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Synthesis of Optically Active α-Furfuryl Amine Derivatives and Application to the Asymmetric Syntheses

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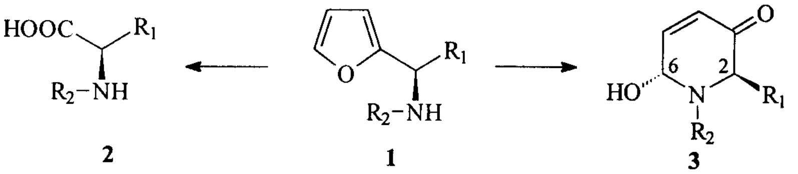
1. Introduction

Optically active α-furfuryl amine derivatives have aroused the interest of organic chemists in recent years, because they are very useful building blocks for the syntheses of a considerable number of nitrogen containing natural products, such as α- amino acids, β-lactams, indolizilines, quinolizidines and piperidine alkaloids.

It is well known that furan ring can be easily converted to a carboxylic acid (**1**→ **2** in Scheme 1) by ozonolysis[1] or oxidation with $RuCl_3/NaIO_4$.[2] The oxidation and subsequent rearrangement of furfuryl alcohols to dihydropyranones has been known for some time.[3] However, when this type of reaction was initially applied to α-furfuryl amine derivatives, only pyridine derivatives was obtained,[4] which limited the usefulness of this process to a considerable extent, because the chirality presented at the α-furfuryl amine derivatives was lost. Ciufolini reported in 1986 that α-furfuryl amine derivatives like furfuryl alcohols in oxidation could also be rearranged to dihydropyridone **3** by using aza-Achmatowicz reaction[5a] (i.e. using bromine in an alcohol solvent). In our research work,[6] we found that similar oxidation and rearrangement of α-furfuryl amine derivatives could be performed in the Lefebvre oxidation condition (i.e. with m-CPBA as an oxidant) to obtain dihydropyridone **3**.[5b]

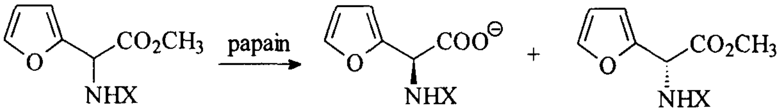


Scheme 1

In this review, we would like to describe the synthetic methods for preparation of α-furfuryl amine derivatives in optically pure forms and their applications to the synthesis of some nitrogen containing natural products and their analogues.

2. Synthesis of optically active α-furfuryl amine derivatives

Various racemic α-furfuryl amine derivatives have been prepared and used as starting materials or intermediates in synthesis.[7] One method commonly used to prepare this kind of α-furfuryl amine is the addition of organometallic reagents to imines.[7c] other methods include reduction of oximes[7e] and the Ben-Ishai reaction[8]. Although optically active α-(2-furyl)ethylamine was prepared *via* resolution of (±)-α-(2-furyl)ethylamine by using D-tartaric acid, reported by Terent'ev et al.[9] in 1964, and enantioselective hydrolysis of *N*-protected furylglycine methyl esters catalyzed by papain was successfully performed by Wong and Ciufolini[10] in 1988 (Scheme 2), there was no efficient and generally applicable method for preparation of optically active α-furfuryl amine derivatives until Zhou et al.[6] reported the kinetic resolution of racemic α-furfuryl amine derivatives using modified Sharpless epoxidation reagent.



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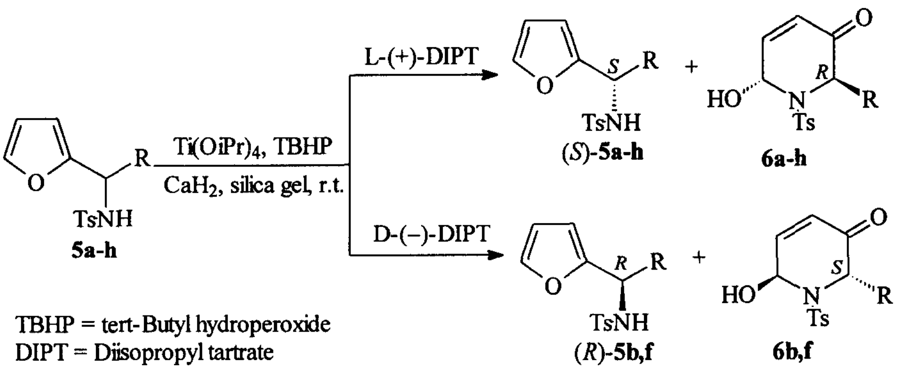
X		% conversion	%e.e. of ester
a C_6H_5CO-	20% MeOH	43	40
b C_2H_5OCO-	20% DMF	50	>97

Scheme 2

2.1 Kinetic resolution of racemic α-furfuryl amine derivatives

2.1.1 Using stoichiometric amount of modified Sharpless asymmetric epoxidation reagent

Although Sharpless asymmetric epoxidation reagent has been widely used for the kinetic resolution of compounds that bear an α-hydroxy group next to the double bond, such as secondary allylic alcohols,[11] β-hydroxyamines,[12] β-hydroxysulfides,[13] α-acetylenic alcohols,[13] α-furyl carbinol,[14] 2-thiophenyl carbinol[15] and α-pyrroyl carbinols,[16] this reaction has never been extended to the compounds bearing no hydroxy group. Several years ago, for the first time, Zhou et al.[6] applied the modified Sharpless asymmetric epoxidation reagent[17] to the kinetic resolution of α-furfuryl amine derivatives (Scheme 3).



Scheme 3

This kinetic resolution process occurred in high enantioselectivity and high chemical yield (Table 1). It provided a highly efficient and general method for synthesis of optically active α-furfuryl amine derivatives, as well as chiral dihydropyridone. The absolute configurations of optically active α-furfuryl amine derivatives were determined by circular dichroism[18] and chemical conversion.[6] It is interesting that the enantioselectivity of this reaction was opposite to that expected from the empirical rule reported by Sharpless et al,[11] i.e. the fast-reacting enantiomer was (*R*)-enantiomer when L-(+)-DIPT was used, whereas the (*S*)-enantiomer was fast reacting one when D-(–)-DIPT was used.

Table 1. Results of Kinetic Resolution of **5** by Modified Sharpless Reagent

				Slow-reacting enantiomer			
Substrate 5	R	Ligand	Time(d)	Yield(%)	$[\alpha]^{20}_D$	e.e.(%)	Ab. config
a	Me	L-(+)-DIPT	2	50	–7.0	90	*S*
b	Et	L-(+)-DIPT	2	47	–5.0	93	*S*
c	Pr	L-(+)-DIPT	2	46	–5.3	95	*S*
d	n-Bu	L-(+)-DIPT	2	46	–5.0	90	*S*
e	i-Bu	L-(+)-DIPT	2	47	–7.4	91	*S*
f	n-Hex	L-(+)-DIPT	3	45	–4.3	100	*S*
g	Allyl	L-(+)-DIPT	3	44	–2.5	100	*S*
h	Vinyl	L-(+)-DIPT	3.5	46	–3.3	95	*S*
b	Et	D-(–)-DIPT	3	50	+5.0	94	*R*
f	n-Hex	D-(–)-DIPT	3.5	50	+4.5	99	*R*

				Fast-reacting enantiomer		
Substrate **6**	R	Ligand	Time(d)	Yield(%)	$[\alpha]^{20}_D$	Ab. config.
a	Me	L-(+)-DIPT	2	41	−1.4	2*R*, 6*R*
b	Et	L-(+)-DIPT	2	45	−3.1	2*R*, 6*R*
c	Pr	L-(+)-DIPT	2	47	−3.6	2*R*, 6*R*
d	n-Bu	L-(+)-DIPT	2	46	−1.8	2*R*, 6*R*
e	i-Bu	L-(+)-DIPT	2	43	−2.2	2*R*, 6*R*
f	n-Hex	L-(+)-DIPT	3	46	−2.4	2*R*, 6*R*
g	Allyl	L-(+)-DIPT	3	35	−4.2	2*R*, 6*R*
h	Vinyl	L-(+)-DIPT	3.5	—	—	
b	Et	D-(−)-DIPT	3	46	+1.7	2*S*, 6*S*
f	n-Hex	D-(−)-DIPT	3.5	48	+2.5	2*S*, 6*S*

Table 2. Results of Kinetic Resolution of **5** by Catalytic Amount of Modified Sharpless Reagent

				Slow-reacting enantiomer				Fast-reacting enantiomer		
Entry	Substrate	Method[a]	Time(d)	Yield(%)	$[\alpha]^{20}_D$	e.e.	Config.	Yield(%)	$[\alpha]^{20}_D$	Config.
1	(±)-**5a**	A	1	47	−7.2	90	*S*	10	−1.2	2*R*,6*R*
		B	1	10	−7.7	100	*S*	8	−1.1	2*R*,6*R*
		C	2	0				0		
2	(±)-**5c**	A	1.5	45	−5.1	90	*S*	48	−3.0	2*R*,6*R*
		B	1	30	−6.2	100	*S*	65	−1.2	2*R*,6*R*
		C	2	0				0		
3	(±)-**5d**	A	1	47	−5.0	90	*S*	50	−2.1	2*R*,6*R*
		B	1	28	−5.1	100	*S*	67	−1.3	2*R*,6*R*
		C	2	0				0		
4	(±)-**5e**	A	1.5	49	−7.4	90	*S*	46	−1.8	2*R*,6*R*
		B	1	23	−7.5	100	*S*	73	−1.2	2*R*,6*R*
		C	2	0				0		

a. Method A: 10 mol% of $Ti(Oi\text{-}Pr)_4$, 12 mol% of L-(+)-DIPT, 4A MS (15-20 wt% based on substrate), 5-10 mol% CaH_2. Method B: 10 mol% of $Ti(Oi\text{-}Pr)_4$, 12 mol% of L-(+)-DIPT, 4Å MS (15-20 wt% based on substrate). Method C: 10 mol% of $Ti(Oi\text{-}Pr)_4$, 12 mol% of L-(+)-DIPT, 5-10 mol% CaH_2 and 5-10 mol% of silica gel.

2.1.2 Using catalytic amount of modified Sharpless epoxidation reagent

Kinetic resolution of racemic α-furfuryl amine derivatives can also be achieved by using the catalytic amount of modified Sharpless epoxidation reagent. This process, by employing 10 mol% of $Ti(Oi\text{-}Pr)_4$, 12 mol% of L-(+)-DIPT and 2.5 eq. of TBHP in the presence of molecular sieves and CaH_2 (Method A), at 20°C for 1-2 days to achieve 45-50% conversion as shown in Table 2, gave the slow-reacting products in high enantioselectivity (90% ee) and high chemical yield (45-49%). The fast-reacting products were also obtained in high chemical yield

(46-50%) with somewhat lower enantioselectivity (81-86% ee, based on comparison of the literature optical rotations[6]).[19]

2.1.3 Preparation of racemic α-furfuryl amine derivatives

The racemic α-furfuryl amine derivatives were prepared from p-toluenesulfonamide in two steps. The p-toluenesulfonamide was treated with $SOCl_2$ to give *N*-sulfinyl p-toluenesulfonamide, which was reacted with furaldehyde to form the furfuryl imine in 82% yield after column chromatography.[20,6b] Recently, we improved this method simply by heating the p- toluenesulfonamide with the furaldehyde diethyl acetal at 160°C to afford the furfuryl imine in 97%.[21] Reaction of the imine with organolithiums or Gringard reagents in THF at -78°C afforded the α-furfuryl amine derivatives. It is worth noting that when propylene magnesium bromide or vinyl lithium was reacted with the imines, the other functional group in the resulting α-furfuryl amine derivatives (**5g** and **5h**) was not sensitive to the kinetic resolution reagents. It made this method more useful for introduction of a wide range of substituents (R) in molecule **5** (Scheme 3).

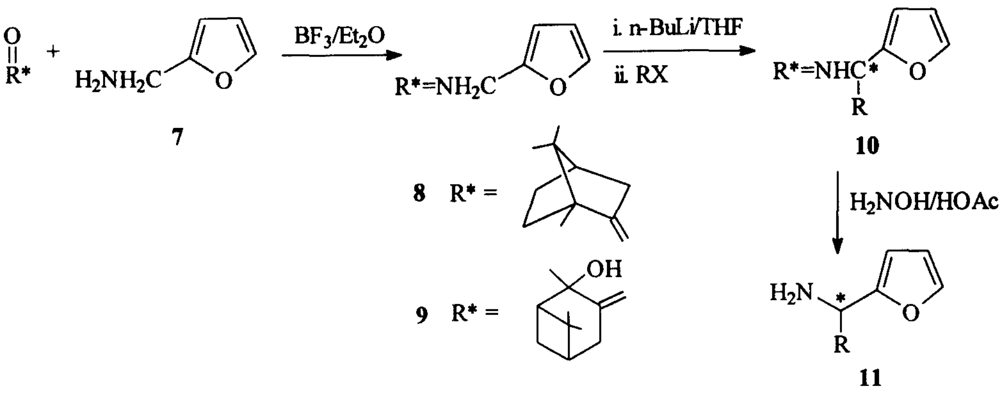
2.2 Asymmetric synthesis of α-furfuryl amine or its derivative from imines

Two methods have been reported for the asymmetric synthesis of α-furfuryl amine and its derivative. Both of them afforded the enantiomerically pure forms from the imines bearing a chiral auxiliary. They consisted of three steps, including preparation of optically active imines from the chiral auxiliary and furan derivatives, asymmetric introduction of alkyl groups into the chiral imines and final removal of the auxiliary.

2.2.1 Alkylation of chiral imines

Jiang[22,23] reported that optically active α-furfuryl amine derivatives could be synthesized *via* the alkylation of chiral imine **8** or **9**, which could be easily prepared by condensing of 2-furfuryl amine with the chiral auxiliary, (+)-camphor or (–)-2-hydroxypinan-3-one in the presence of a Lewis acid (Scheme 4).

Alkylation was carried out by treatment of chiral imine **8** or **9** with butyl lithium followed by alkylation. It showed that two chiral auxiliaries exhibited the same stereochemical effect, both of them gave enantioselective products with (*R*)-configuration. When (+)-camphor was used as the auxiliary,[22] the alkylation showed different enantioselectivity (5~67%) depending on the alkylation reagents (Table 3). However, in alkylation of the imine **9**, when (–)-2-hydroxypinnan-3-one was used as chiral auxiliary,[23] the reaction gave high enantioselectivity (91~98%) and moderate chemical yield (48~67%) (Table 4). It showed that (–)-2-hydroxypinnan-3-one is a more effective chiral auxiliary.



Scheme 4

Table 3. Results of Alkylation of **8** Using (+)-Camphor as the Auxiliary

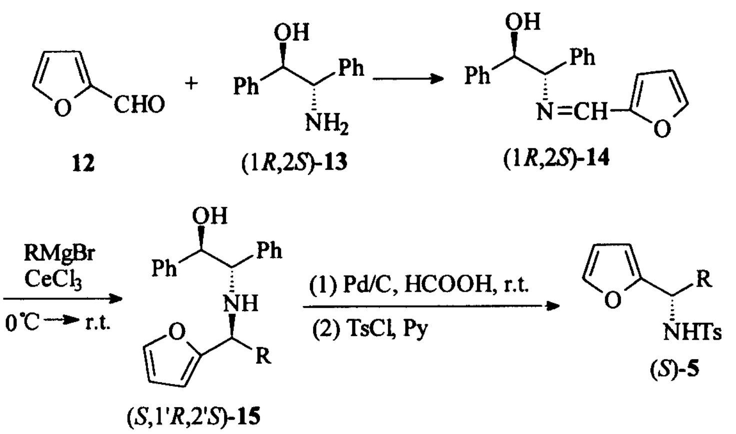
R	Product	Yield (%)	d.e. (%)	ab. config.
a CH_3	**10a**	67	5	*R*
b CH_2=$CHCH_2$	**10b**	80	33	*R*
c $(CH_3)_2CH$	**10c**	77	63	*R*
d $C_6H_5CH_2$	**10d**	90	60	*R*
e p-$CH_3C_6H_5CH_2$	**10e**	87	67	*R*

Table 4. Results of Alkylation of **9** Using (–)-2-Hydroxypinnan-3-one as the Auxiliary

R	Product	Yield (%)	e.e. (%)	ab. config.
a CH_3	**11a**	59	91.4	*R*
b CH_2=$CHCH_2$	**11b**	48	96.0	*R*
c $(CH_3)_2CH$	**11c**	52	92.5	*R*
d $C_6H_5CH_2$	**11d**	60	>98	*R*
e p-$CH_3C_6H_5CH_2$	**11e**	67	>98	*R*

2.2.2 Addition of organometallic reagents to the chiral imine

More recently Zhou[24] developed a method for the synthesis of optically active α-furfuryl amine derivatives *via* the addition of organometallic reagents to the chiral imine (1*R*,2*S*)-**14** or its enantiomer (1*S*,2*R*)-**14** derived from 2-furaldhyde (**12**) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1*R*,2*S*)-**13** or its enantiomer (1*R*,2*S*)-2-amino-1,2-diphenylethanol (1*S*,2*R*)-**13** (Scheme 5).



Scheme 5

The enantiomers, (1*R*,2*S*)-2-amino-1,2-diphenylethanol and (1*S*,2*R*)-2-amino-1,2-diphenylethanol exhibited the opposite stereochemical effects in the addition reaction (Scheme 5). Addition of organometallic reagents to the chiral imine (1*R*,2*S*)-**14** produced the (*S*)-α-furfuryl amine derivatives. Whereas, when (1*S*,2*R*)-2-amino-1,2-diphenylethanol was used as a ligand, the addition reaction gave the (*R*)-α-furfuryl amine derivatives. In all cases, the addition showed excellent enantioselectivity and high chemical yields (Table 5 and Table 6).

Table 5. Results of Addition of Organometallic Reagents to the Chiral Imine (1*S*,2*R*)-**14**

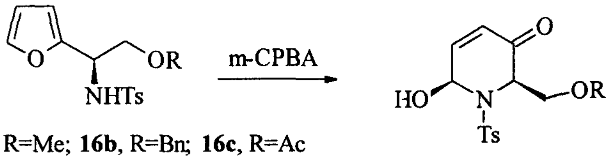
	R	Product	$[\alpha]^{20}_{D}$	Yield(%)	d.e.(%)	ab. config.
a	Et	(*R*,1'*S*,2'*R*)-**15a**	+71.6	79	94.2	*R*
b	n-Bu	(*R*,1'*S*,2'*R*)-**15b**	+49.6	75	96.3	*R*
c	c-Hex	(*R*,1'*S*,2'*R*)-**15c**	+48.3	77	98.5	*R*
d	Allyl	(*R*,1'*S*,2'R)-**15d**	+49.9	86	99.3	*R*

Table 6. Results of Addition of Organometallic Reagents to the Chiral Imine (1*R*,2*S*)-**14**

	R	Product	$[\alpha]^{20}_{D}$	Yield(%)	d.e.(%)	ab. config.
a	Et	(*S*,1'*R*,2'*S*)-**15a**	−65.2	91	92.4	*S*
b	n-Bu	(*S*,1'*R*,2'*S*)-**15b**	−51.1	85	97.8	*S*
c	c-Hex	(*S*,1'*R*,2'*S*)-**15c**	−55.6	69	98.7	*S*
d	Allil	(*S*,1'*R*,2'*S*)-**15d**	−46.2	83	99.6	*S*
e	n-Pent	(*S*,1'*R*,2'*S*)-**15e**	−43.0	87	98.5	*S*
f	n-Pr	(*S*,1'*R*,2'*S*)-**15f**	−56.7	80	83.9	*S*
g	n-Hex	(*S*,1'*R*,2'*S*)-**15g**	−83.0	83	97.8	*S*
h	Bn	(*S*,1'*R*,2'*S*)-**15h**	−78.4	78	99.5	*S*

2.3 Concise preparation of chiral hydroxymethyl-α-furfuryl amine derivative *via* the Sharpless asymmetric dihydroxylation

Chiral hydroxymethyl-α-furfuryl amine derivative **16** is a very useful building block for the synthesis of certain kind of natural piperidine alkaloids, because it is easily transformed into the dihydropyridone **17**[25] (Scheme 6). Zhou[26a,b,27] and Altenbach[26c] have applied this building block to the total synthesis of 1-deoxyazasugars and (+)-desoxoprosophylline.

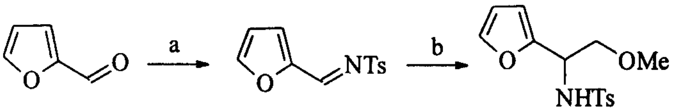


16a, R=Me; **16b**, R=Bn; **16c**, R=Ac
16

17

Scheme 6

Chiral **16a** was initially obtained from the kinetic resolution of racemic **16a**, which was prepared by addition of an organometallic reagent to α-furfuryl imine **18** (Scheme 7).[26a] As the yield of racemic **16a** was poor, it was difficult to obtain the chiral **16a** in a large quantity. Thus we developed the following method to synthesize chiral **16a** (Scheme 8).

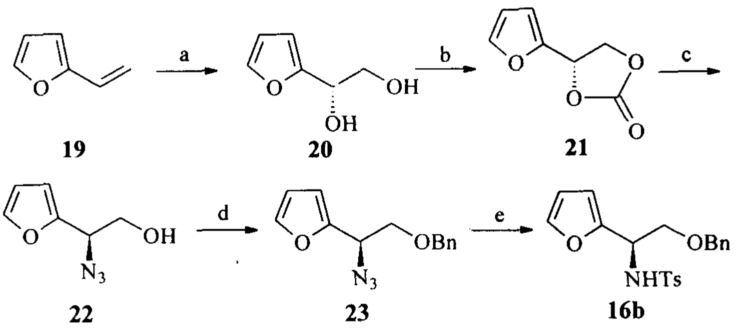


12 **18** **16a**

Scheme 7

Reagents and Conditions: a. i. $HC(OEt)_3$, Amberlite H^+, r.t., 4h; ii. $TsNH_2$, 150°C; b. $ClCH_2OCH_3$, LiBr, $SnCl_2$, BuLi, -78°C.

Starting from α-furyl ethylene **19**,[28] as depicted in Scheme 8, the chiral **16b** was synthesized in 5 steps in an overall yield of 58% employing Sharpless asymmetric dihydroxylation[29] as a key step. This concise method exhibited high chemical yield and high enantioselectivity on a multi-gram scale.[30]

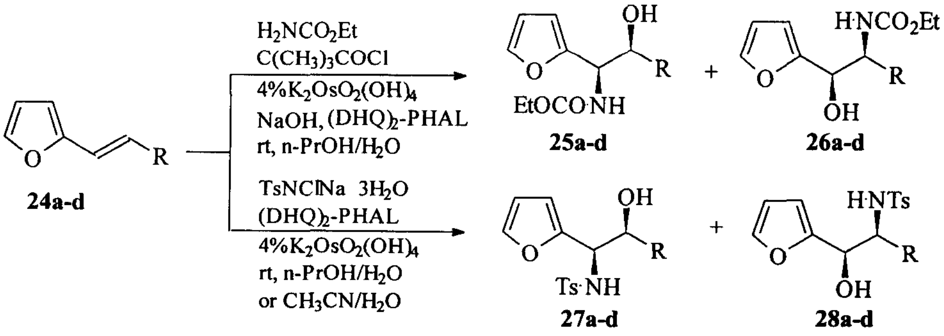


Scheme 8

Reagents and Conditions: a. $(DHQD)_2$-PHAL, $K_2OsO_2(OH)_4$, K_2CO_3, 0°C, 10h, 92%; b. $(MeO)_2CO$, KOH, 60→90°C, 94%, 92%e.e.; c. NaN_3, DMF, H_2O, 120°C, 10h, 91%, 91%e.e.; d. NaH, BnBr, 81%; e. i. $LiAlH_4$, THF, reflux; ii. TsCl, Py, 0°C, 91% in 2 steps, 94%e.e. (after recrystallization).

2.4 Preparation of chiral α-furfuryl amine derivatives *via* the asymmetric aminohydroxylation

Asymmetric aminohydroxylation (AA reaction), reported recently by Sharpless,[31] is a very useful method for introducing both amino and hydroxy groups directly to the olefins with high enantioselectivity. We envisioned that application of AA reaction to the α-furyl ethylene derivatives (**24a-d**) could produce the α-furfuryl amine derivatives (**25a-d** or **27a-d**), which might be the useful chiral building blocks for the synthesis of polyhydroxylated indolizidine alkaloids, such as castanospermine, which is a potent inhibitor of glycosidase and glycoprotein processing[32](Scheme 9).



a. $R=CH_2CH_2OBn$; b. R=H; c. $R=CH_2OBn$; d. $R=CO_2Me$

Scheme 9

Aminohydroxylations of **24a-24d** were carried out by using chloramine T (TsNClNa) or $EtO_2CNClNa$ as oxidant-nitrogen sources. As shown in Table 7, aminohydroxylations of α-furyl ethylene derivatives afforded relatively low yield and low regioselectivity, except aminohydroxylations of **27d** using chloramine T (TsNClNa). We found that in the presence of 1.5 eq. of K_2CO_3 the yield of aminohydroxylation of **27d** alone was improved, with high regioselectivity.[33] According to the recent work of Sharpless, the regioselectivity may be greatly increased by using *N*-bromoacetamide as an oxidant-nitrogen source.[31d]

Table 7. The Results of Asymmetric Aminohydroxylation of α-Furfuryl Ethene and its Derivatives

Substrate	Reagent	Time(h)	Product (conversion yield)		Regioselectivity
24a	$EtCO_2NClNa$	24	**25a**(37.7)	**26a**(27.7)	**25a**/**26a**=1.4/1
24b	$EtCO_2NClNa$	24	**25b**(26.7)	**26b**(56.7)	**25b**/**26b**=1/2.1
24c	$EtCO_2NClNa$	24	**25c**(34.0)	**26c**(20.9)	**25c**/**26c**=1.6/1
24d	$EtCO_2NClNa$	24	**25d**(36.2)	**26d**(20.3)	**25d**/**26d**=1.8/1
24b	TsNClNa	24	**27b**(17.5)	**28b**(31.2)	**27b**/**28b**=1/1.8
24c	TsNClNa	24	**27c**, **28c**(49.0)[a]		--
24d	TsNClNa	24	**27d**(40.1)		--

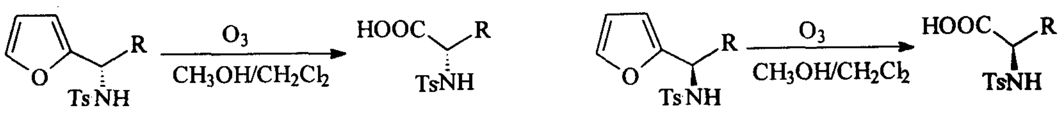
a. **27c** and **28c** could not be separated by column chromatography.

3. Synthetic applications

Optically active α-furfuryl amine derivatives can be applied directly to the synthesis of α-amino acids by oxidation of furan ring to carboxyl group **1**→**2** (Scheme 1). The more important application of these compounds is that they can be converted into the dihydropyridone derivatives **1**→**3** (Scheme 1) *via* the aza-Achmatowicz reaction or Lefebvre oxidation. Compound **3** can also be obtained directly from the kinetic resolution of α-furfuryl amine derivatives. Compound **3** is a versatile building block for the synthesis of nitrogen containing natural products, because it can serve as the substrate for the facile introduction of different functionality.

3.1 α-Amino acids

α-Amino acids exist abundantly in nature and they have been used as chiral building blocks for the synthesis of complex nitrogen containing molecules. Considerable efforts have been made to develop enantioselective syntheses of natural and unnatural α-amino acids.[34] Optically active α-furfuryl amine derivatives provide convenient precursors for the syntheses of α-amino acids in enantiomerically pure form. Zhou[35] has successfully synthesized several natural and unnatural α-amino acids *via* the oxidation of the furan ring in α-furfuryl amine derivatives (*S*)-**5a-e** and (*R*)-**5a-e**, the slow-reacting enantiomers from the kinetic resolution of (dl)-**5a-e** using the modified Sharpless asymmetric epoxidation reagent (Scheme 10). The results are shown in Table 8.



(*S*)-**5a-e** (*S*)-**29a-e** (*R*)-**5a-e** (*R*)-**29a-e**

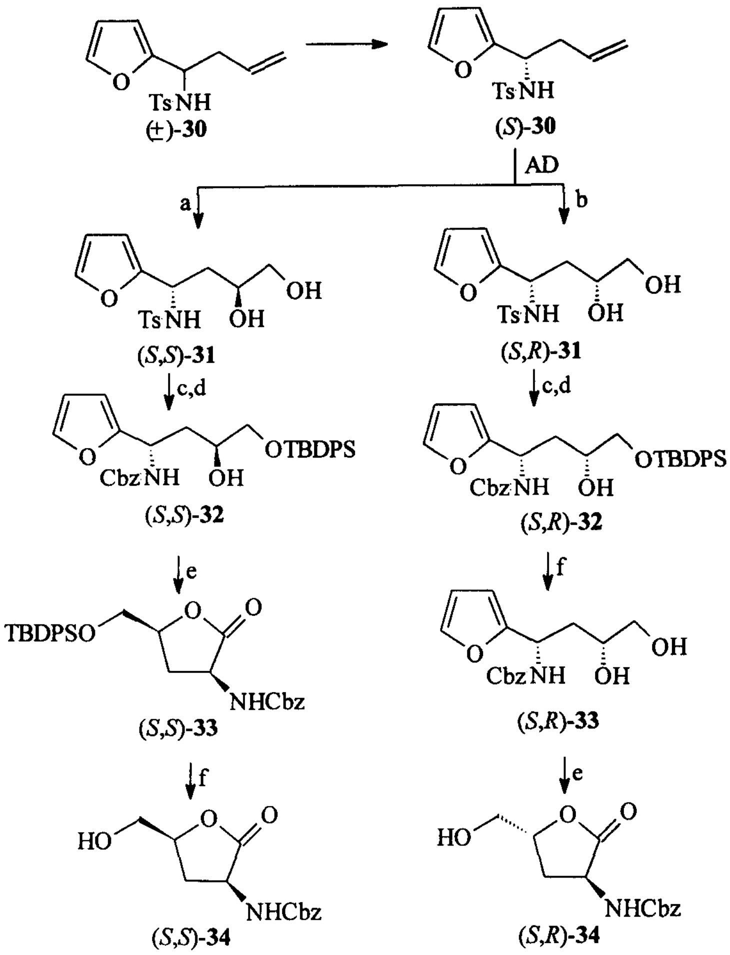
Scheme 10

Table 8. Conversion of α-Furfuryl Amine Derivatives (*S*)-**5a-e** and (*R*)-**5a-e** to α-Amino Acids (*S*)-**29a-e** and (*R*)-**29a-e**

	R	mp(°C)		Yield(%)		$[\alpha]_{20}^{D}$	
		(*S*)-**29**	(*R*)-**29**	(*S*)-**29**	(*R*)-**29**	(*S*)-**29**(solv.)	(*R*)-**29**(solv.)
a	CH_3	136-137	135-136	82	80	–5.9(EtOH)	+5.4(EtOH)
b	Pr	133-134.5	134-135.5	85	88	+18.3($CHCl_3$)	–20($CHCl_3$)
c	Bu	123-124.5	124-124.5	89	88	+25.0($CHCl_3$)	–28.0($CHCl_3$)
d	i-Bu	122-123	122-123.5	86	82	+3.7(EtOH)	–3.6(EtOH)
e	Ph	161-163	162-163.5	88	85	–2.3(Me_2CO)	+2.4(Me_2CO)

A more complex α-amino acid derivative, (2*S*,4*S*)-[(benzyloxycarbony) amino]-4-hydroxymethyl butyric acid γ-lactone (*S*,*S*)-**34**, which was a precursor[36a] used for synthesis of the antibiotic, clavalanine, and its three stereoisomers (*R*,*R*)-**34**, (*S*,*R*)-**34**, (*R*,*S*)-**34**, were synthesized from α-furfuryl amine derivative (*S*)-**30** and (*R*)-**30**, respectively (Scheme 11).[36b]

As outlined in Scheme 11, (*S*)-**30**, obtained from kinetic resolution,[6] was subjected to Sharpless asymmetric dihydroxylation[29] with $(DHQ)_2$-PYR or $(DHQD)_2$-PYR as the ligand to give (*S*,*S*)-**31** or (*S*,*R*)-**31**. Transformation of the furan ring into the carboxylic acid *via* ozonolysis in the presence of sodium hydrogen carbonate followed by deprotection with n-Bu_4NF afforded the target molecules (*S*,*S*)-**34**. When (*S*,*R*)-**32** was ozonized under the same condition as that of (*S*,*S*)-**32**, the protected δ-hydroxy-α-amino lactone (*S*,*R*)-**34** could not be detected. Since the two bulky protected groups in (*S*,*R*)-**32** are in a *trans* orientation during formation of the five-membered lactone ring, it is difficult to construct. Thus, (*S*,*R*)-**32** was selectively deprotected with n-Bu_4NF to yield (*S*,*R*)-**33**, which on ozonolysis, using the same condition as that of (*S*,*S*)-**32**, gave the (*S*,*R*)-**34**. Similarly γ-lactones (*R*,*R*)-**34** and (*R*,*S*)-**34** were prepared from (*R*)-**30**. The overall yield of (*S*,*S*)-**34**, (*S*,*R*)-**34**, (*R*,*R*)-**34** and (*R*,*S*)-**34** were 36%, 35%, 36% and 38%, respectively.



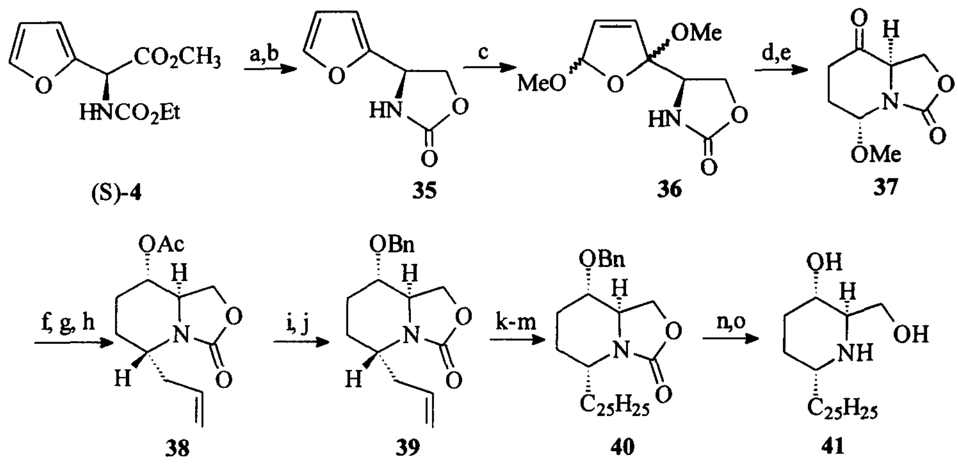
Scheme 11

Reagents and conditions: a. $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, $(DHQ)_2$-PYR, t-BuOH:H_2O=1:1, r.t., 1d, (95%); b. $K_2OsO_2(OH)_4$, K_2CO_3, $K_3Fe(CN)_6$, $(DHQD)_2$-PYR, t-BuOH:H_2O=1:1, r.t., 1d, (93%); c. i. TBDPSCl, imidazole, THF, r.t. (94% for (*S*,*S*)-**31**, 92% for (*S*,*R*)-**31**); d. Na/naphthalene, DME, -78°C; ii. CbzCl, Na_2CO_3 (aqueous), 0°C;(68% for (*S*,*S*)-**32**, 65% for (*S*,*R*)-**32**); e. O_3, CH_2Cl_2:MeOH=12.5:1, $NaHCO_3$, -78°C (66% for (*S*,*S*)-**33**, 68% for (*S*,*R*)-**33**); f. n-Bu_4NF, THF, r.t. (92%).

3.2 Polysubstituted piperidine alkaloids

3.2.1 (+)-Desoxoprospinine and (+)-Desoxoprosophylline

In 1986, Ciufolini[5] recognized that the aza-Achmatowicz reaction of α-furfuryl amine derivatives (**1**→**3** in Scheme 1) could be a practical route to indolizidines, quinolizidines and piperidines. In 1988, a practical procedure was reported for the preparation of optically active *N*-protected furylglycine derivatives *via* an enantioselective hydrolysis using the papain enzyme as a catalyst (Scheme 2).[10] The strategy was demonstrated through the total synthesis of (+)-desoxoprospinine, an alkaloid from *Prosopis africana Taub*[37] (Scheme 12).

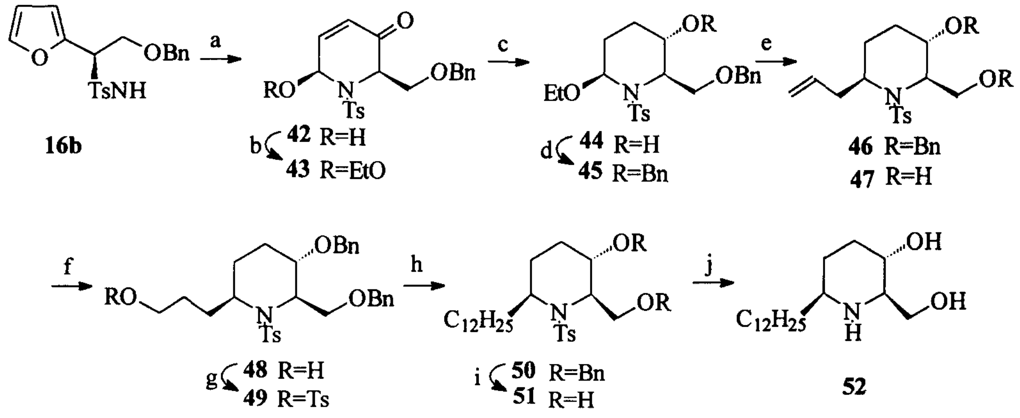


Scheme 12

Reagents and conditions: a. $LiAlH_4$, ether, -78°C (93%); b. NaH, THF, 25°C (83%); c. Br_2, MeOH, -40°C (96%); d. H_2, $Rh(Al_2O_3)$ (92%); e. 10 mol% TfOH, 2 mol of H_2O, THF, 25°C (77%); f. $NaBH_4$, EtOH, -60°C (90%); g. Ac_2O, pyridine (98%); h. $Me_3SiCH_2CH=CH_2$, $TiCl_4$, CH_2Cl_2, 25°C (88%); i. K_2CO_3, MeOH (98%); j. NaH, BnBr, THF (95%); k. O_3, CH_2Cl_2, MeOH, then Me_2S (90%); l. $n\text{-}C_9H_{18}CH=PPh_3$, THF, reflux (35%); m. H_2, Pd/C, 1000 psi (100%); n. aqueous NaOH, EtOH, reflux (97%); o. Li, liquid NH_3 (77%).

After conversion of (*S*)-4 into 35, the aza-Achmatowicz reaction[5] afforded 36. Hydrogenation and rearrangement gave 37, which was reduced with ethanolic $NaBH_4$ to produce the α-hydroxyl product and the OH-group was subsequently protected with acetic anhydride followed by Hart–Krans allylation with allyltrimethylsilane/$TiCl_4$ to produce α-allylated 38, a trans-2,6-dialkylpiperidine, as an exclusive product. Compound 39 was converted to (+)-desoxoprospinine (41) according to sequence of reactions outlined in Scheme 12.[38]

Zhou[27] recently used the α-furfuryl amine derivative 16b (Scheme 6) as a building block for the first synthesis of the polysubstituted piperidine, desoxoprosophylline (Scheme 13). Treatment of 16b with m-CPBA, afforded the dihydropyridone 42[25], whose hydroxyl group was protected to give 43. Reduction of 43 with sodium borohydride in methanol gave the α-hydroxyl product 44. The configuration at C_3 of 44 has been determined in previous reports.[30,39,40,41] The initial attempt to introduce the side chain at C_6 directly, by reaction of 45 with a Grignard reagent ($C_{12}H_{25}MgBr$), gave low stereoselectivity and yield. However, treatment of 45 with allyltrimethylsilane in the presence of 0.5 eq. of titanium tetrachloride at -75°C led to 46 exclusively. This reaction produced 47 as a major product in the presence of 1.0 eq. of titanium tetrachloride. The stereochemistry of the allyl group was assigned on the basis of comparison with the results obtained from allylation of related compounds.[39,40,42] Hydroboration of **46** with borane-methyl sulfide complex followed by protection of the hydroxyl group with tosylate produced **49**, which was reacted with Grignard reagent ($C_9H_{19}MgBr$) to afford **50**. Finally, deprotection of the hydroxyl group and amino group gave (+)-desoxoprosophylline (**52**).



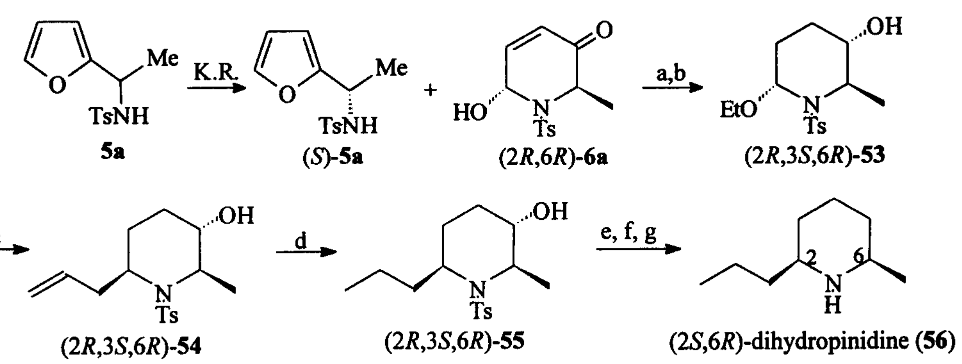
Scheme 13

Reagents and conditions: a. m-CPBA, CH_2Cl_2, r.t. (82%); b. $HC(OEt)_3$, $BF_3{\cdot}OEt_2$, 4Å molecular sieves, THF, 0°C (97%); c. $NaBH_4$, MeOH, 0°C (88%); d. BnBr, NaH, THF, r.t. (85%); e. allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, -78°C (67%); f. i. BH_3-SMe_2, THF; ii. NaOH, H_2O_2 (45%); g. Ts-Im, NaH, THF, 0°C (87%); h. $C_9H_{19}MgBr$, Li_2CuCl_4, THF, 0°C (68%); i. 10% Pd-C, H_2, EtOH (84%); j. Na/NH_3, -78°C (45%).

3.2.2 2,6-Dihydropinidine and (+)-azimic Acid

Piperidine alkaloids have been the subject of a number of synthetic studies during recent years, because of their important biological activity.[43,44] Optically active dihydropyridone derived from α-furfuryl amine derivative provided a good building block for asymmetric synthesis of this type of alkaloid. Zhou has utilized (2*R*,6*R*)-**6a** and (*S*)-**5a** as building blocks for the syntheses of 2,6-dihydropinidine[39] and (+)-azimic acid.[40]

The synthesis of (2*S*,6*R*)-dihydropinidine **56** is outlined in Scheme 14.[39] The dihydropyridone (2*R*,6*R*)-**6a** was converted to (2*R*,3*S*,6*R*)-**53**, which was allylated *via* *N*-sulfonyliminium ion to give the 2,6-*cis* isomer as the major product. Hydrogenation, Barton deoxygenation[45] and removal of the tosyl group yielded (2*S*,6*R*)-dihydropinidine **56** in an overall yield of (48%) in 7 steps.

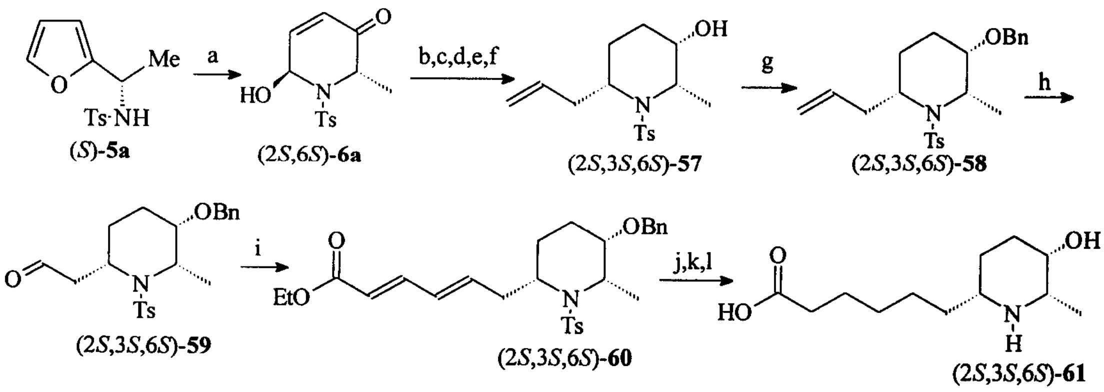


Scheme 14

Reagents and conditions: a. $HC(OEt)_3$, $BF_3{\cdot}Et_2O$ (100%); b. $NaBH_4$, MeOH (90%); c. $CH_2{=}CHCH_2SiMe_3$-$TiCl_4$ (79%); d. H_2, 10% Pd/C (100%); e. NaH, CS_2, MeI, imidazole, THF (86%); f. Bu_3SnH-AIBN, toluene (85%); g. Na/Nap., -78°C (92%).

An identical sequence was employed for the synthesis of unnatural dihydropinidine (2*R*,6*S*)-**56** from (*S*)-**5a**[39] *via* oxidation with m-CPBA.

For (+)-azimic acid, the α-furfuryl amine derivative (*S*)-**5a** was oxidized by m-CPBA to give the dihydropyridone (2*S*,6*S*)-**6a**, which was transformed into (2*S*,3*S*,6*S*)-**57**, in a similar way to the preparation of (2*R*,3*S*,6*R*)-**55**. Inversion of the configuration of the hydroxy group at C_3 by Mitsunobu reaction and ozonolysis of double bond in side chain afforded (2*S*,3*S*,6*S*)-**59**. Treatment of **59** with the arsonium ylide followed by hydrogenation and removal of the protection group yielded (+)-azimic acid (**61**) (Scheme 15).[40]

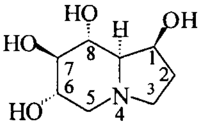


Scheme 15

Reagents and conditions: a. m-CPBA, CH_2Cl_2 (95%); b. $HC(OEt)_3$, $BF_3{\cdot}Et_2O$ (100%); c. $NaBH_4$, MeOH (89%); d. $CH_2{=}CHCH_2SiMe_3$-$TiCl_4$ (79%); e. DEAD, Ph_3P, benzoic acid, THF (88%); f. 3N NaOH in EtOH (98%); g. $C_6H_5CH_2Br$, NaH, Bu_4NI, THF (99%); h. O_3, CH_2Cl_2:MeOH(9:1) (90%); i. $Ph_3As{=}CHCHCO_2Et$, THF:EtOH:H_2O (4:5:1); j. 10% Pd/C, EtOH, H_2 (1 atm) (100%); k. 1N NaOH, EtOH (99%); l. Na/naphthalene, DME (85%).

3.3 Polyhydroxylated indolizidines

Polyhydroxylated indolizidine compounds such as castanospermine (**62**) and swainsonine (**63**) possess potent bioactivity as inhibitors of glucosidase and glycoprotein processing,[32] and also exhibit interesting anticancer, antiviral and immunoregulatory activities.[46] Consequently, much attention has been devoted to the synthesis of these alkaloids using carbohydrate starting materials.[47] Being interested in the asymmetric synthesis of polyhydroxylated indolizidines, Zhou has employed the dihydropyridone, the fast-reacting product of the kinetic resolution of α-furfuryl amine derivative, as a building block for the total synthesis of these alkaloids.



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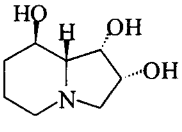

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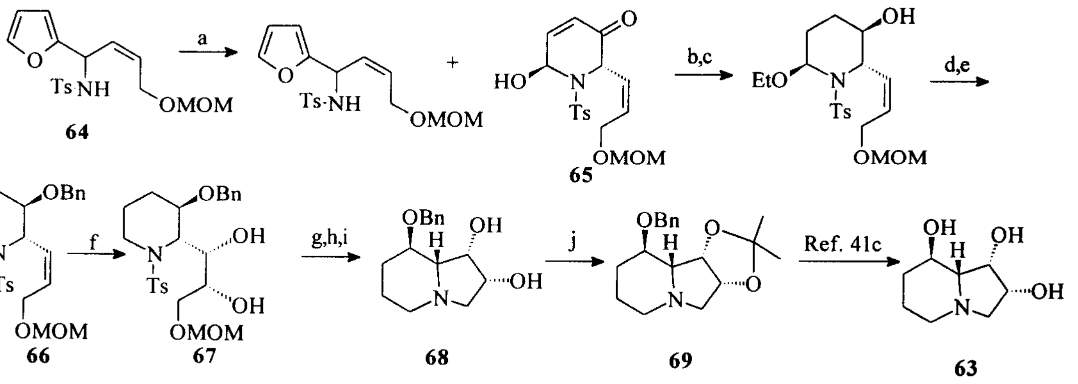
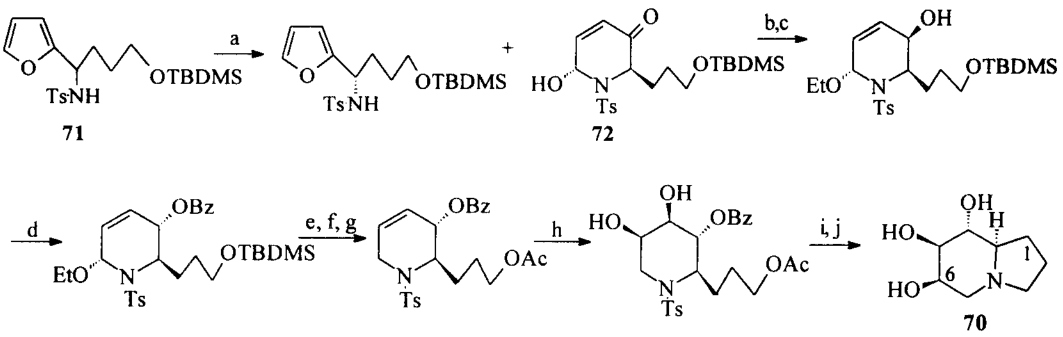
The synthesis of (–)-swainsonine (**63**) is depicted in Scheme 16.[41a,b] Kinetic resolution of **64** according to our reported procedure[6] yielded the dihydropyridone **65**. After protection of the existing hydroxy group and reduction of ketone with sodium borohydride in MeOH, the resulting hydroxyl group was protected with benzyl bromide the ethoxy group was removed to give **66**. While dihydroxylation or **66** with the standard Sharpless asymmetric reagent was unsuccessful,[11,48] it proceeded smoothly in an ultrasonic cleaner to form a separable mixture of desired diol **67** and its epimer in a ratio of 10:1. Removal of the MOM group, deprotection of the nitrogen and ring closure gave **68**, which was converted to **69**, an intermediate for the synthesis of swainsonine. Thus, the formal total synthesis of swainsonine (**63**) was completed.[41c]



Scheme 16

Reagents and conditions: a. Ti(Oi-Pr)$_4$, D-(–)-DIPT, TBHP, silica gel, CaH$_2$, 25°C, 2 days (42%); b. HC(OEt)$_3$, BF$_3$·Et$_2$O, 4Å MS, Et$_2$O, r.t. (92%); c. NaBH$_4$, MeOH, -40 to -30°C (88%); d. BnBr, NaH, Bu$_4$NI (cat), THF (96%); e. NaBH$_4$, HCO$_2$H, -5°C to 0°C (80%); f. OsO$_4$ (cat), NMO, DHQD-CLB, trace MeSO$_2$NH$_2$, acetone-H$_2$O, ultrasonication (73%); g. p-TsOH, t-BuOH, reflux (90%); h. Na/naphthalene, DME, -60°C; i. Ph$_3$P, CCl$_4$, Et$_3$N, DMF (50% two steps); j. MeC(OMe)$_2$Me, p-TsOH, CH$_2$Cl$_2$ (94%).

Recently Zhou et al.[49] have completed the asymmetric total synthesis of 1-deoxy-6-*epi*-castanospermine (**70**) from the dihydropyridone **72**, the fast-reaction product of kinetic resolution of α-furfuryl amine derivative **71**, *via* introduction of three hydroxy groups at C_6, C_7, C_8 and ring closure, after removal of the ethoxyl group at C_2 in the dihydropyridone ring, as outlined in Scheme 17.

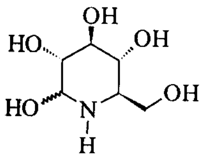


Scheme 17

Reagents and conditions: a. $Ti(Oi\text{-}Pr)_4$, L-(+)-DIPT, TBHP, silica gel, CaH_2, 25°C, 3 days (41%); b. $HC(OEt)_3$, $BF_3{\cdot}Et_2O$, 4Å MS, THF, 0°C (75%); c. $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, -30°C (90%); d. DEAD-TPP, $PhCO_2H$, THF, r.t. (72%); e. Bu_4NF, THF, r.t. (76%); f. Ac_2O, pyridine, DMAP, r.t. (95%); g. HCO_2H, $NaBH_4$, 0°C, (70%); h. DHQ-CBL, OsO_4, $K_3Fe(CN)_6$, K_2CO_3, t-BuOH, H_2O, r.t., 2 days (91%); i. Na/naphthalene, DME, -60°C; j. DEAD-TPP, pyridine (31%, i, j two steps).

3.4 Azasugars and 1-deoxyazasugars

Both azasugars and 1-deoxyazasugars are polyhydroxylated alkaloids. Naturally occurring azasugars and 1-deoxyazasugars such as nojirimycin (**73**), mannojirimycin (**74**), 1-deoxynojirimycin (**75**), and 1-deoxymannojirimycin (**76**) exhibit potent biological activity as glycosidase inhibitors.[50] The reported methods for the asymmetric synthesis of these alkaloids were mainly from carbohydrates and lack flexibility and general applicability.[50c,51] To develop a concise and flexible method for construction of this kind of alkaloids is important in order to probe their structure-activity relationships.



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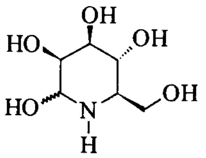

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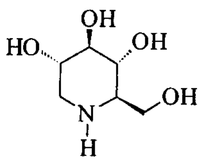

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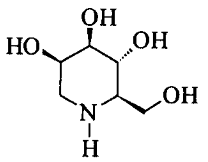

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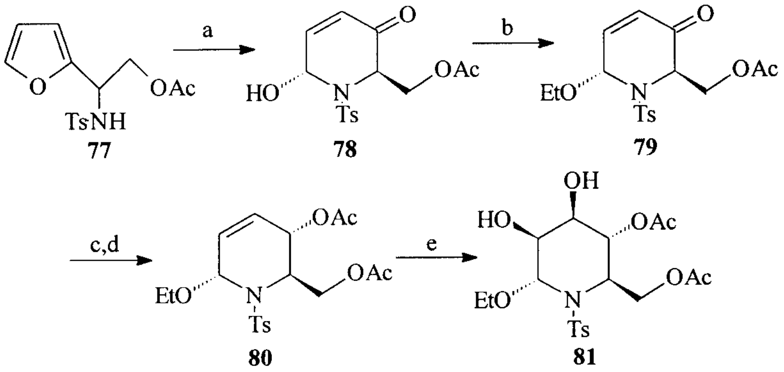
At almost the same time, Altenbach[26c] and Zhou[26a,b] recognized that the oxidation product of α-furfuryl amine derivative was a flexible building block for the synthesis of polyhydroxylated alkaloids. In Altenbach's report, they started from the (dl)-α-furfuryl amine derivative **77** and obtained the dihydropyridone **78** *via* oxidation with m-CPBA. The carbonyl group then was converted to the hydroxy group by Luche reduction,[52] followed by protection of the resulting alcohol to obtain **80**. Finally *cis*-dihydroxylation of **80** by employing the method of Shing et al.[53] led exclusively to the protected *rac*-mannojirimycin derivative **81** (Scheme 18).



Scheme 18

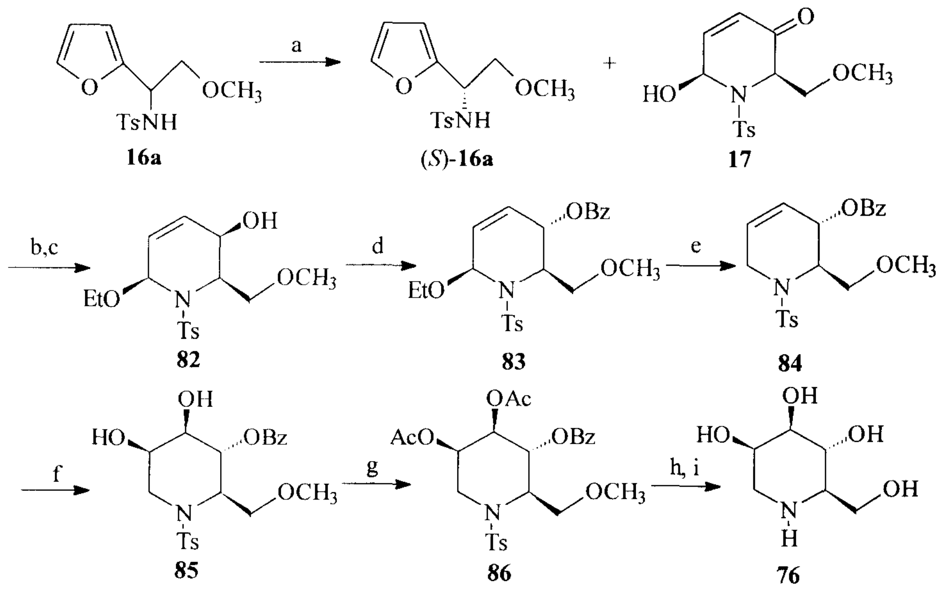
Reagents and conditions: a. *m*-CPBA, CH_2Cl_2, 30°C, 4.5 h (70%); b. EtOH, $Ce(NH_4)_2(NO_3)_6$, r.t. (95%); c. $NaBH_4$, $CeCl_3$, 0°C, 1 h (95%); d. DMAP, Ac_2O, CH_2Cl_2, NEt_3 (93%); e. $RuCl_3$, $NaIO_4$, CH_3CN, EtOAc, H_2O (3:3:1), 30 sec. (68%).

In Zhou's research,[26a,b] the starting material was the (dl)-α-furfuryl amine derivative (**16a**), which was prepared from α-furaldehyde in three steps in 40% overall yield. Kinetic resolution of **16a** by Zhou's method[6] yielded (*S*)-**16a** and **17**, the former could be converted to the enantiomer of **17** by treatment with m-CPBA. Both **17** and its enantiomer can be applied to the synthesis of polyhydroxylated alkaloids.

Zhou et al.[26a,b] employed the **17** as a building block for synthesis of (–)-1-deoxymannojirimycin (**76**). As depicted in Scheme 19, treatment of **17** with triethyl orthoformate followed by reduction with Luche reagent afforded solely the alcohol **82**, in which the configuration of hydroxy group was found to be opposite to that desired for the target molecule. Inversion of this configuration was successfully achieved by employing Mitsunobu reaction. Removal of ethoxy group of **83**, followed by Sharpless asymmetric dihydroxylation led exclusively to diol **85**, which was converted to diacetate **86**. Finally deprotection of **86** afforded (–)-1-deoxymannojirimycin (**76**) in 5.8% overall yield from the α-furfuryl amine derivative **16a**.

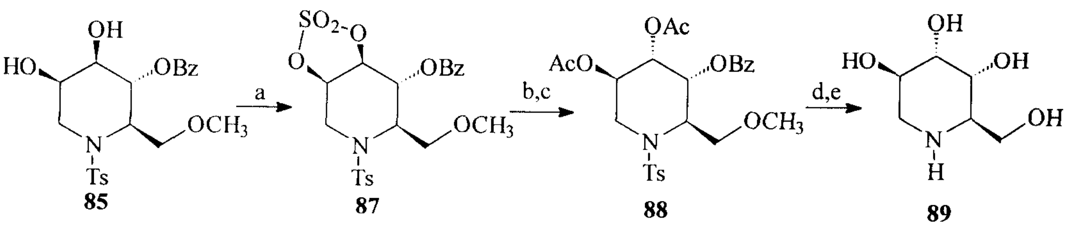
We attempted to synthesize (+)-1-deoxynojirimycin (**75**), for which **85** was used as the starting material as outlined in Scheme 20. compound **85** was first converted into the cyclic sulfate **87** by a reported procedure.[54] However, **87** failed to undergo ring opening when it was treated with ammonium benzoate. We found that treatment of **87** with 50% H_2SO_4 produced the diol, which was subsequently protected with Ac_2O to give the diacetate **88**. The configuration of **88** was determined by 2D-NOESY spectrum, from which it was concluded that the ring opening of the cyclic sulfate **87** was occurred at C_4 instead of at C_5 as expected. Removal of all protecting groups in **88** afforded (–)-1-deoxyaltronojirimycin (**89**), not (+)-1-deoxynojirimycin (**75**), in overall yield of 21.5%.[26] In the same way as the syntheses of (–)-1-deoxymannojirimycin (**76**) and (–)-1-

deoxyaltronojirimycin (**89**), (+)-1-deoxymannojirimycin and (+)-1-deoxyaltronojirimycin have been synthesized from dihydropyperidone **17** and its enantiomer.[26a,b]



Scheme 19

Reagents and conditions: a. a. Ti(Oi-Pr)$_4$, L-(+)-DIPT, TBHP, silica gel, CaH$_2$, 25°C, 3 days; b. HC(OEt)$_3$, BF$_3$·Et$_2$O, 4Å MS, THF, 0°C (77%); c. NaBH$_4$, CeCl$_3$·7H$_2$O, MeOH, -30°C, (72%); d. DEAD-TPP, PhCO$_2$H, THF, r.t. (92%); e. NaBH$_4$,, HCO$_2$H, 0°C, (87%); f. (DHQ)$_2$-PHAL, OsO$_4$, K$_3$Fe(CN)$_6$, K$_2$CO$_3$, t-BuOH, H$_2$O, r.t., 2 days (85%); g. Ac$_2$O, pyridine, DMAP, r.t. (100%); h. BBr$_3$, CH$_2$Cl$_2$, -78°C (72%) i. Na/naphthalene, DME, -60°C (51%).



Scheme 20

Reagents and conditons: a. i. SOCl$_2$, NEt$_3$, CCl$_4$; ii. NaIO$_4$, RuCl$_3$·3H$_2$O (73%); b. 50% H$_2$SO$_4$ (aq.), THF (77%); c. Ac$_2$O, pyridine, DMAP, r.t. (100%); d. BBr$_3$, CH$_2$Cl$_2$, -78°C (79%); e. Na/naphthalene, DME, -60°C (49%).

4. Conclusion

Chiral α-furfuryl amine derivatives are very useful in organic synthesis. They can be prepared by kinetic resolution using the modified Sharpless epoxidation reagent, or by asymmetric alkylation of the chiral imine, or by asymmetric addition of the organometallic reagents to the chiral imine. Furthermore the chiral hydroxy methyl α–furfuryl amine (Scheme 8) derivative and the chiral α–furfuryl amine derivatives (**25a-d, 27a-d**) could also be prepared by using the Sharpless asymmetric dihydroxylation and Sharpless asymmetric aminohydroxylation as key steps, respectively.

Dihydropyridone derivatives, which could be obtained directly from kinetic resolution of racernic α-furfuryl amine derivatives or prepared by oxidation of chiral α-furfuryl amine derivatives with m-CPBA, are versatile building blocks for the synthesis of numbers of alkaloids.

Both chiral α-furfuryl amine derivatives and dihydropyridone derivatives have been used for the synthesis of the natural and unnatural α-amino acids, δ-hydroxy-α-amino lactones, β-lactam antibiotic clavalanine, (2*R*,6*R*)-dihydropinidine and its enantiomers, (+)-azimic acid, swainsonine, 1-deoxy-6-*epi*-castanospermine, as well as 1-deoxymannojirimycin and 1-deoxyaltranojirimycin and their enantiomers. We believe that optically active α-furfuryl amine derivatives will attract more attention from organic chemists.

Acknowledgments:

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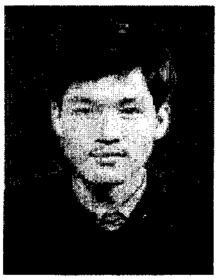
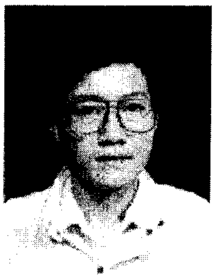
Biographical sketch

Wei-Shan Zhou

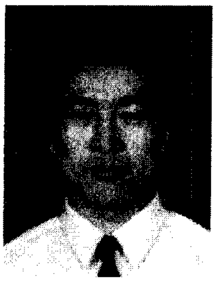


Zhi-Hui Lu

Yi-Ming Xu



Li-Xin Liao



Zhi-Min Wang

Wei-Shan Zhou was born in Shaoxing, Zhejiang in 1923, and received his Diploma of Pharmaceutical Chemistry from School of Pharmacy in National Medical College of Shanghai in 1949. He spent several years at the Pharmacy School of First Shanghai Medical College and Department of Chemistry of Academy of Military Medical Sciences. Then he removed to the Department of Natural Product Chemistry, Institute of Organic Chemistry, Chinese Academy of Sciences under the direction of the late Professor Huang Minlon in 1956. He was appointed associate professor and professor at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in 1960 and 1979, respectively. He was invited as Visiting Professor at the Centre of Neurochemistry, Laboratory of Chemistry of natural products, CNRS, 1984 in Strasbourg, France. In 1991, He was elected member of the Chinese Academy of Sciences. He was engaged in the research on the synthesis of steroids, terpenoids and asymmetric syntheses. For his contribution to chemistry, he has received numerous honors which include Chinese Academy Award, National Natural Science Award, National Invention Award, National Science and Technology Progress Award and Hong Kong Qui Shi Science and Technologies Foundation Award.

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