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Diastereoselective reduction of chiral N-*tert*-butanesulfinimines for the synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b] thiopyran-4-amine 7,7-dioxide : An important intermediate for dorzolamide

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ABSTRACT

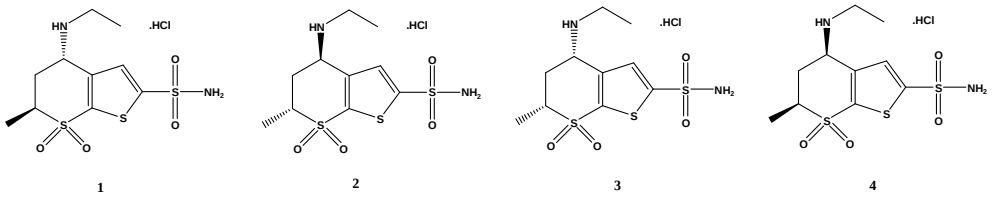
A new asymmetric synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide ***(9a)*** *and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine* ***(19a),*** *an important intermediate for the preparation of Dorzolamide* ***(1)*** *by diasteroselective reduction of chiral (R)-N-tert-butanesulfinimines* ***(7&17)***

Keywords: R(+)-*tert*-butanesulfinamide, S(-)-*tert*-butanesulfinamide, Borane, Sodium borohydride, Titanium tetraethoxide.

INTRODUCTION

Dorzolamide Hydrochloride [1] is known chemically as (4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide **(1)** used for antiglaucoma agent**.** Glaucoma is the pressure within eye can lead to damage to the optic nerve at the back of eye. If untreated, glaucoma may eventually leads to the blindness. People with ocular hypertension have an increased risk glaucoma. Dorzolamide works by blocking the action of an enzyme carbonic anhydrase. Blocking this enzyme reduces the amount of fluid that make in the front part of eye, and this helps to lower the pressure within the eye [2-9].

Dorzolamide contains two chiral centre with four diastereoisomeric forms. The trans- diastereomers having the configuration 4S,6S **(1)** and 4R,6R **(2)**, cis-diastereomers having the configuration 4S,6R **(3)** and 4R,6S **(4)** as given in the Figure **1**.

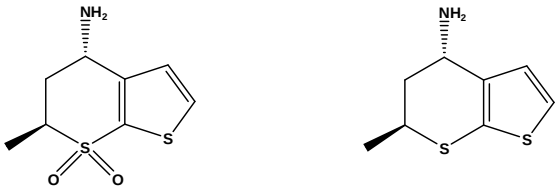


1 2 3 4

Figure-1

The diastereomer Trans-(4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thio pyran-2-sulfonamide 7,7-dioxide **(1)** is marketed as Dorzolamide drug and the remaining three diastereomers **(2,3&4)** is unwanted and needs to be eliminated from the mixture of four isomers.

The (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide **(9a)** and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine **(19a)** is a critical intermedi-ate for the synthesis of Dorzolamide **(1). (Figure-2).**



9a **19a**

Figure-2

Though there are several method have been reported for the preparation of Dorzolamide and its intermediates using classical resolution methods [10-15], enzymatic process [16-18] and asymmetric synthesis [19-27]. No reported process for the preparation of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide **(9a)** and (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine **(19a)** using (R)-N-*tert*-butanesulfinimines **(7&17)** as chiral amine source.

In recent year the asymmetric synthesis of chiral amines using chiral N-*tert*-butanesulfinimines plays a vital role in the synthetic organic chemistry. Ellman's group has prepared many chiral amines using chiral N-*tert*-butanesulfinamide chemistry [28].

As part of our exploratory studies on the synthesis of chiral amines using chiral N-*tert*-butanesulfinimines chemistry [29-30], we prepared successfully the both important new intermediates 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine 7,7-dioxide **(9a)** and 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine **(19a)** through chiral (R)-N-*tert*-butane sulfinimines **(7&17)**. We have also undertaken to study the effect of different reducing agent on both chiral (R)&(S)-N-*tert*-butanesulfinimines **(7&12)** derivatives to understand the effectiveness of our hypothesis. To our surprise we found that the Borane and DIBAL-H is more selective diasteroselective reducing agent for the preparation of chiral amines **(9a&19a)**. We present here the investigation of different reducing agent for diastereoselective reduction on both (R)&(S)-N-*tert*-butanesulfinimines **(7&12)** and its results.

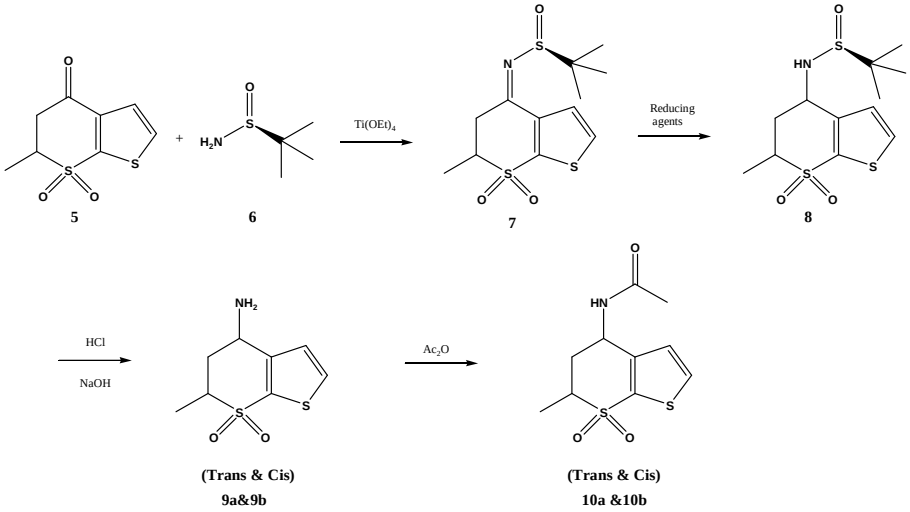
RESULTS AND DISCUSSION

We started our synthesis from known intermediate 5,6-dihydro-4H-6-methylthieno[2,3-b]thiopyran-4-one-7,7-dioxide **(5)** [31]. Condensation of Ketone **(5)** with R(+)-*tert*-butane sulfinamide **(6)** in the presence of using titanium tetraethoxide as water scaventure in 1,4-Dioxane solvent at reflux temperature gave 70% yield of (R)-N-*tert*-butanesulfinimine **(7)**.

The use of Sodium borohydride as reducing agent for the reduction of (R)-N-*tert*- butanesulfinimine **(7)** in alcoholic solvent gave the sulfinylamine **(8)**. Sulfinylamine **(8)** was hydrolysed with hydrochloric acid gave the hitherto unknown intermediate 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide **(9)**. On acetylation of amine **(9)** with acetic anhydride in the presence of triethylamine in dichloromethane solvent gave 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide **(10).** To our surprise we found that, the product 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide **(10)** obtained from the sodium borohydride reduction gave only the unwanted cis-isomer (**10b)**, which was confirmed by NMR and HPLC**.**

By encouraging above results, we have extended our investigation to understand further using different reducing agent for the reduction of (R)-N-*tert*-butanesulfinimine **(7)**. When we used the borane and DIBAL-H as reducing agent gave predominately of required trans-isomer of **10a** and was confirmed by NMR and HPLC**.** Exclusively the cis-isomer of **10b** was formed by using Sodium borohydride+L-tartaric acid, Sodium borohydride+L-proline and

Sodiumtriacetoxyboro- hydride as reducing agent. These reactions are summarized in the **Scheme 1** and results are tabulated in **Table 1.**



Scheme 1

Table 1. Diastereoselective reduction on (R)-N-*tert*-butanesulfinimine (7) and its data

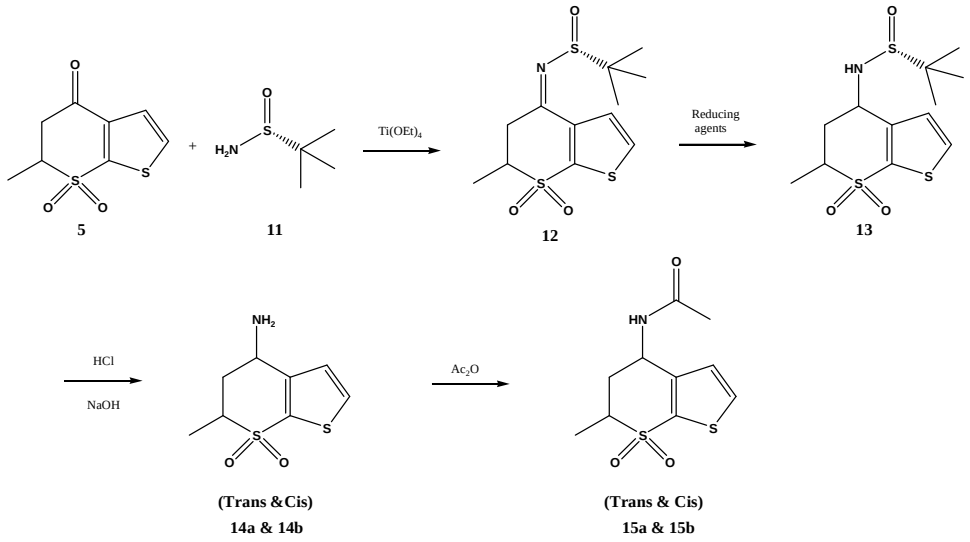
No.	Reducing Agents	HPLC (%)	
		Trans (10a)	Cis (10b)
1	Borane	70.44	29.30
2	DIBAL-H	74.00	25.74
4	$NaBH_4$	-	99.94
5	$NaBH_4$ – L(+)Tartaric acid	-	99.03
6	$NaBH_4$ – L(+)Proline	-	99.83
7	Sodiumtriacetoxyborohydride	-	98.85
8	Sodium cyanoborohydride	NR	NR
9	Raney Nickel	NR	NR
10	Palladium on carbon	NR	NR
11	Rhodium on carbon	NR	NR

** NR – No reaction*

Similarly we have studied the diastereoselective reduction of opposite isomer (S)-N-*tert*-butanesulfinimine **(12),** prepared from Ketone **(5)** and S(-)-*tert*-butanesulfinamide **(11).** Using borane as reducing agent gave the mixture of trans & cis-isomers of **15 (15a&15b)**, and sodium borohydride gave only cis-isomer of **15b**. These reactions are summarized in the **Scheme 2** and these results are tabulated in **Table 2.**

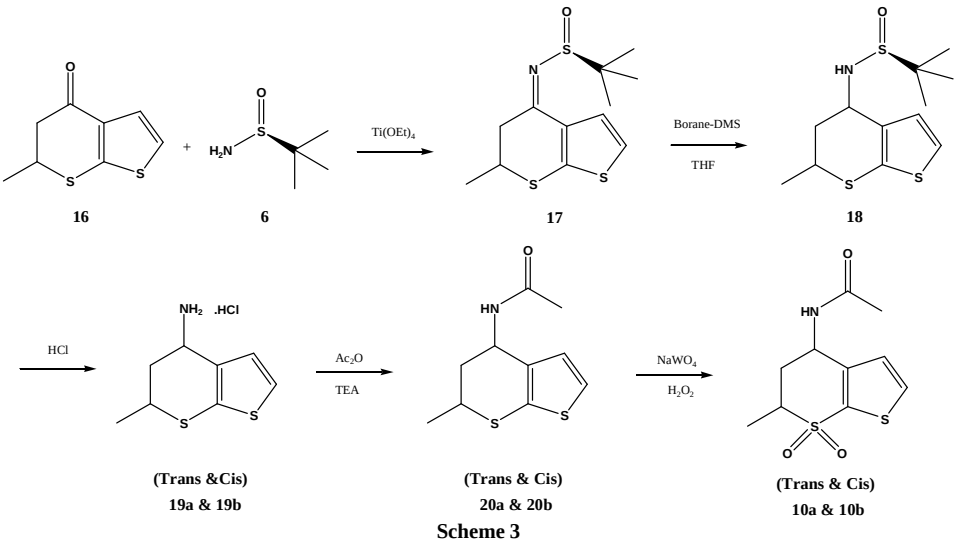
Table 2. Diastereoselective reduction on (S)-N-*tert*-butanesulfinimine (11) and its data

No.	Reducing Agents	HPLC (%)	
		Trans - 15a	Cis – 15b
1	Borane	70.95	28.80
2	$NaBH_4$	-	99.93



Scheme 2

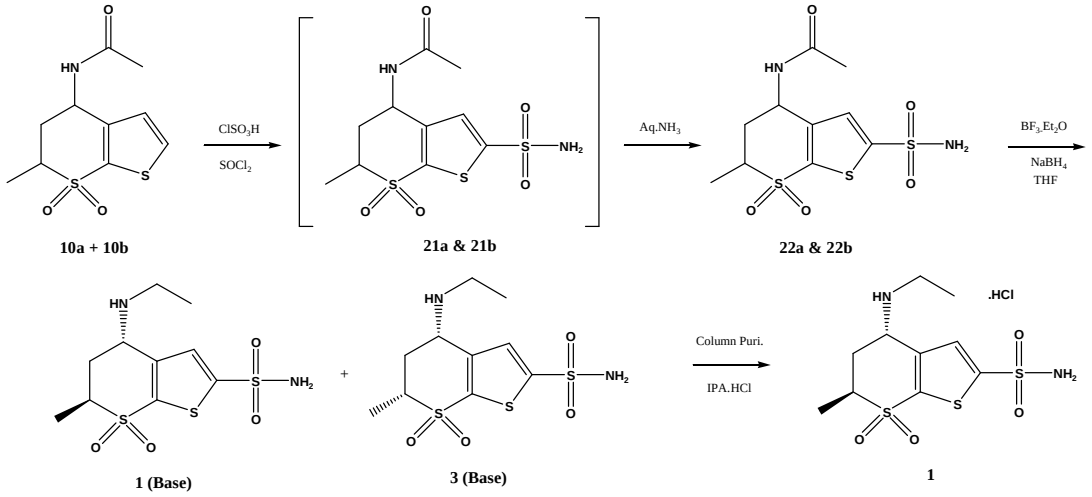
Further we have also extended for studies on the synthesis of (4S,6S)-5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine **(19a)** by applying the same strategy of synthetic protocol to understand its effectiveness. The 5,6-dihydro-4H-6-methylthieno[2,3-b]thiopyran-4-one **(16)** [31] was condensed with R(+)-*tert*-butanesulfinamide **(6)** in the presence of using titanium tetraethoxide in 1,4-Dioxane solvent gave chiral (R)-N-*tert*-butanesulfinimine (**17**). Reduction of sulfinimines **(17)** with borane in THF solvent gave sulfinylamine **(18)**. Sulfinylamine **(18)** was hydrolysed with IPA-HCl gave the chiral amine intermediate 5,6-dihydro-6-methyl-4H-thieno-[2,3-b]thiopyran-4-amine hydrochloride (**19a&19b**). The acylation of **19** in the presence of acetic anhydride and triethylamine gave the mixture of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran **(20a&20b).** Oxidation of **20** using hydrogen peroxide in the presence of sodium tungstate gave 70% of trans-5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide **(10a)** and 30% of cis-5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide **(10b).** These reactions are summarized in the **Scheme 3.**



Scheme 3

Further the veracity and the usefulness of the compound **10** prepared from this method by converting in to final drug Dorzolamide **(1)** by the known method. The compound **10** obtained from (R)-N-*tert*-butanesulfinimines **7&17** gave the predominately the drug Dorzolamide **(1)** along with minor other isomers was removed by column purification.

The prepared Dorzolamide **(1)** was confirmed by comparing with the compound prepared from the reported method and by spectral data. These reactions are summarized in the **Scheme 4.**



Scheme 4

Amide **15** obtained from (S)-N-*tert*-butanesulfinimine **(12)** gave the exclusively trans-isomer 4R,6R (**2**) and cis-isomer 4R,6S (**4**). These results are tabulated in **Table 3.**

Table 3. Diastereoselective reduction on N-*tert*-butanesulfinimines (7,12&17) and its data

No.	Sulfinimine	Reducing Agents	Chiral HPLC (%)			
			Trans-4S,6S (1)	Trans-4R,6R (2)	Cis-4S,6R (3)	Cis-4R,6S (4)
1	7	Borane	63.64	0.07	33.29	3.00
2	7	DIBAL-H	61.11	0.08	35.69	3.12
3	7	$NaBH_4$	1.44	0.66	72.62	25.28
4	7	$NaBH_4$ – L(+)Tartaric acid	0.23	0.20	62.96	36.61
5	7	$NaBH_4$ – L(+)Proline	0.68	-	74.14	25.16
6	7	Sodiumtriacetoxyborohydride	1.19	-	67.59	31.12
7	12	Borane	-	61.90	9.51	28.59
8	12	$NaBH_4$	0.03	0.45	27.77	71.75
9	17	Borane	65.27	0.05	30.15	4.53

MATERIALS AND METHODS

Melting points were taken on a Branstead Melting point apparatus (Model - 9300) in open capillary tubes and are uncorrected. IR spectrum were recorded as Neat or KBr using Perkin-Elmer 2000 FT TR spectrometer. Both ^{1}H-NMR(400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a Bruker NMR spectrometer instrument. All mass spectra were recorded using electrospray ionization (ESI) technique on an API 2000, ABS triple quadrupole instrument. Chiral HPLC was done using Chiral AD-H 250 x 4.6mm,(SRC-906) column using n-hexane:Ethanol: Diethylamine(80:20:0.1) and Flow 0.5ml/min. at 254nm. Column chromatography was performed over silica gel (BDH 100-200 mesh) and TLC with silica gel GF 254. All reagents and solvents employed were of commercial grade and were used as such, unless otherwise specified.

I. General procedure for making N-*tert*-butanesulfinimines

Titanium tetraethoxide (2.0eq.) was added to a stirred solution of Ketone (**5/16**) and N-*tert*-butanesulfinamide (**6/11**) (1.1eq.) in 1,4-Dioxane at room temperature. The mixture was refluxed until completion (5-10 hr.), the reaction mass was cooled and saturated sodium chloride solution was added. The reaction mass was filtered through celite and the aqueous layer was extracted with ethyl acetate. The organic layer was concentrated and purified through column chromatography.

R_S-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methyl-7,7-dioxo-thieno[2,3-b] thiopyran-4-ylidene)-amide (7)

Prepared from the Ketone **(5)** and R(+)-*tert*-butanesulfinamide **(6)**. Yield : 70.1%; ^{1}H-NMR ($CDCl_3$): δ 7.55-7.56(dd,1H,J=2.81,4.97Hz), 7.42-7.45(t,1H,J=5.5Hz), 3.32-4.26 (m,3H), 1.49-1.50(d,3H,J=6.77Hz), 1.29(s,9H); ^{13}C-NMR (DMSO-d_6)(Cis&Trans): δ 164.44, 163.78, 141.90, 141.64, 141.23, 130.23, 130.17, 125.85, 59.40, 58.93, 56.69, 56.65, 36.32, 35.75, 22.79(3C), 22.65(3C), 11.44, 11.38; IR (KBr,cm^{-1}) : 2964, 2926, 1583, 1409, 1310, 1264, 1146, 1071, 765, 725; MS (m/z) = 320.3$[M+1]^+$; SOR : -60.2° (c=1in Methanol at 25°C)

S_S-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methyl-7,7-dioxo-thieno[2,3-b] thiopyran-4-ylidene)-amide (12)

Prepared from the Ketone **(5)** and S(-)-*tert*-butanesulfinamide **(11)**. Yield : 65.7% ; ^{1}H-NMR ($CDCl_3$): δ 7.53-7.55(dd,1H,J=2.90,5.05Hz), 7.41-7.43(t,1H,J=5.37Hz), 3.34-4.25 (m,3H), 1.47-1.49(d,3H,J=6.60Hz), 1.28(s,9H); ^{13}C-NMR (DMSO-d_6)(Cis&Trans): δ 164.39, 163.77, 141.86, 141.62, 141.22, 130.25, 130.19, 128.95, 59.37, 58.92, 56.67, 56.64, 36.31, 35.74, 22.78(3C), 22.64(3C), 11.44, 11.37; IR (KBrt,cm^{-1}) : 2967, 2930, 1583, 1409, 1310, 1264, 1146, 1071, 767, 723; MS (m/z) = 320.3$[M+1]^+$; SOR : +61.4° (c=1in Methanol at 25°C)

R_S-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methylthieno[2,3-b]thiopyran-4-ylidene]-amide (17)

Prepared from the Ketone **(16)** and R(+)-*tert*-butanesulfinamide **(6)**. Yield :68.5% ; ^{1}H-NMR ($CDCl_3$): δ 7.45-7.50(dd,1H,J=5.40,11.00Hz), 7.00-7.01(t,1H,J=5.52Hz), 3.60-3.87(m,2H), 2.78-3.12 (m,1H), 1.44-1.47(d,3H), 1.28(s,9H); ^{13}C-NMR (DMSO-d_6)(Cis&Trans): δ 169.04, 168.92, 145.0, 144.79, 133.52, 133.45, 126.11, 126.06, 121.74, 121.70, 57.43, 57.25, 39.52. 39.29. 38.97. 38.66. 22.41(3C), 22.30(3C), 19.88, 19.82; IR (Neat,cm^{-1}) : 2962, 2926, 1736, 1570, 1506, 1453, 1422, 1388, 1268, 1180, 1070, 902, 750, 651; MS (m/z) = 288.2$[M+1]^+$; SOR : -75.1° (c=1in Methanol at 25°C)

II. Procedure for making 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10&15)) from N-*tert*-butanesulfinimines (7&12)

Preparation of R_S-2-Methylpropane-2-sulfinic acid (5,6-dihydro-6-methyl-7,7-dioxo-thieno[2,3-b] thiopyran-4-yl)-amide (8)

The Borane-DMS complex solution 2M in THF (0.1252moles) was added slowly to a stirred solution of N-*tert*-butylsulfinylimine **(7/12)** (20 gm, 0.0626 moles) in 200ml of THF at room temperature. The mixture was stirred for 18 hr. at room temperature. Quenched the reaction by adding water and extracted in Dichloromethane. The organic extracts washed with brine solution and concentrated. Purified through column chromatography to get 14.5 gm of Sulfinamide **(8/13).**

Yield : 72.04%; IR (KBr,cm^{-1}) : 3345, 3249, 2977, 1421, 1404, 1306, 1271, 1140, 1055, 1039, 752, 682, 610; MS (m/z) = 322.2$[M+1]^+$; SOR : +8.53° (c=1in Chloroform at 25°C)

Preparation of 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (9)

The Sulfinamide **(8)** (14.0gm) is treated with 70.0 ml of IPA-HCl solution (~14%) and stirred for 5.0hr. at room temperature. After completion of reaction, the mass was concentrated, basified the sodium hydroxide solution and extracted in Ethyl acetate. Concentrated the organic layer to get 9.4 gm of amine **(9a&9b)**. Isolated as free base. Yield : 85.0 % ; IR (Neat,cm^{-1}) : 3371, 2932, 1293, 1267, 1140, 1040, 913, 881, 757, 685, 671; MS (m/z) = 218.1$[M+H]^+$.

Trans-9a : ^{13}C-NMR ($CDCl_3$): δ147.02, 130.77, 127.79, 52.80, 44.83, 38.84, 11.16.
Cis-9b : ^{13}C-NMR ($CDCl_3$): δ 148.47, 134.52, 130.61, 126.79, 56.82, 48.65, 41.00, 10.84.

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10)

Triethylamine (17.96gm, 0.1775moles) was added slowly to a stirred solution amine hydrochloride **(9)** (9.0gm, 0.0354moles) in 90 ml of Dichloromethane at 0-5°C. Acetic anhydride (7.24gm, 0.071 moles) was added slowly at 0-5°C and stirred for 1.0hr. The reaction mass was quenched by adding water and separated. The organic layer was washed with 5% HCl solution, sat.$NaHCO_3$ and water. Concentrated the organic layer to get 5.6gm of acetamide **(10a&10b).**

Yield : 60.9% ; IR (KBr,cm^{-1}) : 3242, 3058, 1650, 1549, 1413, 1374, 1305, 1138, 1007, 752, 691; MS (m/z) = 260.4 $[M+H]^+$; MR :176.2-182.1°C .

Trans-10a : ^{1}H-NMR (DMSO-d_6): δ 8.53-8.56(d,1H,J=8.14Hz), 7.94-7.96(d,1H,J=5.17Hz), 7.01-7.02(d,1H, J=4.85Hz), 5.15-5.17(m,1H), 3.76-3.80(m,1H), 2.37-2.41(m,1H), 2.15-2.25(m,1H), 1.83(s,3H), 1.30-1.34(d,3H).; ^{13}C-NMR (DMSO-d_6): δ168.95, 144.89, 135.58, 131.99, 128.16, 53.00, ,42.00, 35.56, 22.91, 10.79.

Cis-10b : ^{1}H-NMR (DMSO-d_6): δ 8.49-8.51(d,1H,J=8.63Hz), 7.93-7.94(d,1H,J=6.36Hz), 6.93-6.95(d,1H, J=4.77Hz), 5.22-5.26(m,1H), 3.85-3.88(m,1H), 2.37-2.41(m,1H), 2.15-2.25(m,1H), 1.88(s,3H), 1.30-1.34(d,3H); ^{13}C-NMR (DMSO-d_6): δ169.36, 146.61, 135.15, 131.75, 127.44, 55.80, 45.11, 36.46, 22.91, 10.54.

III. Alternative synthesis of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thio pyran-7,7-dioxide (10) from N-*tert*- butanesulfinimine (17)

Preparation of 5,6-dihydro-4H-4-amino-6-methylthieno[2,3-b]thiopyran hydrochloride (19)
The Borane-DMS complex solution 2M in THF (0.0696moles) was added slowly to a stirred solution of N-*tert*-butylsulfinylimine **(17**) (10 gm, 0.0348moles) in 100ml of THF at room temperature. The mixture was stirred for 18 hr. at room temperature. Quenched the reaction by adding water and extracted in Dichloromethane. The organic extracts washed with brine solution and concentrated get 8.5 gm of sulfonamide **(18).** The Sulfinamide **(18)** is treated with 50.0 ml of IPA-HCl solution (~14%) and stirred for 5.0hr. at room temperature. After completion of reaction, the mass was concentrated, stirred with Ethyl acetate and filtered to get 5.1 gm of amine hydrochloride **(19a19b)**

Yield : 66.1% ; ^{1}H-NMR (DMSO-d_6): δ 8.45-8.61 (br,3H), 7.40-7.42(t,1H,J=5.56Hz), 7.23-7.37(dd,1H,J= 5.32, 47.0Hz), 4.53(m,1H), 3.64(m,1H), 1.77-2.53(m,3H), 1.34-1.35(d,3H,J= 6.64Hz); ^{13}C-NMR (DMSO-d_6): δ 133.46, 132.17, 129.47, 128.89, 128.18, 127.23, 123.00, 122.65, 46.95, 44.42, 37.23, 37.13, 35.60, 33.17, 20.51, 20.18; IR (KBr,cm^{-1}) :3092, 2921. 2636. 2611. 2019. 1608. 1514. 1447. 1417. 1389. 1266. 1038. 1025 ; MS (m/z) = 169.0$[M+H]^+$.

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran (20)
Triethylamine (8.2gm, 0.0811moles) was added slowly to a stirred solution amine hydrochloride **(19)** (4.5gm, 0.0203moles) in 45 ml of Dichloromethane at 0-5°C. Acetic anhydride (3.2gm, 0.0406 moles) was added slowly at 0-5°C and stirred for 1.0hr. The reaction mass was quenched by adding water and separated. The organic layer was washed with 5% HCl solution, sat.$NaHCO_3$ and water. Concentrated the organic layer to get 4.0gm of **20a&20b.**
Yield : 86.7% ; IR (KBr,cm^{-1}) :3291, 3092, 3073, 2964, 2908, 1637, 1549, 1537, 1444, 1421, 1369, 1255, 1127, 995, 883, 730, 719; MS (m/z) = 228.1$[M+H]^+$; MR : 194.2-195.9°C.

^{1}H-NMR (DMSO-d_6): δ 8.26-8.28(d,1H), 7.24-7.27(d,1H), 6.80-6.88(d,1H), 5.00-5.05(m,1H), 3.28-3.65(m,1H), 1.64-2.27(m,3H), 1.29-1.37(d,3H); ^{13}C-NMR (DMSO-d_6): δ 169.20, 168.35, 134.42, 132.53, 130.57, 129.42, 128.82, 127.72, 122.07, 121.86, 45.55, 42.66,39.34, 38.42, 38.07, 34.17, 22.97, 22.92, 20.77, 20.51;

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-7,7-dioxide (10)
Amide **(20)** (3.5 gm, 0.0154moles) was dissolved in ethylacetate(35.0 ml) at room temperature. Sodium tungstate dihydrate (0.5gm, 0.0015moles) and Sulfuric acid(0.1ml) was added and cooled to 0-5°C. 30% hydrogen peroxide(0.054moles) was added dropwise at below 10°C. The reaction mixture was heated to reflux and maintained for 2.0hr. After completion, the reaction mass was cooled and separated the layer. The product organic layer was washed with 5% sodium sulfite solution and water. The organic layer was concentrated, hexane is added and stirred. The product was filtered and dried to get 2.5 gm of **10a&10b**.

Yield : 62.6% ; IR (KBr,cm^{-1}) : 3244, 3060, 1649, 1547, 1448, 1414, 1372, 1304, 1138, 1007, 751, 714, 691,682, 588, 510; MS (m/z) = 260.1$[M+H]^+$; MR : 172.0-182.0°C .

Trans-10a: ^{1}H-NMR (DMSO-d_6): δ 8.54-8.56(d,1H,J=8.40Hz), 7.94-7.96(d,1H,J=5.76Hz), 7.01-7.02 (d,1H,J=4.88Hz), 5.15-5.18(m,1H), 3.76-3.80(m,1H), 2.37-2.41(m,1H), 2.18-2.25(m,1H), 1.83(s,3H), 1.32-1.34(d,3H).; ^{13}C-NMR (DMSO-d_6): δ169.00, 144.88, 135.59, 131.94, 128.16, 53.02, ,42.03, 35.56, 22.89, 10.79.

Cis-10b: ^{1}H-NMR (DMSO-d_6): δ 8.49-8.51(d,1H,J=8.64Hz), 7.93-7.94(d,1H,J=5.80Hz), 6.94-6.95(d,1H,J=4.84Hz), 5.19-5.26(m,1H), 3.85-3.89(m,1H), 2.37-2.41(m,1H), 2.18-2.25(m,1H), 1.88(s,3H), 1.30-1.32(d,3H).; ^{13}C-NMR (DMSO-d_6): δ169.41, 146.59, 135.16, 131.71, 127.45, 55.83, 45.13, 36.46, 22.89, 10.54.

IV. Preparation of Dorzolamide(1)

Preparation of 5,6-dihydro-4H-4-acetylamino-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (22)

Amide **(10)** (5.0gm, 0.0193moles) was added slowly to chlorosulfonic acid (10.0ml) at below 10°C. The reaction mixture was heated gradually to 50-55°C and stirred for 6.0 hr. The mass was cooled to room temperature and added Thionyl chloride(10.0ml). The mixture was heated again to 50-55°C and stirred for 4.0hr. The reaction was quenched in to ice water at 10°C. Filtered and washed with chilled water to get sulfonylchoride **(21)**. The wet sulfonylchoride **(21)** was added slowly into to a solution of Acetone(40.0ml) and aqueous ammonia(20.0ml) at below 10°C and stirred. The reaction mixture was concentrated under vacuum and diluted with water.The pH was adjusted to 6-7 using con.hydrochloric acid and stirred. Filtered, washed with water and dried to get 4.5 gm of **22a&22b**.

Yield : 68.9% ; IR (KBr,cm^{-1}) :3337, 3248, 3056, 1653, 1527, 1447, 1354, 1296, 1166, 1137, 1030, 1005, 911, 696; MS (m/z) = 337.0[M+H]$^{+}$; MR ; 222.0-238°C.
Trans-22a : ^{1}H-NMR (DMSO-d_6): δ 8.68-8.70(d,1H,J=8.36Hz), 8.00(br,2H), 7.44(s,1H), 5.17-5.21(m,1H), 3.89-3.98(m,1H), 2.23-2.46 (m,2H), 1.87(s,3H), 1.37-1.38(d,3H,J=6.71Hz); ^{13}C-NMR (DMSO-d_6): δ 169.27, 150.13, 144.92, 138.46, 129.92, 53.46, 42.05, 35.01, 22.89, 10.78.

Cis-22b : ^{1}H-NMR (DMSO-d_6): δ 8.62-8.64(d,1H,j=8.57Hz), 8.00(br,2H), 7.34(s,1H), 5.25-5.26(m,1H), 3.98(m,1H), 2.23-2.46 (m,2H), 1.92(s,3H), 1.34-1.3(d,3H); ^{13}C-NMR (DMSO-d_6): δ 169.68, 149.95, 146.66, 138.10, 129.14, 56.15, 45.10, 35.93, 22.89, 10.43.

(4S,6S)-4-(Ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide7,7-dioxide hydrochloride (1)

Sodium borohydride (0.89 gm, 0.0236moles) was added slowly in to a stirred suspension of the compound **22** (4.0gm, 0.0118moles) in 40.0ml of THF at 0-10°C. Borontrifluoride-etherate (3.36gm, 0.0238moles) was added slowly at below 10°C. The reaction mixture was heated to 40-45°C and stirred for 8.0hr. After completion of reaction, the mass was cooled and acidified with con.hydrochloric acid and stirred for 10.0hr. at room temperature. Concentrated the mass and diluted with Water. The pH was adjusted to 7-7.5 using sodium hydroxide solution and stirred. The product was filtered and washed with water and dried to get 3.0 gm of trans and cis mixture.

In chiral HPLC Trans(4S6S)-63.64% and Cis(4S6R)-33.29% showed. Purified this mixture through column chromatography to get pure 1.3 gm of Trans-4S,6S and was treated with IPA-HCl in Ethyl acetate to get the hydrochloride salt of 1.3 gm of Trans-4S6S **(1)**.

Yield : 30.5% ; ^{1}H-NMR (DMSO-d_6): δ 9.94(br,1H), 9.66(br,1H), 8.18(s,2H), 8.02(s,1H), 4.69 (br,s,1H), 4.35-4.39(m,1H), 3.19(m,1H), 3.05(m,1H), 2.78-2.82(m,1H), 2.50-2.59(m,1H), 1.37-1.39(d,3H,J=6.68Hz), 1.27-1.31(t,3H,J=7.01Hz); ^{13}C-NMR (DMSO-d_6): δ149.96, 142.20, 137.61, 130.99, 51.84, 49.49, 41.04, 30.97, 11.40, 10.23; IR (KBr,cm^{-1}) :3371, 3117, 2989, 2936, 2688, 2452, 1589, 1535, 1447, 1418, 1344, 1305, 1290, 1158, 1132, 1077, 1022, 916, 741, 700, 643, 604, 561, 507, 474; MS (m/z) = 325.0[M+H]$^{+}$; SOR : -8.3(C=1in MeOH at 24°C); Chiral : 100%.

CONCLUSION

In summery, we have demonstrated a new asymmetric diastereoselective reduction protocol to get the different diastereoisomers from the same chiral source of N-*tert*-butanesulfinimines. This is highly useful for the synthetic organic chemist for the synthesis of chiral amines.

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