

A Facile Transformation of the δ -Hydroxy- α -Amino Lactones from α -Furfuryl Amide¹

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Abstract: (S)- and (R)- α -furfuryl amides, obtained from the kinetic resolution of (R, S)- α -furfuryl amide using the modified Sharpless asymmetric epoxidation, have been transformed into four δ -hydroxy α -amino lactones (1S, 3S)-1, (1R, 3R)-1, (1S, 3R)-1, (1R, 3S)-1, using Sharpless asymmetric dihydroxylation as the key step. The much more efficient method of the addition of chiral aldimine **10** with allylic Grignard reagent for preparation of (S, S)-1 was also achieved. © 1998 Elsevier Science Ltd. All rights reserved.

Introduction

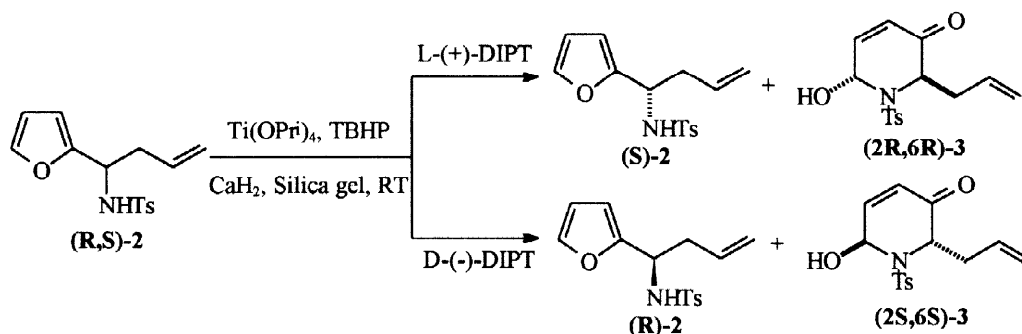
Interest in the unusual amino acids, such as non-protein hydroxy α -amino acids, has increased rapidly in recent decades¹. Amino acids containing one or more hydroxy groups form an important class of naturally occurring compound, isolated as the metabolites of plants, bacteria, moulds, and lower marine animals². In addition, they are very useful precursors in the synthesis of β -lactams³. So far many efficient and convenient synthetic methods have been developed by a number of organic chemists.

The (2S, 4S) - δ - hydroxy - α - amino lactone, (2S, 4S) - 2 - [(benzyloxycarbonyl) amino] - 4 - hydroxymethyl butyric acid γ -lactone (2S, 4S) - **1** has been used as a precursor for the synthesis of a β -lactam, **Clavalanine**, isolated from *Streptomyces clavuligerus*⁴ in 1983. This precursor was first synthesized by the Hoffmann-La-Roche group from D-xylose in the total synthesis of clavalanine⁵. Later, Williams and co-workers⁶ successfully prepared (2S, 4S) - **1** using an electrophilic glycine template which was obtained by optical resolution of a suitable racemic precursor. Ariza and co-workers⁷ synthesized (2S, 4S) - **1** starting with D-ribonolactone. Schmidt and co-workers⁸ prepared (2S, 4S)-**1** from optically active 2,3-O-isopropylideneglycer-aldehyde.

We previously reported that the kinetic resolution of α -furfuryl amide **2** afforded two versatile chiral building blocks, α -furfuryl amide (S) - **2** or (R) - **2** and dihydropyridinone¹⁰ (2R, 6R) - **3** or (2S, 6S) - **3** when L - (+) - DIPT or D - (-) - DIPT was used as a chiral ligand respectively. Both of them are key intermediates for synthesis of alkaloids¹² and α -amino acids¹³. Herein we wish to report the preparation of (2S, 4S) - **1** and its

¹ In memory of the late professor Yu Wang (1910-1997)

isomers⁹ through the kinetic resolution of α -furfuryl amide **2** and the Sharpless asymmetric dihydroxylation¹¹ (Scheme 1).

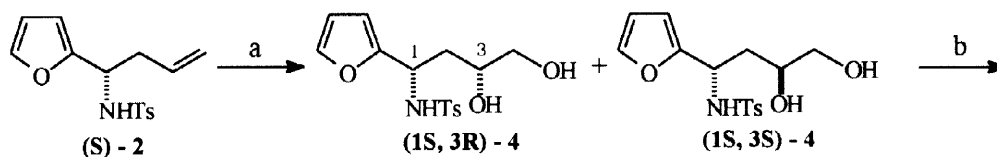


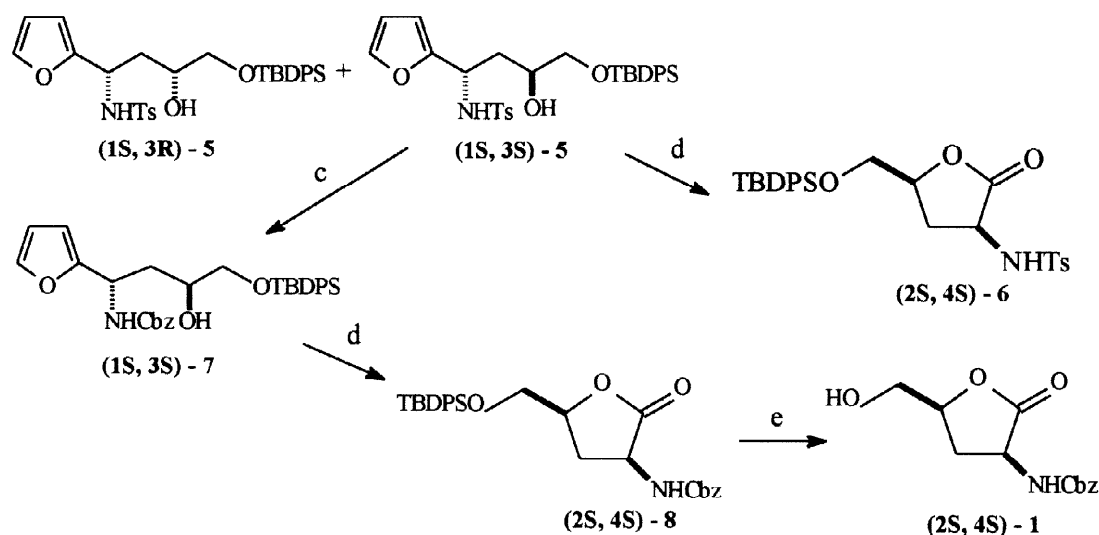
Scheme 1

Results and Discussion

The synthesis of δ -hydroxy - α -amino lactone (2S, 4S)-**1** is shown in Scheme 2. Dihydroxylation of (S) - α - furfuryl amide **2** with potassium osmate in the presence of potassium ferricyanide and potassium carbonate without ligands gave almost 1:1 of (1S, 3S) - **4** and (1S, 3R) - **4**, whereas using Sharpless asymmetric dihydroxylation of (S) - α - furfuryl amide **2** with (DHQ)₂ - PYR as a chiral ligand¹¹ yielded a mixture of the major product 1, 2 - glycol (1S, 3S) - **4** and the minor product (1S, 3R) - **4**, which could not be separated by column chromatography. Finally we found that selective protection of the primary hydroxyl with *tert*-butyl diphenylsilyl group could afford two separable products (1S, 3S) - **5** and (1S, 3R) - **5**.

Oxidation of the furfuryl group in (1S, 3S) - **5** to lactone with RuCl₃ / NaIO₄ in CH₃CN / CCl₄ / H₂O system¹⁴ gave a complicated mixture instead of the expected product. Ozonization¹⁵ of (1S, 3S) - **5** in the presence of sodium hydrogen carbonate in the mixture of CH₂Cl₂ : MeOH = 12.5 : 1 as solvent afforded (2S, 4S) - **6** in reasonable yield. Because the amino group in the known compound⁸ was protected by benzyloxycarbonyl group, we attempted to convert the tosyl group into the benzyloxycarbonyl group for comparison. Surprisingly, we could not obtain the desired product on detosylation of (2S, 4S) - **6** with sodium naphthalenide. Probably, the five-membered lactone was opened to give a complicated mixture during detosylation. Therefore we turned to detosylation of the compound (1S, 3S) - **5** with sodium naphthalenide, followed by protection of the amino group with benzyloxycarbonyl group to give (1S, 3S) - **7**. Ozonization of (1S, 3S) - **7** using the same procedure as that of (1S, 3S) - **5** afforded the desired compound (2S, 4S) - **8**. Finally, deprotection of (2S, 4S) - **8** with tetrabutylammonium fluoride gave the known compound (2S, 4S) - **1**⁸ (Scheme 2).

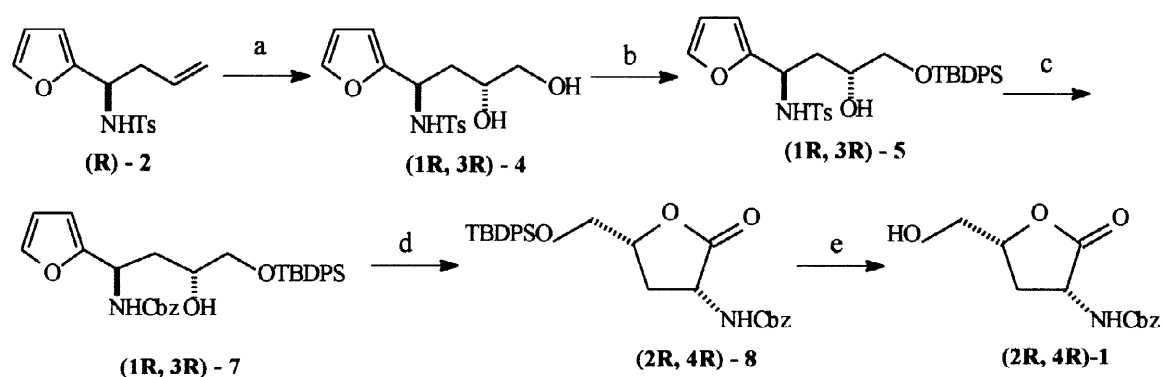




Scheme 2

Reagents and conditions: a, $K_3Fe(CN)_6$, K_2CO_3 , $(DHQ)_2$ -PYR, $K_2OsO_2(OH)_4$, $tBuOH : H_2O = 1:1$, $0^\circ C$, 95%; b, TBDPSCl, Imidazole, r.t., 94%; c, i) Na, naphthalene, DME, $-78^\circ C$; ii) CbzCl, Na_2CO_3 , EtOAc/ H_2O , r.t., 68% (two steps); d, O_3 , $NaHCO_3$, $CH_2Cl_2 : MeOH = 12.5 : 1$, $-78^\circ C$, (1S, 3S)-5 \rightarrow (2S, 4S)-6 in 66%; (1S, 3S)-7 \rightarrow (2S, 4S)-8 in 65%; e, $^nBu_4N^+F^-$, THF, r.t., 92%.

Synthesis of the (2R, 4R)-1⁸ was similar to that of the (2S, 4S)-1 as depicted in Scheme 3.

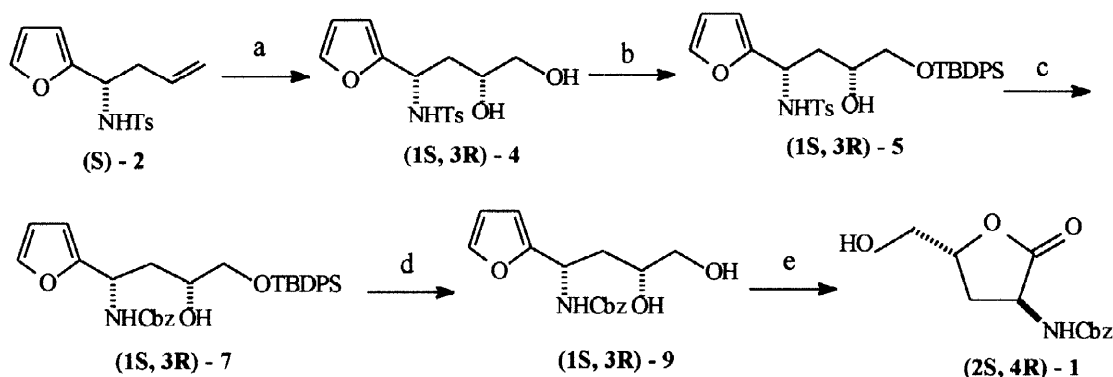


Scheme 3

Reagents and conditions: a, $K_3Fe(CN)_6$, K_2CO_3 , $(DHQD)_2$ -PYR, $K_2OsO_2(OH)_4$, $tBuOH : H_2O = 1:1$, $0^\circ C$, 93%; b, TBDPSCl, Imidazole, r.t., 92%; c, i) Na, naphthalene, DME, $-78^\circ C$; ii) CbzCl, Na_2CO_3 , EtOAc/ H_2O , r.t., 68% (two steps); d) O_3 , $NaHCO_3$, $CH_2Cl_2 : MeOH = 12.5 : 1$, $-78^\circ C$, 66%; e, $^nBu_4N^+F^-$, THF, r.t., 93%.

In the synthesis of the (2S, 4R)-1, the procedures from (S)-2 to (1S, 3R)-7 were the same as those of (2S, 4S)-1. However, the protected δ -hydroxy- α -amino lactone (2S, 4R)-8 could not be obtained as (2S, 4S)-8 when (1S, 3R)-7 was ozonized under the same condition as that of (1S, 3S)-7. Since these two bulky protected groups are in trans-orientation during the formation of five membered lactone ring, it is difficult to construct the ring structure. Thus (1S, 3R)-7 was deprotected first with tetrabutylammonium fluoride to yield

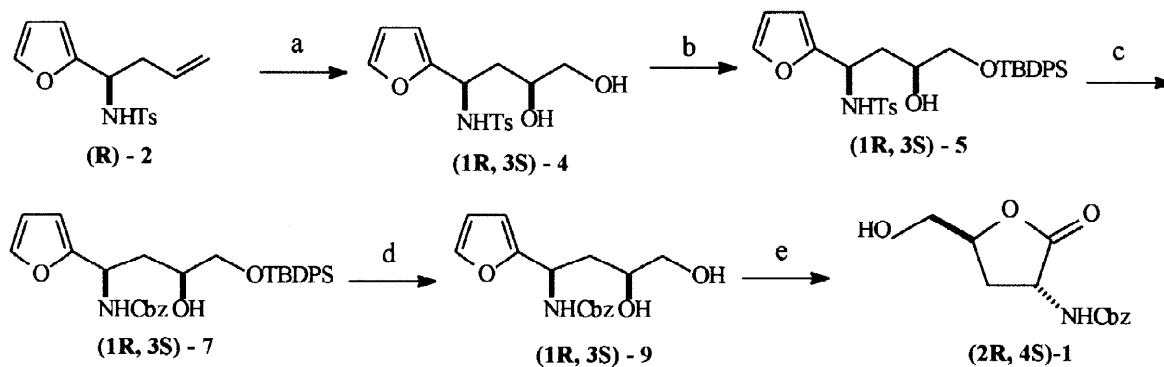
(2S, 4R) - 9 which gave the known compound (2S, 4R) - 1⁸ on ozonization in the same condition as that of (2S, 4S) - 8 (Scheme 4).



Scheme 4

Reagents and conditions: a, $K_3Fe(CN)_6$, K_2CO_3 , (DHQD)₂ - PYR, $K_2OsO_2(OH)_4$, $tBuOH : H_2O = 1:1$, 0°C, 93%; b, TBDPSCl, Imidazole, r.t., 92%; c, i) Na, naphthalene, DME, -78°C; ii) CbzCl, Na_2CO_3 , EtOAc/ H_2O , r.t., 65% (two steps); d, $nBu_4N^+F^-$, THF, r.t., 92%; e, O_3 , $NaHCO_3$, $CH_2Cl_2 : MeOH = 12.5 : 1$, -78°C, 68%.

Synthesis of the known isomer (2R, 4S) - 1⁸, utilizing (R) - 2 as a starting material, was similar to that of (2S, 4R) - 1 as depicted in Scheme 5.

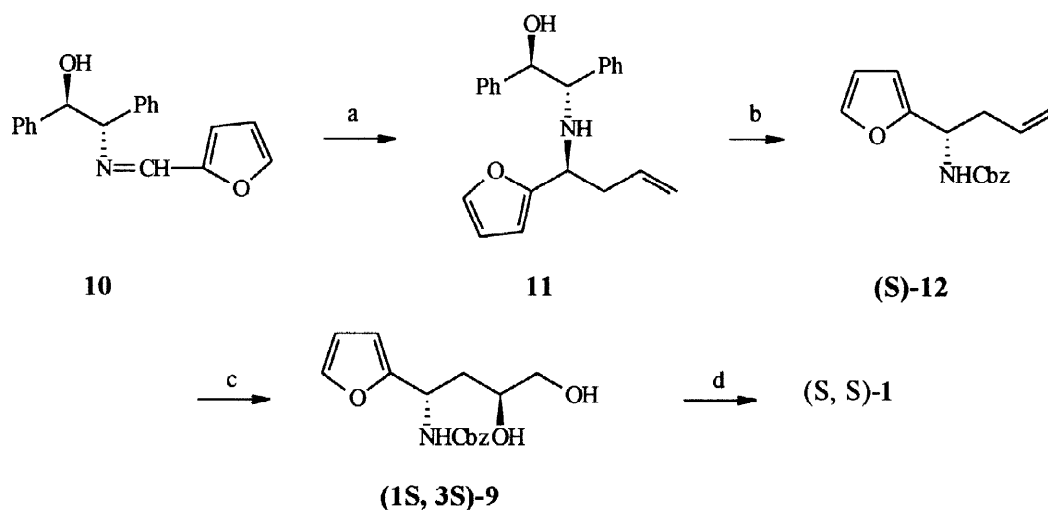


Scheme 5

Reagents and conditions: a, $K_3Fe(CN)_6$, K_2CO_3 , (DHQ)₂ - PYR, $K_2OsO_2(OH)_4$, $tBuOH : H_2O = 1:1$, 0°C, 94%; b, TBDPSCl, Imidazole, r.t., 93%; c, i) Na, naphthalene, DME, -78°C; ii) CbzCl, Na_2CO_3 , EtOAc/ H_2O , r.t., 67% (two steps); d, $nBu_4N^+F^-$, THF, r.t., 93%; e, O_3 , $NaHCO_3$, $CH_2Cl_2 : MeOH = 12.5 : 1$, -78°C, 70%.

In addition, we used the newly developed method¹⁶ for the direct synthesis of chiral α -furfuryl amide via the diastereoselective addition of organometallic reagent to chiral imine **10** for the synthesis of δ -hydroxy- α -amino lactone (2S, 4S)-**1** as shown in Scheme 6. Addition of chiral aldimine **10** with allylic Grignard reagent yielded the amine derivative **11** which was subjected to hydrogenation in the presence of formic acid and methanol with $Pd-C$ ¹⁷ to remove the amino protecting group followed by the reaction with benzyloxycarbonyl

chloride to give (S)-12. Sharpless asymmetric dihydroxylation of (S)-12 with (DHQD)₂-PHAL as a ligand afforded (1S, 3S)-9 which on ozonization in the same condition as that of (2S, 4S) - 8. This method for preparation of the Clavalanine precursor is much simpler than the synthetic method mentioned above.



Scheme 6

Reagents and Conditions: a, AllylicMgBr, CeCl₃, THF, 0°C→r.t., 85%; b, i) Pd-C, 4.4% HCOOH in MeOH, r.t.; ii) CbzCl, K₂CO₃, 0°C, 85% (2 steps); c, AD-mix-α, K₂CO₃, NaHCO₃, K₃Fe(CN)₆, 0°C, 89%; d, O₃, NaHCO₃, CH₂Cl₂: MeOH = 12.5 : 1, - 78°C, 74%.

Conclusion

Four δ-hydroxy-α-amino lactones have been synthesized from the furfuryl amide (S) - 2 and (R) - 2 respectively, which were obtained from the kinetic resolution of the α -furfuryl amide (R, S) - 2. The overall yields of (2S, 4S) - 1, (2S, 4R) - 1, (2R, 4R) - 1, (2R, 4S) - 1 are 36%, 35%, 36% and 38%, respectively, in 5 steps. (2S, 4S)-1 was also prepared by the addition of chiral aldimine with allylic Grignard reagent method in an overall yield of 47% in four steps.

Experimental

Melting points were determined with a Buchi 535 melting point apparatus and were uncorrected. All additions were made by syringes. Reactions were monitored by using thin layer chromatography (TLC). The silica gel used in epoxidation and flash chromatography was silica gel H (300 mesh) which was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Shimadzu IR 400 spectrometer. ¹H-NMR spectra were recorded on a Bruker AM-300 (300MHz) with CDCl₃ as solvent and values were reported in ppm, using TMS or residual CHCl₃ as internal standard. MS spectra were conducted on a Finnigan 4021 GC-MS instrument and JMS-01U spectrometer. The optical rotations, [α]_D²⁰, were measured on a Perkin-Elmer 241 MC autopol spectrometer III automatic polarimeter. Element analysis were performed by Analytical department of

this institute. Dichloromethane was distilled from calcium hydride. Tetrahydrofuran was freshly distilled from LiAlH_4 . Dimethoxyether was freshly distilled from sodium. Diisopropyl tartrate (DIPT) was obtained from Aldrich Chemical Co.. Titanium (IV) isopropoxide was distilled under reduced pressure and stored under inert atmosphere. 85% *tert*-Butyl hydroperoxide (TBHP) was obtained from Merk-Schuchardt Co., which was further purified according to the literature¹⁸. Calcium hydride was obtained from Fluka-Garantie Co.

N - tosyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy - butyl amine - (1S, 3S) - 4:

To a well stirred solution of $\text{K}_3\text{Fe}(\text{CN})_6$ (0.85 g, 2.58 mmol), K_2CO_3 (0.36 g, 2.58 mmol) and $(\text{DHQ})_2\text{-PYR}$ (37.9 mg, 5% eq.) in 30 mL of $^t\text{BuOH} : \text{H}_2\text{O} = 1 : 1$, was added (S) - 2 (0.250 g, 0.86 mmol) and $\text{K}_2\text{OsO}_2(\text{OH})_4$ (15.8 mg, 5% eq.) at 0°C. After the reaction mixture was stirred for 12 h, Na_2SO_3 (0.7 g, 5.2 mmol) was added, the mixture was stirred for an additional hour at r.t.. The solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 x 25 mL). The combined organic layer was washed with brine, dried (MgSO_4) and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [ether-dichloromethane (30 : 10)] to afford a solid (1S, 3S) - 4 (0.265 g, 95%). $[\alpha]_D^{20} - 2.1^\circ$ (c 3.8, EtOH); M.p. 100.6 - 102.3°C; IR (ν_{max} , cm^{-1}): 3300 (N - H), 3250 (OH), 1600 (Ph); $^1\text{H-NMR}$ δ (CDCl_3): 1.74 (*m*, 1H, 2 - H_a), 1.87 (*m*, 1H, 2 - H_b), 2.41 (*s*, 3H, TsCH_3), 3.43 (*dd*, 1H, $J = 3.9, 6.9$ Hz, 4 - H_a), 3.55 (*dd*, 1H, $J = 4.0, 6.9$ Hz, 4 - H_b), 4.00 (*dd*, 1H, $J = 3.3, 6.3$ Hz, 3 - H), 4.68 (*m*, 1H, 1 - H), 5.23 (*d*, 1H, $J = 6.3$ Hz, N - H), 5.83 (*d*, 1H, $J = 3.1$ Hz, furyl), 6.13 (*dd*, 1H, $J = 1.9, 3.1$ Hz, furyl), 7.15 (*d*, 1H, $J = 1.9$ Hz, furyl), 7.26 (*d*, 2H, $J = 10.1$ Hz, Ph), 7.68 (*d*, 2H, $J = 7.9$ Hz, Ph); MS (m/z): 170 ($\text{M}^+ - \text{Ts}$), 155 (Ts^+), 91 (PhCH_3^+); HRMS for $\text{C}_8\text{H}_{12}\text{NO}_3$: Calcd.: 170.0899; Found: 170.0858.

N - tosyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenylsilyloxy butyl amine - (1S, 3S) - 5:

To a solution of (1S, 3S)-4 (0.150 g, 0.461 mmol) in 15 mL of THF, was added imidazole (0.037 mg, 0.557 mmol) and TBDPSCl (0.144 mL, 0.557 mmol) respectively. After the reaction was stirred for 2 h at r.t., water (0.5 mL) was added. Working up as usual way afforded a crude oil which was purified by flash column chromatography on silica gel [petroleum ether - ethyl acetate (90 : 10)] to afford a solid (1S, 3S) - 5 (0.244 g, 94%). $[\alpha]_D^{20} - 2.3^\circ$ (c 2.1, EtOH); M.p. 115.6 - 116.8°C; IR (ν_{max} , cm^{-1}): 3450 (N - H), 3250 (OH), 1600 (Ph); $^1\text{H-NMR}$ δ (CDCl_3): 1.04 (*s*, 9H, ^tBu), 1.74 - 1.64 (*ddd*, 1H, $J = 3.9, 10.0, 18.2$ Hz, 2 - H_a), 1.85 - 1.77 (*ddd*, 1H, $J = 3.9, 7.6, 14.3$ Hz, 2 - H_b), 2.38 (*s*, 3H, TsCH_3), 3.45 (*dd*, 1H, $J = 7.1, 10.2$ Hz, 4 - H_a), 3.53 (*dd*, 1H, $J = 4.2, 10.2$ Hz, 4 - H_b), 3.85 (*m*, 1H, 3 - H), 4.70 (*m*, 1H, 1 - H), 5.65 (*d*, 1H, $J = 8.9$ Hz, N - H), 5.97 (*d*, 1H, $J = 3.2$ Hz, furyl), 6.16 (*dd*, 1H, $J = 1.8, 3.2$ Hz, furyl), 7.16 (*d*, 1H, $J = 1.8$ Hz, furyl), 7.22 - 7.19 (*d*, 2H, $J = 8.1$ Hz, Ph), 7.44 - 7.37 (*m*, 5H, Ph), 7.67 - 7.60 (*m*, 5H, Ph); MS (m/z): 408 ($\text{M}^+ - \text{Ts}$), 241 ($\text{M}^+ - \text{OTBDPS-furyl}$); 154 [($\text{M}^+ + 1$) - TBDPS -Ts]; Anal. Calc. for $\text{C}_{31}\text{H}_{37}\text{O}_5\text{NSSi}$: C, 66.04; H, 6.62; N, 2.48; Found: C, 66.00; H, 6.60; N, 2.42.

N - Tosyl - 4 - 'butyldiphenyl silyloxy - 2 - butyl amine - lactone - (2S, 4S) - 6:

To a solution of (1S, 3S)-5 (210 mg, 0.373 mmol) in 25 mL of CH₂Cl₂ and 2 mL of MeOH and NaHCO₃ (6.3 mg, 0.075 mmol), was bubbled O₃ at -78°C till the solution became blue. N₂ was bubbled to bring out O₃ until the solution became colourless, then Me₂S (1.2 mL) was added. Working up in the way as described for (2S, 4S)-8 afforded (2S, 4S) - 6 (132 mg, 66%). [α]_D²⁰ + 4.0° (c 2.0, EtOH); IR (ν_{\max} , cm⁻¹): 3350 (N - H), 1780 (C = O), 1600 (Ph); ¹H-NMR δ (CDCl₃): 1.04 (s, 9H, 'Bu), 2.18 - 2.26 (m, 1H, 3 - H_a), 2.44 (s, 3H, TsCH₃), 2.61 - 2.66 (m, 1H, 3 - H_b), 3.71 (dd, 1H, *J* = 3.9, 11.8 Hz, 5 - H_a), 3.91 (dd, 1H, *J* = 3.1, 11.8 Hz, 5 - H_b), 3.99 (m, 1H, 4 - H), 4.48 (m, 1H, 2 - H), 5.13 (d, 1H, *J* = 3.7 Hz, N - H), 7.32 - 7.46 (m, 10H, Ph), 7.62 (d, 2H, *J* = 7.1 Hz, Ph), 7.78 (d, 2H, *J* = 8.3 Hz, Ph); MS (*m/z*): 446 (M⁺ - 'Bu), 91 (Ph); Anal. Calc. for C₂₈H₃₃O₅NSSi: C, 64.21; H, 6.35; N, 2.67; Found: C, 63.86; H, 6.38; N, 2.60.

N - benzyloxycarbonyl - 1 - (1'-furfuryl) - 3 - hydroxy - 4 - 'butyldiphenyl silyloxy butyl amine - (1S, 3S) - 7:

The mixture of naphthalene (450 mg, 3.52 mmol) and sodium (100 mg) in 10 mL of 1, 2 - dimethoxyethane was stirred for 2 hr at r.t.. The solution of (1S, 3S)-5 (73 mg, 0.130 mmol) in 5 mL of DME was added at -78°C. After being stirred for 1h at the same temperature, 3 mL of saturated NH₄Cl (aq.) was added. The inorganic salt was filtrated off. Working up as usual way followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (20 : 10)] afforded an oil which was dissolved in the mixture of 10 mL of ethyl acetate and 4 mL of saturated aqueous Na₂CO₃, 35% benzyl chloroformate in toluene (0.35 mL) was added at 0°C. After the reaction mixture was stirred for 0.5 h, working up as usual way followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90:10)] afforded an oil (1S, 3S) - 7 (47 mg, 68%). [α]_D²⁰ - 2.9° (c 1.8, EtOH); IR (ν_{\max} , cm⁻¹): 3400 (N - H), 3300 (OH), 1720 (C = O, Cbz), 1600 (Ph); ¹H-NMR δ (CDCl₃): 1.05 (s, 9H, 'Bu), 1.88 (dd, 2H, *J* = 4.3, 8.6 Hz, 2 - H), 3.58 (d, 2H, *J* = 4.1 Hz, 4 - H), 3.78 (m, 1H, 3 - H), 5.10 (m, 1H, 1 - H), 5.12 (s, 2H, Bn -), 5.69 (d, 1H, *J* = 8.3 Hz, N - H), 6.17 (d, 1H, *J* = 3.0 Hz, furyl), 6.31 (dd, 1H, *J* = 1.8, 3.0 Hz, furyl), 7.16 (d, 1H, *J* = 1.8 Hz, furyl), 7.39 - 7.43 (m, 10H, Ph), 7.61 - 7.64 (m, 5H, Ph); MS (*m/z*): 543 (M⁺), 408 (M⁺ - COOBn); HRMS for C₂₄H₃₀NO₃Si: Calcd: 408.1996; Found: 408.1987.

N - benzyloxycarbonyl - 4 - 'butyldiphenyl silyloxy - 2 - butyl amine lactone - (2S, 4S) - 8:

To a well-stirred solution of (1S, 3S)-7 (110 mg, 0.203 mmol) and NaHCO₃ (5 mg, 0.04 mmol) in the mixture of 25 mL of CH₂Cl₂ and 2 mL of MeOH, was bubbled O₃ at -78°C until a blue colour appeared. N₂ was bubbled to remove excess O₃ until the solution became colourless, then Me₂S (0.5 mL) was added. After stirring at r.t. for 12 h, the solution was concentrated under pressure to give a crude oil which was purified by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90 : 10)] to afford an oil (2S, 4S) - 8 (67 mg, 65%). [α]_D²⁰ + 3.9° (c 2.1, EtOH); IR (ν_{\max} , cm⁻¹): 3350 (N - H), 1780 (C = O, lactone), 1720 (C

= O, Cbz), 1600 (Ph); $^1\text{H-NMR}$ δ (CDCl_3): 1.00 (*s*, 9H, ^tBu), 2.10 (*m*, 1H, 3 - H_a), 2.78 (*m*, 1H, 3 - H_b), 3.72 (*dd*, 1H, $J=3.7, 7.9$ Hz, 5 - H_a), 3.91 (*dd*, 1H, $J=3.5, 9.4$ Hz, 5 - H_b), 4.50 (*m*, 1H, 4 - H), 4.55 (*m*, 1H, 2 - H), 5.14 (*d*, 2H, Bn, $J=6.5$ Hz), 5.32 (*d*, 1H, $J=5.8$ Hz, N - H), 7.33 - 7.48 (*m*, 10H, Ph), 7.62 - 7.66 (*m*, 5H, Ph); MS (m/z): 446 ($\text{M}^+ - \text{Bu}^t$), 310 ($\text{M}^+ - \text{Bu}^t - \text{COOBn}$); HRMS for $\text{C}_{25}\text{H}_{24}\text{NO}_5\text{Si}$: Calcd: 446.1423; Found: 446.1456.

N - benzyloxycarbonyl - 4 - hydroxy - 2 - butyl amine lactone - (2S, 4S) - 1:

To a solution of (2S, 4R)-**8** (46 mg, 0.09 mmol) in 5 mL of THF, was added $^t\text{Bu}_4\text{N}^+\text{F}^-$ (52 mg, 0.2 mmol). After the reaction was stirred for 2 h at r.t., 1 mL of water was added. Working up as usual way followed by flash column chromatography on silica gel [methanol-dichloromethane (20 : 10)] afforded a solid (2S, 4S) - **1** (22 mg, 92%). $[\alpha]_{\text{D}}^{20} + 6.0^\circ$ (*c* 1.6, MeOH); { lit.⁸: $[\alpha]_{\text{D}}^{20} + 6.6^\circ$ (*c* 0.24, MeOH) }; M.p. 116.3 - 117.3°C; { lit.⁸: M.p. 118°C }; IR (ν_{max} , cm^{-1}): 3350 (N - H), 1780 (C = O, lactone), 1720 (C = O, Cbz), 1600 (Ph); $^1\text{H-NMR}$ δ (CDCl_3): 2.30 - 2.35 (*m*, 2H, 3 - H), 3.43 - 3.57 (*m*, 2H, 5 - H), 4.45 (*dd*, 1H, $J=10.2, 17.4$ Hz, 4 - H), 4.56 (*dd*, 1H, $J=2.4, 8.7$ Hz, 2 - H), 5.03 (*s*, 1H, OH), 5.05 (*s*, 2H, Bn), 7.32 - 7.36 (*m*, 5H, Ph), 7.78 (*d*, 1H, $J=8.5$ Hz, N - H); MS (m/z): 149 ($\text{M}^+ + 1 - \text{OBn}$), 129 ($\text{M}^+ - 1 - \text{COOBn}$), 107 (BnO).

N - tosyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy - butyl amine - (1R, 3R) - 4:

As described for the preparation of its enantiomer (1S, 3S) - **4** from (S) - **2**, compound (1R, 3R) - **4** was prepared from (R) - **2** (0.157 g, 0.54 mmol); the product (0.163 g, 93%) had M.p. 100.9 - 102.2°C; $[\alpha]_{\text{D}}^{20} + 2.3^\circ$ (*c* 2.6, EtOH). The spectral data were identical with those of (1S, 3S) - **4**.

N - tosyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenylsilyloxy butyl amine - (1R, 3R) - 5:

As described for the preparation of its enantiomer (1S, 3S) - **5** from (1S, 3S) - **4**, compound (1R, 3R) - **5** was prepared from (1R, 3R) - **4** (0.540 g, 1.66 mmol); the product (0.860 g, 92%) had M.p. 115.7 - 116.6°C; $[\alpha]_{\text{D}}^{20} + 2.2^\circ$ (*c* 2.1, EtOH). The spectral data were identical with those of (1S, 3S) - **5**.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenyl silyloxy butyl amine - (1R, 3R) - 7:

As described for the preparation of its enantiomer (1S, 3S) - **7** from (1S, 3S) - **5**, compound (1R, 3R) - **7** was prepared from (1R, 3R) - **5** (115 mg, 0.204 mmol); the product (75 mg, 68%) had $[\alpha]_{\text{D}}^{20} + 3.5^\circ$ (*c* 1.8, EtOH). The spectral data were identical with those of (1S, 3S) - **7**.

N - benzyloxycarbonyl - 4 - 'butyldiphenyl silyloxy - 2 - butyl amine lactone - (2R, 4R) - 8:

As described for the preparation of its enantiomer (2S, 4S) - 8 from (1S, 3S) - 7, compound (2R, 4R) - 8 was prepared from (1R, 3R) - 7 (100 mg, 0.184 mmol); the product (61 mg, 66%) had $[\alpha]_D^{20}$ - 3.9° (c 2.1, EtOH). The spectral data were identical with those of (2S, 4S) - 8.

N - benzyloxycarbonyl - 4 - hydroxy - 2 - butyl amine lactone - (2R, 4R) - 1:

As described for the preparation of its enantiomer (2S, 4S) - 1 from (2S, 4S) - 8, compound (2R, 4R) - 1 was prepared from (2R, 4R) - 8 (51 mg, 0.10 mmol); the product (25 mg, 93%) had M.p. 114.5 - 115.8 °C; {lit.⁹: M.p. 116°C}; $[\alpha]_D^{20}$ - 6.3° (c 1.8, MeOH), {lit.⁸: $[\alpha]_D^{20}$ - 7.1° (c 0.37, MeOH)}. The spectral data were identical with those of (2S, 4S) - 1.

N - tosyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy - butyl amine - (1S, 3R) - 4:

To a well stirred solution of $K_3Fe(CN)_6$ (0.76 g, 2.31 mmol), K_2CO_3 (0.32 g, 2.31 mmol) and (DHQD)₂-PYR (30 mg, 5% eq.) in 30 mL of ^tBuOH : H₂O = 1 : 1, was added (S) - 2 (0.224 g, 0.77 mmol), $K_2OsO_2(OH)_4$ (14.2 mg, 5% eq.) at 0°C. After the reaction was stirred for 12 h, Na_2SO_3 (0.6 g, 4.6 mmol) was added, stirred for 1 h at r.t. Working up in the way as described for (1S, 3S)-4 followed by flash column chromatography on silica gel [ether-dichloromethane (30 : 10)] afforded (1S, 3R) - 4 (0.23 g, 93%). $[\alpha]_D^{20}$ -2.4 (c 3.5, EtOH); M.p. 98.5 - 100°C; IR(ν_{max} , cm^{-1}): 3300 (N - H), 3250 (OH), 1600 (Ph); ¹H-NMR δ (CDCl₃): 1.93 (ddd, 1H, *J* = 3.0, 5.5, 13.0 Hz, 2 - H_a), 2.01 (*m*, 1H, 2 - H_b), 2.39 (*s*, 3H, TsCH₃), 3.43 (*dd*, 1H, *J* = 4.0, 6.9 Hz, 4 - H_b), 3.57 (*dd*, 1H, *J* = 3.3, 6.3 Hz, 4 - H_a), 3.64 (*m*, 1H, 3 - H), 4.66 (*m*, 1H, 1 - H), 5.35 (*d*, 1H, *J* = 6.2 Hz, N - H), 5.96 (*d*, 1H, *J* = 3.2 Hz, furyl), 6.12 (*dd*, 1H, *J*₁ = 1.9, 3.2 Hz, furyl), 7.15 (*d*, 1H, *J* = 1.9 Hz, furyl), 7.22 (*d*, 2H, *J* = 8.4 Hz, Ph), 7.63 (*d*, 2H, *J* = 8.2 Hz, Ph); MS (*m/z*): 326 (*M*⁺ + 1), 170 (*M*⁺ - Ts), 155 (Ts⁺), 91 (PhCH₃⁺). HRMS for C₈H₁₂NO₃: Calcd.: 170.0817; Found: 170.0796.

N - tosyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenylsilyloxy butyl amine - (1S, 3R) - 5:

To a solution of (1S, 3R)-4 (0.540 g, 1.66 mmol) in 20 mL of THF, was added imidazole (0.180 g, 2.66 mmol), TBDPSCI (0.51 mL, 1.99 mmol) respectively. The reaction being stirred for 2h at r.t., water (3 mL) was added. Working up in the way as described for (1S, 3S)-5 followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90 : 10)] afforded a solid (1S, 3R) - 5 (0.86 g, 92%). $[\alpha]_D^{20}$ - 2.8° (c 1.9, EtOH); M.p. 107.2 - 108.8°C; IR (ν_{max} , cm^{-1}): 3450 (NH), 3250 (OH), 1600 (Ph); ¹H-NMR δ (CDCl₃): .04 (*s*, 9H, ^tBu), 1.83 - 1.75 (ddd, 1H, *J* = 2.5, 7.6, 6.7 Hz, 2 - H_a), 1.96 - 1.87 (ddd, 1H, *J* = 1.4, 6.7, 15.2 Hz, 2 - H_b), 2.37 (*s*, 3H, Ts-CH₃), 3.40 (*dd*, 1H, *J* = 6.9, 9.2 Hz, 4 - H_a), 3.52 (*dd*, 1H, *J* = 4.1, 9.2 Hz, 4 - H_b), 3.54 (*m*, 1H, 3 - H), 4.59 (*m*, 1H, 1 - H), 5.42 (*d*, 1H, *J* = 6.2 Hz, N - H), 5.99 (*d*, 1H, *J* = 3.2 Hz, furyl), 6.12 (*dd*, 1H, *J*₁ = 1.8 Hz, *J*₂ = 3.2 Hz, furyl), 7.13 (*d*, 1H, *J* = 1.8 Hz, furyl), 7.20 - 7.18 (*d*, 2H, *J* = 8.1 Hz, Ph), 7.44 -

7.35 (*m*, 5H, Ph), 7.63 - 7.58 (*m*, 7H, Ph); MS (*m/z*): 408 (M^+ - Ts), 241 (M^+ - OTBDPS - furyl); Anal. Calc. for $C_{31}H_{37}O_5N$ SSi: C, 66.04; H, 6.62; N, 2.48; Found: C, 66.19; H, 6.81; N, 2.39.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenyl silyloxy butyl amine - (1S, 3R) - 7:

The mixture of naphthalene (500 mg, 3.85 mmol) and sodium (120 mg) in 10 mL of 1, 2 -dimethoxyethane was stirred for 2 hr at r.t.. The solution of (1S, 3R)-5 (80 mg, 0.142 mmol) in 5 mL of DME was added at -78°C. After being stirred for 1h at the same temperature, 3 mL of saturated NH_4Cl (aq.) was added. The inorganic salt was filtrated off. Working up as usual way was followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (20 : 10)] to afford an oil which was dissolved in the mixture of 15 mL of ethyl acetate and 5 mL of saturated aqueous Na_2CO_3 , 35% benzyl chloroformate in toluene (0.4 mL) was added at 0°C. After the reaction was stirred for 0.5 h, Working up as usual way followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90:10)] afforded an oil (1S, 3R) - 7 (50 mg, 65%). $[\alpha]_D^{20}$ - 2.9° (c 1.6, EtOH); IR (ν_{max} , cm^{-1}): 3400 (N - H), 3300 (OH), 1720 (C = O, Cbz), (Ph); 1H -NMR δ ($CDCl_3$): 1.05 (*s*, 9H, 'Bu), 1.88 (*m*, 2H, 2 - H), 3.59 (*m*, 2H, 4 - H), 3.79 (*m*, 1H, 3 - H), 5.10 (*m*, 1H, 1 - H), 5.12 (*s*, 2H, Bn), 5.68 (*d*, 1H, $J = 8.2$ Hz, N - H), 6.16 (*d*, 1H, $J = 1.8$ Hz, furyl), 6.30 (*dd*, 1H, $J = 1.8$, 3.0 Hz, furyl), 7.38 (*d*, 1H, $J = 3.0$ Hz, furyl), 7.40 - 7.44 (*m*, 10H, Ph), 7.62 - 7.67 (*m*, 5H, Ph); MS (*m/z*): 543 (M^+), 408 (M^+ - Cbz); HRMS for $C_{24}H_{30}O_3NSi$: Calc.: 408.1995; Found: 408.1989.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy butyl amine - (1S, 3R) - 9:

To a solution of (1S, 3R)-7 (190 mg, 0.35 mmol) in 8 mL of THF, was added $^nBu_4NF^+$ (130 mg, 0.385 mmol). After the mixture was stirred for 2 h at r.t., 2 mL of water was added. Working up as usual way followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (40 : 10)] afforded a solid (1S, 3R) - 9 (96 mg, 93%). $[\alpha]_D^{20}$ -13.8° (c 2.0, EtOH); M.p. 56 - 58°C; IR (ν_{max} , cm^{-1}): 3400 (N - H), 3250 (OH), 1720 (C = O, Cbz), 1600 (Ph); 1H -NMR δ ($CDCl_3$): 1.84 (*m*, 2H, 2 - H), 3.51 (*m*, 1H, 4 - H_a), 3.62 (*m*, 1H, 4 - H_b), 3.80 (*m*, 1H, 3 - H), 5.10 (*m*, 1H, 1 - H), 5.14 (*s*, 2H, Bn), 5.31 (*d*, 1H, $J = 7.7$ Hz, N - H), 6.21 (*d*, 1H, $J = 2.9$ Hz, furyl), 6.32 (*m*, 1H, furyl), 7.28 (*d*, 1H, $J = 4.2$ Hz, Furyl), 7.36 (*m*, 5H, Ph); MS (*m/z*): 305 (M^+), 170 (M^+ - Cbz); HRMS for $C_8H_{12}O_3N$: Calc.: 170.0818; Found: 170.0799.

N - benzyloxycarbonyl - 4 - hydroxy - 2 - butyl amine lactone - (2S, 4R) - 1:

To a solution of (1S, 3R)-9 (50 mg, 0.164 mmol) in 10 mL of mixed solvent of CH_2Cl_2 : MeOH = 1 : 1) and $NaHCO_3$ (16.8 mg, 0.2 mmol) at -78°C, was bubbled O_3 untill the solution showed blue. Working up in the way described for (1S, 3S)-8 followed by flash column chromatography on silica gel [CH_2Cl_2 : MeOH (10 : 30)] afforded a solid (30 mg, 68%). M.p. 120.5 - 121.9°C; { lit.⁸ 123°C }; $[\alpha]_D^{20}$ - 46 (c 1.3, MeOH); { lit.⁸: $[\alpha]_D^{20}$ - 50.1 (c 0.48, MeOH) }; IR (ν_{max} , cm^{-1}): 3350 (N - H), 1780 (C = O, lactone), 1720 (C = O,

Cbz), 1600 (Ph); $^1\text{H-NMR}$ δ (CDCl_3): 1.84 (*m*, 1H, 3 - H_a), 2.31 - 2.40 (*m*, 1H, 3 - H_b), 3.46 - 3.63 (*m*, 2H, 5 - H), 4.41 - 4.49 (*m*, 1H, 4 - H), 4.55 (*m*, 1H, 2 - H), 5.03 (*s*, 1H, OH), 5.05 (*s*, 2H, Bn), 7.35 (*m*, 5H, Ph), 7.75 (*d*, 1H, $J = 8.4$ Hz, N - H); MS (m/z): 149 ($\text{M}^+ + 1$ - OBn), 129 ($\text{M}^+ - 1$ - COOBn), 107 (BnO).

N - tosyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy - butyl amine - (1R, 3S) - 4:

As described for the preparation of its enantiomer (1S, 3R) - 4 from (S) - 2, compound (1R, 3S) - 4 was prepared from (R) - 2 (0.250 g, 0.86 mmol); the product (0.262 g, 94%) had M.p. 98.7 - 100.3°C; $[\alpha]_{\text{D}}^{20} + 2.4^\circ$ (c 2.9, EtOH). The spectral data were identical with those of (1S, 3R) - 4.

N - tosyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenylsilyloxy butyl amine - (1R, 3S) - 5:

As described for the preparation of its enantiomer (1S, 3R) - 5 from (1S, 3R) - 4, compound (1R, 3S) - 5 was prepared from (1R, 3S) - 4 (0.350 g, 1.08 mmol); the product (0.563 g, 93%) had M.p. 107.5 - 108.9°C; $[\alpha]_{\text{D}}^{20} + 2.9^\circ$ (c 2.0, EtOH). The spectral data were identical with those of (1S, 3R) - 5.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3 - hydroxy - 4 - 'butyldiphenyl silyloxy butyl amine - (1R, 3S) - 7:

As described for the preparation of its enantiomer (1S, 3R) - 7 from (1S, 3R) - 5, compound (1R, 3S) - 7 was prepared from (1R, 3S) - 5 (400 mg, 0.71 mmol); the product (258 mg, 67%) had $[\alpha]_{\text{D}}^{20} + 4.5^\circ$ (c 1.8, EtOH). The spectral data were identical with those of (1S, 3R) - 7.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy butyl amine - (1R, 3S) - 9:

As described for the preparation of its enantiomer (1S, 3R) - 9 from (1S, 3R) - 7, compound (1R, 3S) - 9 was prepared from (1R, 3S) - 7 (230 mg, 0.42 mmol); the product (120 mg, 93%) had M.p. 59 - 61°C; $[\alpha]_{\text{D}}^{20} + 14.6^\circ$ (c 3.9, EtOH). The spectral data were identical with those of (1S, 3R) - 9.

N - benzyloxycarbonyl - 4 - hydroxy - 2 - butyl amine lactone - (2R, 4S) - 1:

As described for the preparation of its enantiomer (2S, 4R) - 1 from (1S, 3R) - 9, compound (2R, 4S) - 1 was prepared from (1R, 3S) - 9 (100 mg, 0.328 mmol); the product (61 mg, 70%) had M.p. 118.3 - 120.1°C; { lit.⁸ 121°C }; $[\alpha]_{\text{D}}^{20} + 41.0^\circ$ (c 0.35, MeOH); { lit.⁸: $[\alpha]_{\text{D}}^{20} + 47.9^\circ$ (c 0.52, MeOH) }. The spectral data were identical with those of (2S, 4R) - 1.

N-(1', 2' - diphenyl - 1' -hydroxy) - 1 - furfuryl - 3 - ene - butylamine 11

To a solution of CeCl_3 (1.77g, 7.17 mmol) in 10 ml of THF was added allylic magnesium bromide (0.020 mmol) at 0°C. After being stirred for 4h, 10 (2.086g, 7.17 mmol) was added. The reaction mixture was stirred for an additional hour at 0°C, then warmed to r.t. and stirred for 10 h, then 10 ml of saturated aqueous NH_4Cl was added. Worked up as usual way to give an oil which was purified by flash column

chromatography on silica gel [petroleum ether-ethyl acetate (90 : 10)] to afford a solid **11** (1.97 g, 82%). $[\alpha]_D^{20}$ - 46.2° (c 0.8, EtOH); M.p. 78 - 80°C; $^1\text{H-NMR}$ $\delta(\text{ppm})$: 2.47 (*dd*, 2H, $J = 6.6, 6.9$ Hz), 3.77 (*m*, 1H), 3.91 (*d*, 1H, $J = 5.2$ Hz), 4.89 (*d*, 1H, $J = 5.2$ Hz), 5.04 (*m*, 2H), 5.56-5.67 (*m*, 1H), 6.07 (*d*, 1H, $J = 3.0$ Hz, furyl), 6.24 (*dd*, 1H, $J = 1.8, 3.0$ Hz, furyl), 7.02 - 7.12 (*m*, 3H, furyl, Ph), 7.16-7.27 (*m*, 8H, Ph). MS(*m/e*): 334 ($\text{M}^+ + 1$), 292 ($\text{M}^+ - \text{Allyl}$). HRMS for ($\text{C}_{22}\text{H}_{24}\text{O}_2\text{N}$) Calc.: 334.1719; Found : 334.1763.

N - benzyloxycarbonyl -1-furfuryl-3-ene-butylamine-(S)-12:

To a solution of Pd/C (500 mg) in 300 ml of 4.4% formic acid in methanol was added **11** (1.0 g, 3.0 mmol) at r.t.. The reaction mixture was stirred for 4 h. After being filtrated off the solid, the mixture was concentrated and the residue was dissolved in 50 ml of acetyl acetate. The solution was washed with NaHCO_3 saturated aqueous and the organic layer was dried over Na_2SO_4 , and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90 : 10) to (30 : 70)] to afford an oil. The oil was dissolved in 10 ml of acetyl acetate and 3 ml of saturated aqueous Na_2CO_3 at 0°C, then benzyloxycarbonyl chloride (0.5 ml) was added. The reaction mixture was stirred for 2 h at 0°C. Worked up as usual way to give an oil which was purified by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90 : 10)] to afford (S)-**12** (0.692 g, 85%). $[\alpha]_D^{20}$ - 3.2° (c 2.2, EtOH); M.p. 61 - 63°C; IR (ν_{max} , cm^{-1}): 3350 (N - H), 1720 (C = O, Cbz); $^1\text{H-NMR}$ $\delta(\text{ppm})$: 2.62 (*dd*, 2H, $J = 4.3, 6.8$ Hz), 5.10 (*m*, 2H, Bn), 5.30 (*m*, 2H), 5.69 (*m*, 1H), 6.18 (*d*, 1H, $J = 1.9$ Hz, furyl), 6.30 (*dd*, 1H, $J = 1.9, 3.2$ Hz, furyl), 7.26 - 7.38 (*m*, 6H, furyl, Ph). MS(*m/e*): 230 ($\text{M}^+ - \text{allyl}$), 136 ($\text{M}^+ - \text{Cbz}$). HRMS for ($\text{C}_{13}\text{H}_{12}\text{O}_3\text{N}$) Calc.: 230.0816; Found : 230.0817.

N - benzyloxycarbonyl - 1 - (1' - furfuryl) - 3, 4 - dihydroxy butyl amine -(1S, 3S)-9:

To a well stirred solution of $\text{K}_3\text{Fe}(\text{CN})_6$ (0.182 g, 0.55 mmol), K_2CO_3 (0.076 g, 0.55 mmol) and $(\text{DHQ})_2$ - PHAL (7 mg, 5% eq.) in 4 mL of $^t\text{BuOH} : \text{H}_2\text{O} = 1 : 1$ was added (S)-**12** (0.050 g, 0.184 mmol) and $\text{K}_2\text{OsO}_2(\text{OH})_4$ (4 mg, 5% eq.) at 0°C. After the reaction mixture was stirred for 12 h, Na_2SO_3 (0.3 g, 1.5 mmol) was added, the mixture was stirred for an additional hour at r.t.. The solution was concentrated under reduced pressure, and the residue was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with brine, dried (MgSO_4) and concentrated under reduced pressure to give an oil which was purified by flash column chromatography on silica gel [ether-dichloromethane (30 : 10)] to afford a solid (1S, 3S)-**9** (0.50 g, 89%). $[\alpha]_D^{20}$ - 9.8° (c 0.3, EtOH); M.p. 63 - 65°C; IR (ν_{max} , cm^{-1}): 3300 (N - H), (O - H); $^1\text{H-NMR}$ $\delta(\text{CDCl}_3)$: 1.76 - 1.92 (*m*, 2H, 2 - H), 3.47 (*m*, 2H), 3.79 (*m*, 1H), 5.10 - 5.14 (*m*, 2H, Bn, 1 - H), 5.40 (*d*, 1H, $J = 8.5$ Hz, N - H), 6.20 (*d*, 1H, $J = 1.9$ Hz, furyl), 6.31 (*dd*, 1H, $J = 1.9, 3.0$ Hz, furyl), 7.36 (*m*, 6H, Ph, Furryl); MS (*m/z*): 305 (M^+), 170 ($\text{M}^+ - \text{Cbz}$); HRMS for $\text{C}_8\text{H}_{12}\text{O}_3\text{N}$: Calc.: 170.0795; Found: 170.0773.

N - benzyloxycarbonyl - 4 - hydroxy - 2 - butyl amine lactone - (2S, 4S) - 1:

As described for the preparation of (2S, 4R) - 1 from (1S, 3R) - 9, this (2S, 4S) - 1 was prepared from (1S, 3S) - 9 (20 mg, 0.065 mmol); the product (12 mg, 74%) had M.p. 115 - 116 °C; {lit.⁸: M.p. 118 °C}; $[\alpha]_{\text{D}}^{20} + 6.3^{\circ}$ (c 0.7, MeOH), { lit.⁸: $[\alpha]_{\text{D}}^{20} + 6.6^{\circ}$ (c 0.24, MeOH)}; The spectral data were identical with those of (2S, 4S) - 1.

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