.5µ), Column Temp. 40 °C, RID,: Sensitivity: 65, RID temp.: 35 °C, Run time 40 Min, Flow : 0.8 mL/min. Purity by HPLC (AUC): 99.83% retention time 4.831. Chiral: Column: Chiral PAK IC (250 x 4.6 mm) 5.0 µm, Mobile phase: *n*-Hexane : IPA : TFA (950 : 50l : 1), Diluent : Methanol :mp (1:1), Flow rate: 1.0mL/min, Column temp: 25 °C, Inj. vol: 10 µl. Wave length: 210 nm. Purity by HPLC (area under curve) 100% (*R*,*R* Isomer) retention time 9.331.

Synthesis Of ((1*R*,2*R*)-Cyclohexane-1,2-Diyl)Dimethanol (2)

Red-Al (70% solution in Toluene) (134 g, 460 mmol) was added to solution of **10** (16 g, 93 mmol) in THF (160 mL) at 0-5 °C under nitrogen atmosphere. Reaction mixture was refluxed for 5 h and mixture was cooled to 0 – 5 °C and then added 20% aq. NaOH solution (320 mL). Reaction temperature was allowed to room temperature and stirred for 1h. It was extracted with toluene and organic layer was concentrated to dryness under reduced pressure and residue was cooled to 0 – 5 °C. DCM (2.4 mL) and *n*-hexane (40 mL) were added to the residue and stirred at 0-5 °C for 30 minutes and filtered to obtain

off-white color solid. Yield: 85.2%. ^{1}H-NMR (DMSO d_6, 400MHz): δ 4.37 (t, J = 4.8Hz, 1H), 3.49-3.33 (m, 1H), 3.31-3.26 (m, 1H), 1.71-1.63 (m, 2H), 1.21-1.11 (m, 2H), 1.04 (t, J = 11.2Hz, 1H). ^{13}C-NMR (DMSO d_6, 400MHz): 64.5, 42.1, 29.6, 26.0. HRMS (ESI TOFMS): calcd. for $C_8H_{16}O_2Na$, 145.1229; found, 145.1226. HPLC conditions: Column: Column: Zorbax XDB-C8 (250*4) mm, 3.5µm, Column temp: 40 °C, RID: Sensitivity: 65, RID temp.: 35 °C, Run time: 40 min, Flow: 0.8 ml/min. Purity by HPLC (AUC): 99.28% retention time 5.182.

Synthesis Of ((1*R*,2*R*)-Cyclohexane-1,2-Diyl)Bis(Methylene) Dimethanesulfonate (3)

Methane sulfonyl chloride (12 mL, 150 mmol) was added to a mixture of **2** (10 g, 69 mmol) in DCM (100 mL) and TEA (25.0 mL, 170 mmol) at 0 – 5 °C. It was then allowed to room temperature. Reaction mixture was stirred for 2 h and diluted with DCM (50 mL). Compound was extracted into DCM and washed with water and dried over anhyd. Na_2SO_4. DCM layer was distilled under reduced pressure and the obtained crude compound was further purified using *n*-hexane (100 mL). Yield: 92%, $[\alpha]_D^{20}$ = -27.5° (C=4%, Benzene at 20 °C); lit. $[\alpha]_D^{24.5}$ = -29.2° (C=4%, Benzene at 20 °C).[16] ^{1}H-NMR ($CDCl_3$, 400MHz): δ 4.35 (d, J = 10Hz, 1H), 4.18 (d, J = 10Hz, 1H), 3.03 (s, 3H), 1.82-1.78 (m, 2H), 1.71 (m, 1H), 1.29-1.27 (m, 2H). ^{13}C-NMR (DMSO d_6, 400 MHz): 72.1, 37.0, 36.3, 28.3, 24.7. HRMS (ESI TOFMS): calcd. for $C_{10}H_{20}O_6S_2Na$ 301.0780; found, 301.0778. HPLC conditions: Chemical: Column: Zorbax XDB-C8 (250*4) mm, 3.5µm, Column temp: 40 °C, RID: Sensitivity: 65, RID temp: 35 °C, Run time: 40 min, Flow: 0.8 ml/min. HPLC (AUC): 99.10% retention time 18.041, Chiral: Column: Chiral PAK IC (250 x 4.6 mm) 5.0 µm. Mobile phase: *n*-Hexane : IPA : EtOH : DEA (650 : 200 : 150

: 5), Column temp : 27°C, Flow: 1.0 ml/min, Inj. 10 µl. Purity by HPLC: 99.71 (*R*,*R* Isomer) retention time 24.566 and 0.28% (*R*,*S* isomer) retention time 23.005; Enantiomeric excess (*ee*): 99.43%.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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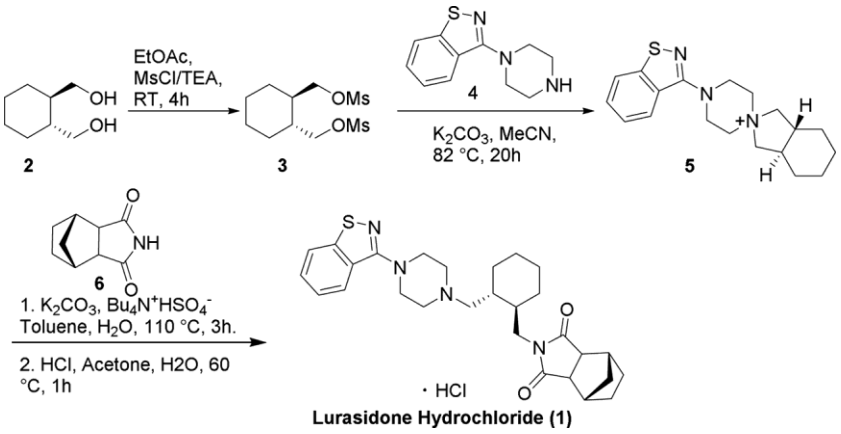
Scheme 1. Synthetic scheme for Lurasidone HCl (1).



Scheme 2. Synthetic scheme of Bis mesylate (3)

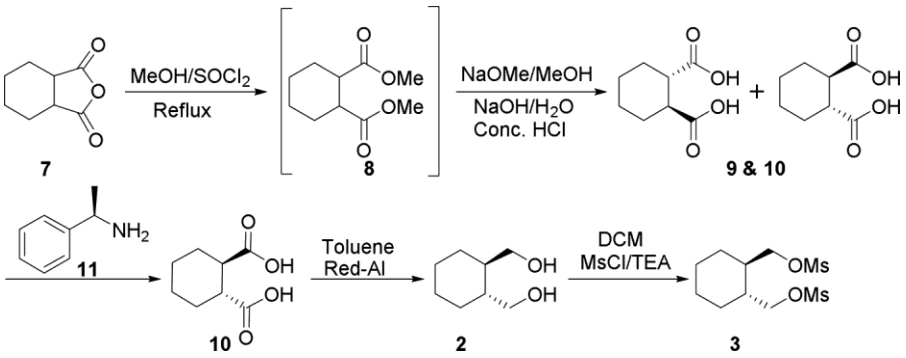
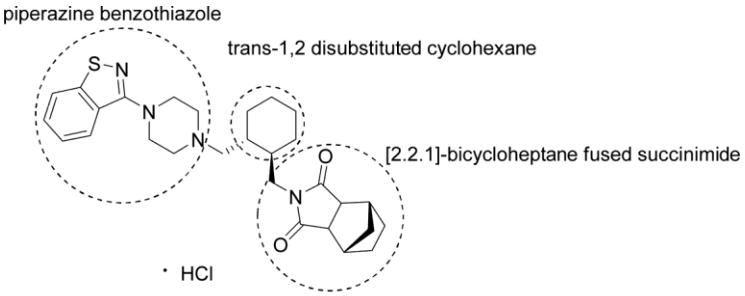


Figure 1



Lurasidone Hydrochloride (1)