Tetrahedron Vol. 49, No. 13, pp. 2641-2654, 1993
Printed in Great Britain

0040-4020/93 $6 00+.00

An Efficient Preparation of Optically Active α-Furfuryl Amide by Kinetic Resolution Using the Modified Sharpless Asymmetric Epoxidation Reagents

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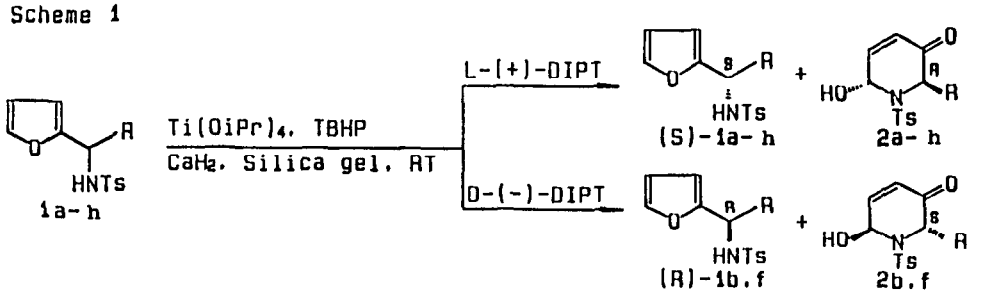
(*Received in China* 12 *October* 1992)

Abstract: Kinetic resolution of α-furfuryl amide was first carried out by using the modified Sharpless asymmetric epoxidation reagent to give the slow-reacting enantiomers, (S)-$\mathbf{1}_{a-h}$ and (R)-$\mathbf{1}_{b,f}$ in high enantioselectivity(90-100% e.e) and high chemical yield (45-50%). Similar results were obtained from the fast-reacting enantiomers. This kinetic resolution exhibits the reversed enantioselectivity.

Kinetic resolution of secondary allylic alcohols by Sharpless asymmetric epoxidation using tert-butyl hydroperoxide (TBHP) in the presence of chiral titanium-tartrate catalyst[1], has been widely used in the synthesis of chiral natural products. This asymmetric epoxidaton reaction is applicable to the kinetic resolution of other substrates, such as β-hydroxyamines[2], β-hydroxy sulfides[3], α-acetylenic alcohols[3], α-furyl carbinol[4] and 2-thiophenyl carbinol[5], which afford a hydroxyl group for coordination to the metal centre and a proximate site capable of accepting an oxygen atom. On the basis of these studies, we started to investigate the possibility of the kinetic resolution of α-furfuryl amide **1a-h** using the modified Sharpless reagent[6]. These compounds are characterized by the presence of a furyl group on the amino-bearing carbon atom and their opitically active form could be of interest to organic chemists.

Scheme 1

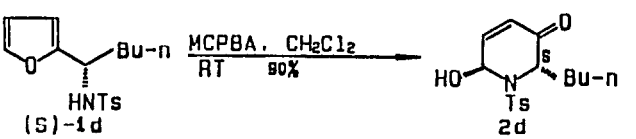


Herein we describe our finding that kinetic resolution of α-furfuryl amides proceeds highly efficiently, thus providing a general method for the synthesis of homochiral **1a-h** (Scheme 1)[7]. The results of the oxidation of **1**, in which substituent R is a primary, secondary alkyl group, or an olefinic group are summarized in Table 1.

The presence of tosyl substituent on the nitrogen atom could avoid the N-oxide formation[10]. It can be seen from Table 1 that kinetic resolution occurs in high enantioselectivity and high chemical yield. All the α-furfuryl amides show the following reactivity feature: When L-(+)-DIPT is used, the fast-reacting enantiomers are the one related to the R enantiomers of **1a-h**; when D-(-)-DIPT is used, the fast-reacting enantiomers are the S enantiomers of **1b,f**. This is just opposite to the empirical selectivity rule given by Sharpless and his coworkers[1]. This reversed sense of enantioselection may be attributed to the steric hindrance of the bulky tosyl group on the nitrogen atom. An alternative explanation for the reversed sense of enantioselection is probably due to the different character of nitrogen atom from oxygen leading to a different coordination fashion of nitrogen to Ti(IV). In these reaction, when using 0.6 eq. of TBHP, no reaction was observed, whereas when the TBHP was increased to 2.0-2.5 eq., the reaction proceeded smoothly to about 50-55% conversion.

In all cases the oxidation products **2a-h** are readily separated by column chromatography on silica gel, since (S)- or (R)-**1** and **2** have quite different R value on silica gel. Compounds **2** can also be readily obtained from (S) or (R)-**1** by oxidation with mCPBA in high yield (Scheme 2). Thus, the present kinetic resolution reaction also serves as a very efficient method for the preparation of various optically active **2**, which are also recognized as important chiral building blocks.

Scheme 2



It is worthy to note that the kinetic resolution of the α-furfuryl amides **1g** and **1h** which have another site of accepting an oxygen atom, occurs in every case via oxidation of furan ring. Therefore the rate of oxiation of the furan ring is far faster than that of other site.

The starting racemic α-furfuryl amides **1a-h** could be readily prepared from the reaction of N-furfuryl-p-toluene sulfonylimine[11] with alkyllithium at -70 °C in 75-80% yield.

The furan ring can be converted into a carboxylic acid by ozonolysis[12] or oxidation using $RuCl_3/NaIO_4$[13].It is evident that the combination of the present kinetic resolution of α-furfuryl amides (Scheme 1) and oxidative cleavage of

Table 1 Results of Kinetic Resolution of 1 by Modified Sharpless Reagent[a]

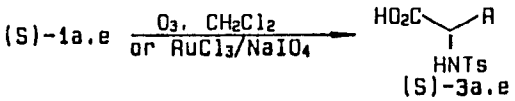
Substrate 1				Slow-reacting enantiomers			
	R	Ligand	Time(d)	Yield(%)[b]	[α]D[c]	e.e(%)[d]	ab.config.[e]
a	Me	L-(+)-DIPT	2	50	-7.0	90	S
b	Et	"	2	47	-5.0	93.3	S
c	Pr	"	2	45.7	-5.3	94.7	S
d	n-Bu	"	2	46	-5.0	90	S
e	i-Bu	"	2	46.5	-7.4	90.7	S
f	n-Hex	"	3	45	-4.3	100	S
g	Ally	"	3	44	-2.5	100	S
h	Vinyl	"	3.5	46.2	-3.3	95	S
b	Et	D-(-)-DIPT	3	50	+5.0	93.5	R
f	n-Hex	"	3.5	49.5	+4.5	99	R

Substrate 1				Fast reacting		enantiomers
	R	Ligand	Time(d)	Yield(%)	[α]D[c]	ab.config.[h]
a	Me	L-(+)-DIPT	2	41[f]	-1.4	2R,6R
b	Et	"	2	45	-3.1	2R,6R
c	Pr	"	2	47.4	-3.6	2R,6R
d	n-Bu	"	2	46	-1.8	2R,6R
e	i-Bu	"	2	43	-2.2	2R,6R
f	n-Hex	"	3	46	-2.4	2R,6R
g	Ally	"	3	35	-4.2	2R,6R
h	Vinyl	"	3.5	0[g]		
b	Et	D-(-)-DIPT	3	46	+1.7	2S,6S
f	n-Hex	"	3.5	48	+2.5	2S,6S

a.The reaction was carried out in CH_2Cl_2 using $Ti(OiPr)_4$ (1.0eq.), L-(+) or D-(-)-DIPT (1.2eq.), 5-10mol% of CaH_2, 10-15mol% of silica gel, and TBHP(2.5eq) at r.t.. b. Unless otherwise noted, isolated yield based on racemic 1 after chromatography on silica gel. c.Optical rotations were measured on Autopol spectrometer III automatic polarimeter.The solvent is ethanol and the conentration range is between 1 and 3. d. Determined by ^{1}HNMR analysis of the corresponding MTPA amides of α-furfuryl amines,which were obtained from the cleavage of tosyl group of 1 by using naphthyl sodium in DME at -78°C.[8] e. Absolute configuration was proved by correlaton of the products of oxidation of 1a,e by RuO_4 with the corresponding (S)-N-tosyl-α-amino acids[9](Scheme 3). f. The reaction was worked up without 1N NaOH,because on treatment with aqueous NaOH, 2a decomposed mostly into a highly water soluble and unidentified product. g.No 2h was obtained after treatment with 1N NaOH. h.It is worthy to note that the oxidation products of 2a-h are nearly the exclusive trans-2,6-disubstituted isomers(95%) from ^{1}H-NMR.

the furan ring (Scheme 3) provides a general and practical method for the synthesis of amino acids (Scheme 3).

Scheme 3



In summary, the present method for the preparation of chiral **1** and **2** is operationally simple and highly efficient and both of them can be used as chiral building blocks for the synthesis of natural products.

Experimental

Melting points were determined with a Buchi 535 melting point apparatus and were uncorrected. All reactions were carried out under dried nitrogen. 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(300mesh) which was produced by Qingdao Chemical Plant, China. IR spectra were measured on a Schimadzu IR 400 spectrometer. ^{1}H-NMR spectra were recorded on JEOL FX-90Q (90MHz), Varian-200 (200MHz), Am-400(400MHz) and AMX-600 (600MHz) with $CDCl_3$ as solvent and values were reported in ppm, using TMS or residual $CHCl_3$ as internal standard. MS spectra were conducted on a Finnigan 4021 GC-MS instrument and JMS-01U spectrometer. The optical rotations were measured on 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 atomosphere. 85% tert-Butyl hydroperoxide (TBHP) was obtained from Merk-Schuchardt Co., which was further purified according to the literature[1], calcium hydride was obtained from Fluka-Garantie Co..

Preparation of N-furfuryl-p-toluene sulfonylimine (4)

This preparation was carried out by using the reported procedure[11] with a slight modification. To a solution of 4.0 g of toluenesulfonylamine, 40 ml of dry benzene, and 4ml of freshly distilled tetrahydrofuran was added 4.0 ml of freshly distilled $SOCl_2$ at room temperature. It was refluxed for about 10 h until HCl gas was not escaped.The solvent was distilled under reduced pressure. The dark colored residue was washed several times with dried n-hexane, filtered under dried nitrogen atomosphere to afford 4 g of colourless solid N-sulfinyl-

p-toluenesulfonamine in 80% yield. 3.3 g of this compound was dissolved in 20ml of dried benzene and 5ml of dried tetrahydrofuran with refluxing. After addition of 1.3ml of furfural, the resulting mixture was refluxing for 8 hr. The solvent was removed under reduced pressure to afford 3.7g of crude product **4** in 97.4% yield, which could be used for next experiment without further purification. A pure sample was obtained by recrystallization from petroleum ether-ethyl acetate. mp. 96.2-98.8°C (Lit.[11] mp.100-102°C).

General procedure for the preparation of racemic N-tosyl-α'-alkyl-α-furfuryl amines 1a-h.

The preparation of N-tosyl-α'-n-butyl-α-furfuryl amide (**1d**) is described as an illustrative case. To a solution of 2.5g (0.01mmol) of **4** in 20 ml of freshly distilled tetrahydrofuran was slowly added 19ml(1.0M) of butyllithium at -50°C. The reaction mixture was stirred at the same temperature for 30min., then added 5ml of saturated aq.NH_4Cl. The resulting mixture was filtered throngh a pad of silica gel. The filtrate was concentrated to give an oil, which after purification by flash column chromatography on silica gel[petroleum ether-ethyl acetate (90:10) as eluent], afforded crystalline **1d** (2.4 g, 80% yield) mp. 64.5-65.5°C IR(film): 3290 (N-H)cm^{-1}; ^{1}H-NMR: 7.60(d,2H,J=8.2), 7.18(d,2H,J=8.2), 7.14 (d,1H,J=1.8), 6.11(dd,1H,J=1.8,J'=3.0), 5.88(d,1H,J=3.0),4 .74(m,1H),4.40(m,1H, J=7.2), 2.38(s,3H), 1.76(m,2H,J=7.0), 1.24(m,4H), 0.84(t,3H,J=7.0); MS m/z: 307 (M+), 250(M+-C_4H_9), 155(Ts+), 109(M+-Ts-C_3H_7), 91(C_6H_5-CH_3+); Anal. Calcd. for $C_{16}H_{21}NSO_3$: C, 62.51%, H, 6.89%, N, 4.55%; Found: C, 62.60%, H, 7.18%, N, 4.21%

N-tosyl-α'-methyl-α-furfuryl amine (**1a**)

The preparation of **1a** was carried out according to genereal procedure by using 10ml of CH_3MgI(1.2M,12mmol) and 1.3g of **4**(5.2mmol) in 15ml of dry THF.The reaction mixture was stirred at -50 °C for 30min. followed by working up as described for **1d** to give **1a** in 90.6% yield. mp. 72-72.3°C. IR(film): 3290 (N-H), 2990, 2950, 1600, 1470cm^{-1}; ^{1}H-NMR: 7.69(d,2H,J=10), 7.22(d,2H,J=10.), 7.16(d,1H,J=1.8), 6.14(dd,1H,J=1.8,J'=3.3), 5.98(d,1H,J=3.3), 5.07(d,1H,J=8.0), 4.53(m,1H,J=8.0,J'=7.1), 2.40(s,3H), 1.42(d,3H,J=7.2); MS m/z: 265(M+), 250(M+ -CH_3), 198 (M+-furan), 110 (M+-Ts),95 (100%); Anal. Calcd.for $C_{13}H_{15}NSO_3$: C, 58.85%, H, 5.70%, N, 5.28%; Found: C, 58.60%, H,5.76%, N, 4.92%

N-tosyl-α'-Ethyl-α-furfuryl amine (**1b**)

The reaction was performed in this case at -70°C for 30min. on using 15ml (1.1M, 16.5mmol.) of Ethyl Lithium, 1.30g of **4** in 15ml of dried THF. Working up in the usual way, afforded 1.2g of crystals of **1b** in 86.3% yield. mp.93-93.5°C. IR(film): 3270(N-H), 1600(Ar), 1470(Ar); ^{1}H-NMR: 7.61(d, 2H, J=8.4), 7.18 (d,2H,J=8.4), 7.13(d,1H,J=1.8), 6.11(dd,1H,J=1.8,J'=3.3), 4.31(dd,1H,J=8.5,J'=

7.4), 2.38(s,3H), 1.83(m,2H,J=7.4,J'=7.3), 0.84(t,3H,J=7.3); MS m/z: 279(M+), 278(M+-1), 262(M++1-H_2O), 250(M+-C_2H_5), 212(M+-furan.), 155(Ts+), 124(M+-Ts), 109(base peak), 91(C_7H_7+); Anal. Calcd. for $C_{14}H_{16}NSO_3$: C, 60.19%,H, 6.13% N, 5.01%; Found: C, 59.89%, H, 5.99%, N, 4.76%

N-tosyl-α'-propyl-α-furfuryl amine (**1c**)

The prepration of **1c** was carried out by using 7ml of propyl lithium (1.6M, 11.2mmol), 0.85g of **4**(3.40mmol) in 15ml of dried THF. The reaction mixture was stirred at -75°C for 30min. to afford 0.80g of crystalline **1c** in 81.9% yield. m.p.: 94-95°C. IR(film): 3250(N-H), 2950, 2930, 2860, 1600, 1465cm^{-1}; ^{1}H-NMR ($CDCl_3$):7.64(d,2H,J=7.6), 7.21(d,2H,J=7.6), 7.15(d,1H,J=2.0), 6.12(dd,1H,J=2.0, J'=3.3), 5.90(d,1H,J=3.3), 4.76(m,1H), 4.40(q,1H,J=6.3,J'=7.20), 2.39(s,3H),0.7 -1.8(br,7H); MS m/z: 293(M+), 292(M+-1), 250(base peak, M+-C_3H_7), 226(M+-furan) 155(Ts+), 138(M+-Ts),123(M+-Ts-CH_3),109(M+-Ts-C_2H_5),91(C_7H_7+); Anal. Calcd. for $C_{15}H_{19}NSO_3$: C, 61.41%, H, 6.53%, N, 4.77%, Found: C, 61.58%, H, 6.55%, N, 4.64%

N-tosyl-α'-isobutyl-α-furfuryl amine (**1e**)

The preparation of **1e** was carried out by using 20ml (1.5M, 30mmol) of isobutyllithium and 2.5g(10mmol)of **4** in 20ml of dried THF. The reaction mixture was stirred at -60°C for 30min. to afford 2.3g of crystalline **1e** in 76% yield. m.p.: 83.2-83.7°C. IR(film): 3290(N-H), 2950, 2930, 2870, 1600, 1470, 1130 cm^{-1} ^{1}H-NMR: 7.60(d,2H,J=8.3), 7.20(d,2H,J=8.30), 7.18(d,1H,J=1.8),6.10(dd,1H,J=1.8, J'=3.6), 4.70(m,1H), 4.50(q,1H,J=7.2,J'=8.0), 2.38(q,1H,J=7.2, J'=8.0), 2.38(s, 3H), 1.60(dd, 2H, J=7.2, J'=3.3), 0.84 (d,6H); MS m/z: 307(M+), 306(M+-1), 250 (M+-C_4H_9,100%), 155(Ts+), 137(M+-CH_3-C_6H_4-SO_2NH), 240(M+-furan),109(M+-Ts-C_3H_7), 91(C_7H_7+); Anal. Calcd. for $C_{16}H_{21}NSO_3$: C, 62.51%, H, 6.89%,N, 4.56%, Found: C, 62.90%, H, 6.88%, N, 4.45%.

N-tosyl-α'-hexyl-α-furfuryl amine (**1f**)

The preparation of **1f** was carried out by using 20ml(1.5M,30mmol)of n-hexyllithium and 2.5g of **4** (10mmol) in 20ml of dried THF. The reaction mixture was stirred at -60°C for 30min. to furnish 2.8g of crstalline **1f** in 82.0% yield. mp: 65.4-65.9°C. ^{1}H-NMR: 7.60(d,2H,J=8.4), 7.18(d,2H,J=8.4), 7.13(d,1H, J=2), 6.10 (dd,1H,J=2.0,J'= 3.2), 5.88(d,1H,J=3.2), 4.74(br,1H), 4.38(t,J=7.6), 2.38(s,3H), 1.77-0.80(br,13H); MS m/z: 335(M+), 336(M++1), 250(M+-C_6H_{13}), 180(M+-Ts), 155 (Ts+), 91 (C_7H_7+,100%), 67 (C_4H_4O+); Anal. Calcd. for $C_{18}H_{25}NSO_3$: C, 64.45%, H, 7.51%, N, 4.17%; Found C, 64.40%, H, 7.56%, N, 3.76%

N-tosyl-α'-propylene-α-furfuryl amine (**1g**)

The preparation of **1g** was carried out by using 25ml(1.2M,30mmol)of propyl-

ene magnesium bromide and 2.5g(10mmol) of **4** in 20ml of dried THF. The reaction mixture was stirred at -50°C for 30min. Working up as usual afforded 2.4g of crystalline **1g** in 83% yield. m.p.: 86.6-88.6°C. IR(film): 3300 (NH) cm^{-1}; ^{1}H-NMR($CO(CD_3)_2$):7.63(d,2H,J=8.0), 7.32(d,2H,J=8.2), 7.28(d,1H,J=1.8), 6.20(dd, 1H,J=1.8,J'=3.2), 6.04(d,1H,J=3.2), 5.60(m,1H), 5.04(q,1H,J=3.3,J'=1.6), 4.95 (dd,1H,J=8.4,J'=1.6), 4.47(t,1H,J=7.4), 2.55(t,2H,J=8.0), 2.38(s,1H); MS m/z: 291 (M+), 250(M+-C_3H_5,100%), 224(M+-furan), 155(Ts+), 136(M+-Ts), 91(C_7H_7+); Anal. Calcd. for $C_{15}H_{17}NSO_3$: C, 61.83%, H, 5.88%, N, 4.81%; Found: C, 62.04%, H, 5.23%, N, 4.81%

N-tosyl-α'-vinyl-α-furfuryl amine (**1h**)

The preparation was carried out by using 20ml(1.0M, 20mmol) of vinyl lithium and 1.0g of **4** in 15ml of dried THF.The reaction mixture was stirred at -50°C for 30min. to give 0.97g of crystalline **1h** in 88.20% yield. mp: 77.9-78.9°C. ^{1}H-NMR: 7.66(d,2H,J=8.0), 7.22(d,2H,J=8.0), 7.26(s,1H), 6.18(s,1H), 6.04(d,1H, J=3.0), 5.90(m,1H), 5.21(d,J=4.2,1H), 5.15(s,1H), 5.03(d,1H,J=4.2), 2.40(s, 3H) MS m/z: 277(M+), 250(M+-C_2H_3), 155(Ts+), 122(M+-Ts), 91(C_7H_7+); Anal. Calcd.for $C_{14}H_{15}NSO_3$: C, 60.63%, H, 5.45%, N, 5.05%; Found: C, 60.62%, H, 5.29%, N,4.99%

General procedure for the kinetic resolution of 1a-h with a stoichiometric amount of Ti(OiPr)$_4$/L-DIPT in the presence of catalytic amount of calcium hydride and silica gel. The preparation of (S)-N-tosy-α'-n-butyl-α-furfuryl amine (**1d**)is deseribed as an illustrative case. To a solution of $Ti(OiPr)_4$ (0.98ml, 3.3 mmol) in CH_2Cl_2(10ml) was added L-(+)-DIPT(0.82 ml, 4.0mmol), 26mg of CaH_2, 40 mg of silica gel under N_2 at 0°C. After 10min, the (dl)-**1d**(1.0g, 3.3 mmol) was added, the raction mixture was stirred for further 10 min.. 0.98ml(8.1mmol) of anhydrous TBHP(8.3M) was then injected. After the raction mixture was stirred for 2 days at r.t., 10ml of 10% aqueous trataric acid solution was added at -20 °C. Vigorously stirring was continued at r.t. for 2 hr. until the aqueous layer became clear. The mixture was filtered off through a pad of celite.The filtrate was concentrated under reduced pressure to give a syrup, which dissolved in ether (20min) treated with NaOH(1N, 10ml) for 30min. at 0°C with vigorously stirring. The organic layer was washed with brine,dried($MgSO_4$) and concentrated under reduced pressure to give an oil, which was purified by using flash column chromotagraphy on silica gel [petroluem ether-ethyl acetate (90:10)] afforded (S)-**1d** (0.46g, 46%, 90%ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride). $[\alpha]_D^{20}$ -5.0°(c 0.83, EtOH). Spectra data (IR, ^{1}HNMR) are identical with those reported for the racemic compound. The above silical gel column was then washed with petroleum ether-ethyl acetate (80:20), working up

as usual to give the oxidation product N-tosyl-2R-n-butyl-6R-hydroxyl-Δ^4-piperidone-3 (**2d**)(0.46g,46%). mp: 84.5-86.2°C, $[\alpha]_D^{20}$ -1.80°(c 1.3, EtOH) IR(film): 3500(OH), 1700(CO) cm^{-1}; ^{1}H-NMR: 7.52(d, 2H, J=8.4), 7.19(d, 2H, J=8.4), 6.71(dd,1H, J=4.4, J'=10.8) , 5.82(d, 1H, J=10.8), 5.77(d, 1H, J=4.4), 4.21(t,1H,J=7.8), 2.32(s,3H), 0.8-1.4(br,9H); MS m/z: 290(M+-H_2O-CH_3), 276(M+-H_2O-C_2H_5), 171(M+-H_2O-C_7H_8-C_3H_7), 108(100%), 91(C_7H_7+); Anal. Calcd. for $C_{16}H_{21}NSO_4$: C, 59.42%, H,6.54%, N, 4.33%; Found: C, 59.27%, H, 6.52%, N, 4.09%

(S)-N-tosyl-α'-methyl-α-furfuryl amine (**1a**)and N-tosyl-2R-methyl-6R-hydroxyl-Δ^4-piperidone-3 (**2a**)

The kinetic resolution of racemic **1a** (573mg, 2.0mmol) was carried out by using 26mg of silica gel, 17mg of CaH_2, 7ml of CH_2Cl_2, 0.65 ml (2.0mmol) of $Ti(OiPr)_4$, 0.54ml (2.3mmol) of L-(+)-DIPT and 0.53ml (8.27M, 4.3mmol) of TBHP. The reaction mixture was stirred at r.t. for 2 days. Working up in the way as described for **1d**, except without treatment with 1N aq. NaOH solution. Purification with flash column chromatrgraphy on silica gel [petroleum ether-ethyl acetate (90:10) as eluent], afforded colourless crystalline (S)-**1a** (286mg, 50% yield, 90%ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride), $[\alpha]_D^{20}$ -7.02°(c 0.92, EtOH). Spectra data (IR, ^{1}H-NMR) are identical with those reproted for the racemic compound. The above silica gel column was then eluted with petroleum ether-ethyl acetate (80:20) to give the oxidation product **2a** (235 mg, 41%). IR:3450(O-H), 1690(CO), ^{1}H-NMR($CO(CD_3)_2$), 7.78(d, 2H, J=8.0), 7.40(d,2H,J=8.0), 7.10(dd,1H,J=10.2,J'=4.4), 6.13(d,1H,J=4.4), 5.91(d, 1H,J=10.2), 4.29(q,1H,J=7.4), 2.40(s,3H), 1.43(d,3H,J=7.4; MS m/z: 281(M+), 280(M+-1), 263(M+-H_2O), 171(M+-1-H_2O-C_7H_7), 107(M+-1-H_2O-Ts), 91(C_7H_7+,100%), 248(M+-H_2O-Me); Anal. Calcd. for $C_{13}H_{15}NSO_4$:C,55.50%, H,5.37%, N,4.98%, Found: C, 55.40%, H, 5.12%, N, 4.82%

(S)-N-tosyl-α'-ethyl-α-furfuryl amine (**1b**)and N-tosyl-2R-ethyl-6R-hydroxyl-Δ^4-piperidone-3 (**2b**)

The kinetic resolution of racemic **1b**(1.0g, 3.6mmol) was performed by using 28mg of CaH_2, 44 mg of silica gel, CH_2Cl_2(10ml) $Ti(OiPr)_4$(1.1ml, 3.7mmol), L-(+)-DIPT(0.90ml, 4.28mmol), and TBHP(1.1ml, 8.3M, 9.0mmol).The reaction mixture was stirred at r.t.for 2 days. Working up in the way as described for **1d**,followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90:10)], afforded colourless cyrstalline (S)-**1b** (0.47g, 47% yield, 93.3%ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride). $[\alpha]_D^{20}$ -5.0°(c 1.08,EtOH).Spectra data was identical with those reported for the race-

mic compound. The above silica gel column was then eluted with petroleum ether-ethyl acetate (80:20) to give the oxidation product **2b**(0.45g, 45% yield),$[\alpha]_D^{20}$ -3.07°(c 1.07, EtOH). IR(film): 3460(OH), 1700(CO)cm^{-1}; ^{1}H-NMR:7.6(d,2H,J=8.4), 7.3(d,2H,J=8.4), 6.8(dd,1H,J=4.4,J'=10.2), 5.92(d,1H,J=10.2), 5.84(d,1H,J=4.4), 4.50(s,1H), 4.18(m,1H), 2.40(s,3H), 0.9-1.4(5H,br); MS m/z:295(M+), 248(M+-H_2O-C_2H_5), 122(M+-H_2O-Ts), 123(100%), 107(M+-H_2O-Ts-CH_3), 91(C_7H_7+); Anal. Calcd. for $C_{14}H_{17}NSO_4$.1/2H_2O: C, 55.24%, H, 5.96%, N, 4.60%; Found: C,54.92%, H, 5.81%, N, 4.16%

(S)-N-tosyl-α'-propyl-α-furfuryl amine (**1c**)and N-tosyl-2R-propyl-6R-hydroxyl-Δ^4-piperidone-3 (**2c**)

The kinetic resolution of racemic **1c**(0.7g,2.4mmol)was carried out by using CaH_2(19mg) silica gel(29mg),$Ti(OiPr)_4$ (0.72ml,2.4mmol), L-(+)-DIPT (0.60ml, 2.9 mmol), CH_2Cl_2 (8ml), and TBHP (0.73ml, 8.3M, 6.0mmol). The reatcion mixture was stirred at r.t. for 2 days. Working up in the way as described for **1d**, following by flash column chromatography on silica gel [petroleum ether-ethyl acetate (90:10)], afforded colourless crystalline (S)-**1c** (0.32g, 45.7% yield, 94.7%ee determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride). $[\alpha]_D^{20}$ -5.3°(c 1.0,EtOH). Spectra data(IR,^{1}HNMR) are identical with those reported for the racemic compound. The silica gel column was then eluted with petroleum ether-ethyl acetate(80:20) give the oxidation product **2c** (0.33g, 47.4% yield), $[\alpha]_D^{20}$ -3.61°(c 1.4, EtOH). mp. 92.0-92.4°C. IR(film) max: 3450(OH), 1700(CO), cm^{-1}; ^{1}H-NMR: 7.6 (d,2H,J=8.4), 7.3 (d,2H,J=8.4), 6.2(dd,1H,J=4.4,J'=10.4), 5.92 (d,1H,J=10.4), 5.84(br,1H), 4.26(t,1H,7.8Hz), 2.40(s,3H),0.84-1.44(br,7H); MS m/z: 291 (M+-H_2O), 276(M+-H_2O-CH_3), 262(M+-H_2O-C_2H_5), 219(M++1-C_7H_7),155(Ts+), 136(M+-H_2O-Ts), 120(M+-1-H_2O-Ts-CH_3), 91(C_7H_7,100%)
Anal. Calcd. for $C_{15}H_{19}NSO_4$: C, 58.23%, H, 6.19%, N, 4.53%; Found: C, 58.78%, H, 6.72%, N, 4.22%;

(S)-N-tosyl-α'-isobutyl-α-furfuryl amine (**1e**) and N-tosyl-2R-isobutyl-6R-hydroxyl-Δ^4-piperidone-3 (**2e**)

The kinetic resolutin of racemic **1e**(1.0g,3.2mmol) was carried out by using CaH_2(26mg) silica gel(40mg), $Ti(OiPr)_4$(0.98ml,3.3mmol),CH_2Cl_2(10ml), L-(+)-DIPT (0.82ml, 4.0mmol) and TBHP (0.98ml,8.3M, 8.1mmol). The reaction mixture was stirred at r.t.for 2 days.Working up in the way as described for **1d**,followed by flash column chromatography on silica gel[petroleum ether-ethyl acetate(90:10)], afforded colourless crystalline (S)-**1e** (465mg, 46.5% yield, 90.7%ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride).$[\alpha]_D^{20}$ -7.4°(c 1.4, EtOH).Spectra data(IR,^{1}H-NMR) are identical with those reported for the racemic compound. The silica gel column was then eluted with petroleum ether-ethyl

acetate(80:20))to give the oxidation product **2e** (0.43g,43% yield). $[\alpha]_D^{20}$ -2.18° (c 1.4, EtOH). m.p.: 92.1-94°C. IR(film): 3500(OH), 1700(CO) cm^{-1}; ^{1}H-NMR: 7.61(d,2H,J=8.4), 7.28(d,2H,J=8.4), 6.76(dd,1H,J=4.3,J'=10.8), 5.93(br,1H),5.82 (br,1H), 4.44(t,1H,J=7.4), 2.40(s,3H), 0.8-1.4(br,9H); MS m/z: 305(M+-H_2O), 290(M+-H_2O-CH_3), 263(M++1-H_2O-C_3H_7), 199(M+-H_2O-C_7H_7-CH_3), 108(100%),91(C_7H_7+). Anal. Calcd. for $C_{16}H_{21}NSO_4$: C, 59.42%, H, 6.54%, N, 4.33%; Found: C, 59.15%, H, 6.40%, N, 4.24%

(S)-N-tosyl-α'-hexyl-α-furfuryl amine (**1f**) and N-tosyl-2R-hexyl-6R-hydorxyl-Δ^4-piperidone-3 (**2f**)

The kinetic resolution of racemic **1f** (1.0g,3.0mmol) was performed by using CaH_2(24mg) silica gel (36mg) ,Ti(OiPr)$_4$(0.90,3.0mmol), CH_2Cl_2(10ml),L-(+)-DIPT (0.75ml 3.7mmol), and TBHP(0.72ml, 8.3M, 5.96mmol). The reaction mixture was stirred at r.t.for 3 days. Working up in the way as described for **1d** followed by flash column chromatography on silica gel[petroleum ether-ethyl acetate(90:10)], afforded colourless crystalline (S)-**1f** (450mg, 45% yield, 100% ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride).$[\alpha]_D^{20}$ -4.3°(c 0.90, EtOH). Spectra data(IR,^{1}HNMR) are identical with those reported for the racemic compound. The silica gel column was then eluted with petroleum ether-ethyl acetate(80:20) to give the oxidation product **2f** (0.46g, 46% yield). $[\alpha]_D^{20}$ -2.4° (c 0.9, EtOH). IR(film): 3500(OH), 1700(CO) cm^{-1}; ^{1}H-NMR: 7.58(d, 2H, J=8.4), 7.25(d,2H,J=8.4), 6.75(dd,1H,J=4.2,J'=10.3), 5.90(br,1H),5.82(1d,1H,J=4.2), 4.3 (t,1H,J=7.8), 3.37(s,1H),2.39(s,3H),0.87-1.39(br,13H); MS m/z:290(M+-H_2O-C_3H_7), 276(M+-H_2O-C_4H_9), 262(M+-H_2O-C_7H_7-C_5H_{11}), 199(M+-H_2O-C_7H_7-CH_3),170(M+-H_2O-C_7H_7-C_6H_{13}), 178(M+-H_2O-Ts), 157(M+-H_2O-C_7H_7-C_6H_{13}), 108(100%), 91(C_7H_7+); Anal. Calcd. for $C_{16}H_{21}NSO_4$:C, 59.42%, H, 6.54%, N, 4.33%; Found:C, 59.15%, H, 6.40%, N, 4.24%

(S)-N-tosyl-α-propylene-α-furfuryl amine (**1g**) and N-tosyl-2R-propenyl-6R-hydroxyl-Δ^4-piperidone-3 (**2g**)

The kinetic resolution of racemic **1g** (1.0g, 3.0mmol) was performed by using CaH_2(19mg) silica gel(24mg), Ti(OiPr)$_4$(1.03,3.45mmol), CH_2Cl_2(10ml), L-(+)-DIPT (0.87ml 4.1mmol), and TBHP (1.0ml, 8.6M, 8.6mmol). The reaction mixture was stirred at r.t.for 3 days. Working up in the way as described for **1d**,followed by flash column chromatography on silica gel[petroleum ether-ethyl acetate(90:10)], afforded colourless crystalline (S)-**1f** (450mg,45% yield, 100% ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride). $[\alpha]_D^{20}$ -2.45°(c 3.0, EtOH). Spectra data(IR,^{1}HNMR) are identical with those reported for the racemic compound. The silica gel column was then eluted with petroleum ether-ethyl acetate (80:20) to give the oxidation product **2g**(0.35g, 35% yield). $[\alpha]_D^{20}$ -4.2°

(c 2.17, EtOAc). m.p.: 98.2-99°C. IR(film): 3495(OH), 1690(CO) cm^{-1}; ^{1}H-NMR: 7.60(d,2H,J=8.4), 7.27(d,2H,J=8.4), 6.80(dd,1H,J=10.2,J'=4.4), 5.94(s,1H), 5.91 (d,1H,J=10.2), 5.80(m,1H,J=10.4),5.16(m,2H,J=10.4),4.41(t,1H,J=7.2),2.70(m,2H), 2.40(s,3H); MS m/z: 307(M+), 290(M+-17), 266(M+-C_3H_5), 250(M+-1-C_3H_5-CH_3), 155 (Ts+), 91(100%,C_7H_7+); Anal. Calcd. for $C_{15}H_{17}NSO_4$:C, 58.61%, H, 5.57%, N, 4.55%; Found: C, 58.30%, H,4.94%, N, 4.36%

(S)-N-tosyl-α'-vinyl-α-furfuryl amine (**1h**)

The kinetic resolution of racemic **1h**(0.9g,3.25mmol) was performed by using CaH_2(26mg), silica gel(42mg), $Ti(OiPr)_4$(0.975ml,3.3mmol), CH_2Cl_2 (10ml), L-(+)-DIPT(0.82ml 3.9mmol), and TBHP(1.0ml, 8.6M, 8.6mmol). The reaction mixture was stirred at r.t.for 3.5 days. Working up in the way as described for **1d**, followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate(93:7)], afforded colourless crystalline (S)-**1h**(450mg, 46.2% yield, 95% ee, determined by ^{1}H-NMR analysis of the ester derived from MTPA chloride). $[\alpha]_D^{20}$ -3.3° (c 0.70, EtOH). Spectra data(IR, ^{1}HNMR) are identical with those reported for the racemic compound. In this case, no oxidation product was obtained during treatment with 1N NaOH solution in the working process.

(R)-N-tosyl-α'-ethyl-α-furfuryl amine (**1b**) and N-tosyl-2R-ethyl-6R-hydroxyl-Δ^4-piperidone-3 (**2b**)

The kinetic resolution of racemic **1b**(0.655 g, 2.3 mmol) was carried out by using CaH_2 (18 mg), silica gel (28 mg), CH_2Cl_2 (10 ml), D-(-)-DIPT (0.59 ml, 2.9 mmol), $Ti(O\text{-}i\text{-}Pr)_4$ (0.70 ml, 2.3 mmol) and TBHP (0.7 ml, 8.3 M, 5.8 mmol). The reaction mixture was stirred at r.t. for 3 days. Working up in the way as described for **1d**, followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate(90:10)], afforded colourless crystalline (R)-**1b**(0.33g, 50.3%, 93.5%ee), $[\alpha]_D^{24}$ +5.0°(c 0.8,EtOH). Spectra data (IR,^{1}HNMR) are identical with those reported for racemic compound. The silica gel column chromatography was then eluted with petroleum ether-ethyl acetate (80:20) to give the oxidation product **2b**(0.30g, 46%). $[\alpha]_D^{22}$ +1.74°(c 3.1, EtOAc); IR(film): 3500(OH), 1700(C=O)cm^{-1}; ^{1}H-NMR($CDCl_3$): 7.60(d,2H,J=8.4), 7.29(d,2H,J=8.4), 6.77(dd,1H,J=4.4,J=10.0), 5.92(d,1H,J=10.0), 5.80(d,1H,J=4.4), 4.50(s,1H), 4.24 (t,1H,J=7.8), 2.40(s,3H), 0.9-1.4(br,5H); MS m/z: 277 (M+-H_2O), 93 (M+-H_2O-Ts-C_2H_5), 91(C_7H_7+, 100%); Anal. Calcd. for $C_{14}H_{17}NSO_4$: C, 55.24%,H, 5.96%, N, 4.60%, Found: C, 54.92%, H, 5.84%, N,4.16%.

(R)-N-tosyl-α'-hexyl-α-furfuryl amine **1f**) and N-tosyl-2R-hexyl-6R-hydroxyl-Δ^4-piperidone-3 (**2f**)

The kinetic resolution of racemic **1f** (0.97g, 2.9 mmol) was carried out by using CaH_2 (23 mg), silica gel (35 mg), CH_2Cl_2 (10 ml), $Ti(O\text{-}i\text{-}Pr)_4$ (0.87 ml, 2.8 mmol), D-(-)-DIPT (0.73 ml, 3.6 mmol) and TBHP (0.87 ml, 8.3 M, 7.2 mmol). The reaction mixture was stirred for 3.5 days at r.t.. Working up in the way as described for **1d**, followed by flash column chromatography on silica gel [petroleum ether-ethyl acetate(90:10)], afforded a colourless crystalline (R)-**1f**(0.48 g, 49.5%, 99%ee). $[\alpha]_D^{24}$ +4.54°(c 5.5, EtOH), spectra data(IR, ^{1}H-NMR) are identical with those reported for racemic compound. The silica gel column was then eluted with petroleum ether-ethyl acetate (80:20) to give the oxidation product **2f** (0.47g, 48%), $[\alpha]_D^{10}$ +2.5°(c 1.2,EtOH). IR(film): 3500 (OH), 1700 (C=O); ^{1}H-NMR($CDCl_3$): 7.58(d,2H,J=8.4), 7.26(d,2H,J=8.4), 6.76(dd,1H,J=4.4,J=10.4), 5.92(d,1H,J=10.4), 5.80(d,1H,J=4.4), 4.29(t,1H,J=7.4), 2.40(s,3H),0.85-1.60(br, 13H); MS m/z: 290(M+-C_3H_7-H_2O), 276(M+-H_2O-C_4H_9), 263(M++1-H_2O-C_5H_{11}), 262(M+-C_5H_{11}-H_2O), 199(M+-H_2O-C_7H_7-C_3H_7), 178(M+-Ts-H_2O), 108(100%), 91(C_7H_7+).

Preparation and analysis of Mosher's ester

1. Removal of N-tosyl group: This reaction was carried out by using the reported procedure8 with a slight modification. To a solution of naphthalene (210mg, 1.64mmol) in 5ml of freshly distilled DME was added Na(37mg, 1.6mmol) at r.t. under nitrogen, stirring at the same temperature for 30min. The reaction was indicated by the green-dark colour, then added with **1d**(150mg, 0.49mmol) in 2ml of DME under -75°C. Stirred at -75°C at r.t. for several mins, the reaction time and temperature varies according to different substrates. After addition of 2.5ml of H_2O, working up as usual way afforded 74mg of yellowish oil(99.8%), which after chromatography could be used for the preparation of MTPA ester.

2. Preparation of MTPA amides of α-furfuryl amine: To a solution of 100ul of pyridine and 20mg of the purified oil in 1ml of CH_2Cl_2 in a 5ml of sharp-bottomed flask was added 1ml of the solution of (50mg/ml) of (R)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride(MTPA chloride). After standing at room temp. for 2 days, the reaction mixture was poured into water, the organic layer was washed successively with 5% HCl solution, 1M NaOH solution, water and brine.After being dried over anhydrous Na_2SO_4,the solvent was removed under reduced pressure. The crude product was purified on the preparative thin layer chromotography. The purified Mosher's ester was analysed on ^{1}H-NMR.

The synthesis of (2S,6S)-2d from (S)-1d

The synthesis of (2S,6S)-**2d** is described as an illustrative case. To a so-

lution of (S)-**1d** (50mg, 0.16mmol) in dry CH_2Cl_2(4ml) were added slowly mCPBA(37 mg,0.21mmol, the reaction was stirred at 30°C. After 30 min., saturated aqueous $NaHCO_3$ solution (10ml) was added, the organic layer was separated, and the aqueous layer was extracted with ether(2x10ml). The combined organic layers were dried($MgSO_4$) and concentrated to give a crude oil, which was purified by column chromatography on silica gel to afforded (2S,6S)-**2d** (39.5mg, 94.6%), spectra data(IR,^{1}H-NMR,MS) are identical with those for the (2R,6R)-**2d** .

The synthesis of (S)-N-tosyl-alanine (3a) from (S)-1a

To the solution of (S)-**1a** (260mg, 0.98 mmol) in 3ml of methanol was passed ozone at -75°C for 20 min. until a light blue colour appeared. N_2 was bubbled at -75°C for 5 min. to remove excess ozone. 2.0ml of Me_2S was added to the solution. After stirring at r.t. for 1 h, the solution was concentrated under reduced pressure, followed by purification with column chromatography on silica gel to afford (S)-**3a** (170mg, 78%). mp. 138.7-139.2°C, $[\alpha]_D^{22}$ -3.7°(c 2.5, EtOH). [Lit.[14] $[\alpha]_D^{25}$ -6.8°, (c 1.3, EtOH); mp.134-135°C]; MS m/z: 243 (M+) 198(M+-CO_2H), 155(Ts+), 91(C_7H_7+). Spectra data (NMR, IR and Ms) are identical with that of a sample derived from natural alanine.

The synthesis of (S)-N-toysl-leucine (3e) from (S)-1e

To a mixture of (S)-**1e** (150 mg, 0.49 mmol) dissolved in $CCl_4/CH_3CN/H_2O$ (2:2:3, 7 ml) was added $NaIO_4$ (0.80 g, 3.74 mmol) and $RuCl_3.3H_2O$ (3.5 mg,0.0134 mmol) at r.t. and the mixture was vigorously stirred for 1.5 h at r.t.. The precipitate was filtered off through a pad of silica gel, extracted with ethyl acetate (2X10 ml). The organic layer was dried ($MgSO_4$) and concentrated to give a crude oil, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate/methanol 70 : 30 : 1) to afford a crystalline **3e** (0.13 g, 93.3%), $[\alpha]_D^{25}$ +1.84°(c 1.2, EtOH). mp. 123-125°C. [Lit.[14] mp.124 °C, $[\alpha]_D^{25}$ +4.5°(c 9, EtOH)]; Spectra data (^{1}HNMR, IR and Ms) are identical with that of a sample derived from natural leucine.

Acknowledgement: This inverstigation was supported by the National Natural Science Foundation of China

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