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Highly enantioselective reduction of symmetrical diacetylaromatics with baker's yeast

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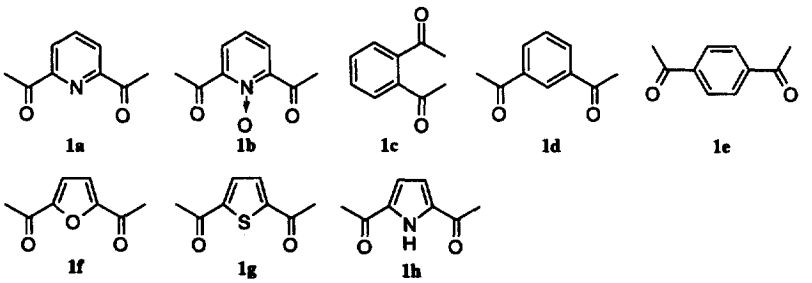
Abstract: Asymmetric reduction of symmetrical diacetylaromatics (**1a**, **1b**, and **1d–g**) with baker's yeast (*Saccharomyces cerevisiae*) provided the corresponding alcohols of high enantiomeric purity. By choosing appropriate reaction conditions, the products were preferentially the monoalcohols over the diols. © 1997 Elsevier Science Ltd

Introduction

Asymmetric reduction of ketones provides efficient access to the synthesis of optically active secondary alcohols which are versatile and convenient building blocks in the synthesis of biologically important compounds;[1] the area has been quite extensively investigated by using chemical and biological methods. Compared with the usual chemical methods[1c,2] such as chiral metal hydride reduction and chiral organoborane reduction, the advantages of biological methods are the milder reaction conditions and higher enantio- and chemoselectivity, especially in the reduction of saturated ketones. Among the microorganisms employed for this purpose, baker's yeast (*Saccharomyces cerevisiae*) is the most promising and popular, because it is inexpensive and its use does not require microbiological experience or special equipment.[3] Therefore the list of carbonyl compounds which can be enantioselectively reduced by baker's yeast is continuously growing. The baker's yeast reduction of monoacetylaromatics was previously reported by three groups,[4] but to our knowledge only one application of this reduction to symmetrical diacetylaromatics has been reported to date.[4c,5] This situation prompted us to investigate the baker's yeast reduction of these types of compounds. In this paper we report on the reduction of 2,6-diacetylpyridine **1a**, 2,6-diacetylpyridine 1-oxide **1b**, 1,2-diacetylbenzene **1c**, 1,3-diacetylbenzene **1d**, 1,4-diacetylbenzene **1e**, 2,5-diacetylfuran **1f**, 2,5-diacetylthiophene **1g**, and 2,5-diacetylpyrrole **1h** with baker's yeast, and the stereochemical outcome of this reaction.



Results and discussion

The substrates for reduction, **1a**, **1d**, and **1e** were commercially available, **1c**,[6] **1g**,[7] and **1h**[8] were prepared according to the procedures reported in literature, and the other substrates **1b** and **1f** were synthesized in good yields as shown in Schemes 1 and 2, respectively.

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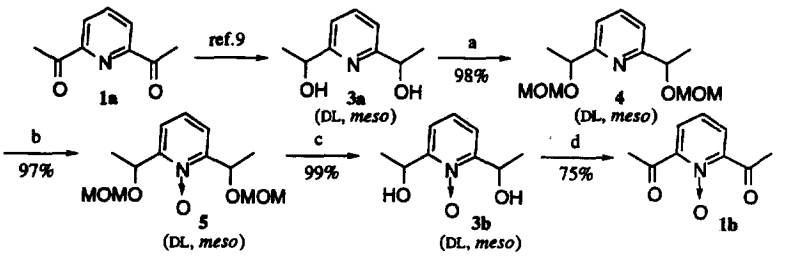
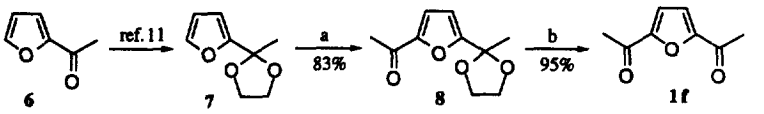


Reaction Conditions : (a) *i*-Pr_2NEt, MOMCl, $CHCl_3$, rt ; (b) PMA[10], CH_2Cl_2, rt ; (c) 5N-HCl, 50°C; (d) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -78°C.

Scheme 1.



Reaction Conditions : (a) *n*-BuLi, THF, -78°C then AcN(OMe)Me, 0°C; (b) AcOH, H_2O, 50°C.

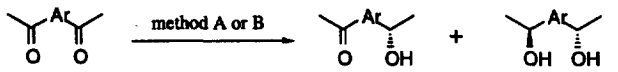
Scheme 2.

At first, reaction conditions were optimized by using **1a** as a substrate. When the baker's yeast reduction of **1a** was carried out by method A as depicted in the experimental section, the mono-reduced product **2a** was obtained exclusively in excellent yield with an enantiomeric purity of 95% ee. The doubly reduced product **3a** could not be detected in the reaction mixture. In order to obtain the diol **3a**, the monoalcohol **2a** was treated again under the same reaction conditions but no reaction took place. We then attempted an alternative procedure (method B) which was a modification of Bailey's one.[4c] The reduction using this method gave 28% (99% ee) of the diol **3a** along with 70% (99% ee) of **2a**. The enantiomeric purities of the reduction products **2a** and **3a** were determined by chiral HPLC analysis. The absolute configurations of **2a** and **3a** were assigned to *S* and *S,S*, respectively, by comparison of their specific rotations with the reported values.[4c] The results for other substrates **1b–h** are summarized in Table 1.

The reduction of **1a**, **1b** and **1d–g** proceeded successfully by using either method A or B, however the reduction of **1c** did not give any reduced product: it gave a purple complex mixture which was assumed to be formed by reaction with amino compounds contained in baker's yeast.[12] **1h** was reduced by method B to give a trace amount of monoalcohol **2h**, which was detected only by ^{1}H-NMR analysis. The determination of its stereochemistry was not attempted because the amount of the isolated **2h** was too small for the analysis. Different results were realized in the reduction of **1b**. It was successfully reduced by method A to give monoalcohol **2b** in 76% yield and diol **3b** in 10% yield. Moreover, this reduction using method B afforded considerable amount of diol **3b** (25%) along with **2b** (38%). The chiral HPLC analysis of **2b** and **3b** by methods A and B revealed that all of them were essentially enantiomerically pure (>99% ee). The absolute configurations of **2b** and **3b** were elucidated by the chemical transformations as shown in Schemes 3 and 4, respectively. Briefly, the hydroxy group of (−)-**2a** from baker's yeast reduction was protected as TBDPS ether to give **9** in 86% yield. The ketalization of the acetyl group of **9** followed by oxidation with permaleic acid(PMA)[10] afforded **11**, which was treated with 5 N HCl to give (+)-**2b**. By the comparison of the specific rotation of **2b** obtained by baker's yeast reduction (entry 3, 4), with that of (+)-**2b** (Scheme 3), the absolute configuration of **2b** from the present reduction was shown to be *S*. The stereochemistry of **3b** was ascertained to be *S,S*, since the specific rotations of **5** and **5′** which were independently prepared from (−)-**3a** and **3b** showed the same value (Scheme 4).

In contrast to **1a** and **1b**, the reduction of **1d–g** by method A proceeded incompletely to give low

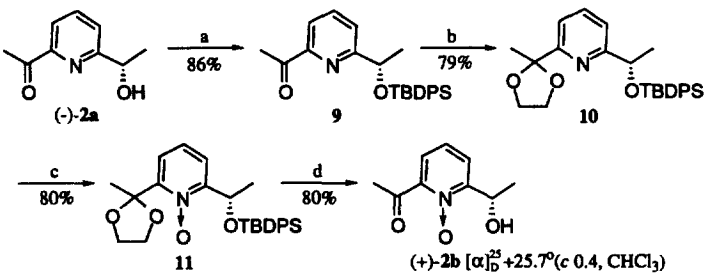
Table 1. Asymmetric reduction of diacetylaromatics with baker's yeast



1a-h **2a-h** **3a-h**

entry	substrate	method[a]	monoalcohol			diol		
			yield(%)[b]	ee(%)	config.	yield(%)[b]	ee(%)	config.
1	**1a**	A	91	95[c]	*S*	0		
2	**1a**	B	70	99[c]	*S*	28	99[c]	*S,S*
3	**1b**	A	76	>99[d]	*S*	10	>99[e]	*S,S*
4	**1b**	B	38	>99[d]	*S*	25	>99[e]	*S,S*
5	**1c**	A	0			0		
6	**1c**	B	0			0		
7	**1d**	A	12	85[c]	*S*	0		
8	**1d**	B	81	94[c]	*S*	2[g]	>99[d,i]	*S,S*
9	**1e**	A	24	98[c]	*S*	1	>99[d]	*S,S*
10	**1e**	B	86	98[c]	*S*	9[h]	>99[d,i]	*S,S*
11	**1f**	A	17	86[f]	*S*	0		
12	**1f**	B	73	84[f]	*S*	0		
13	**1g**	A	6	94[f]	*S*	0		
14	**1g**	B	76	95[f]	*S*	0		
15	**1h**	A	0			0		
16	**1h**	B	trace			0		

[a]See experimental section. [b]Isolated yield. [c]Determined by HPLC analysis using Daicel Chiralcel OB. [d]Determined by HPLC analysis using Daicel Chiralcel OD. [e]Determined by HPLC analysis using Daicel Chiralpak AD. [f]Determined by ^{1}H-NMR analysis of the corresponding (*R*)-MTPA ester. [g]Mixture of DL- and *meso*-compounds (94 : 6). [h]Mixture of DL- and *meso*-compounds (99 : 1). [i]Enantiomeric purity of DL- portion.

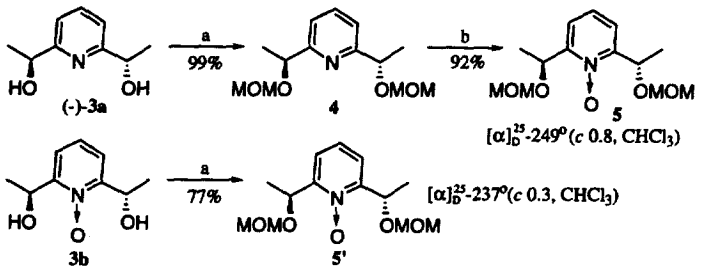


Reaction Conditions : (a) TBDPSCl, imidazole, DMF, rt ; (b) $(CH_2OH)_2$, $HC(OMe)_3$, TsOH, 70°C; (c) PMA, CH_2Cl_2, rt ; (d) 5N HCl, acetone, 70°C.

Scheme 3.

yields of the corresponding monoalcohols **2d–g**. But this reduction was influenced by the choice of reaction conditions. The reduction using method B provided monoalcohols **2d–g** selectively in good yields and in a highly enantioselective manner. The reduction of **1f** and **1g** exclusively gave the monoalcohols **2f** and **2g**, of which absolute configurations and enantiomeric purities were determined by ^{1}H-NMR analysis of the corresponding (*R*)-MTPA esters (Mosher's method).[13]

Moreover, the absolute configuration of **2f** was also confirmed by X-ray analysis of the (*R*)-MTPA ester (Figure 1). On the other hand, **1d** and **1e** were reduced by using method B to give **2d** and **2e** accompanied with diols **3d** and **3e**, which were contaminated with the *meso*-diols in the ratios as indicated in Table 1. The stereochemistry of **2d** was determined to be *S* by ^{1}H-NMR analysis of the corresponding (*R*)-MTPA ester, and that of **2e** to be *S* by the comparison of its specific rotation with that of (*R*)-**2e** reported in the literature.[14] The enantiomeric purities of **2d** and **2e** were revealed



Reaction Conditions : (a) *i*-Pr$_2$NEt, MOMCl, CH_2Cl_2, rt ; (b) PMA, CH_2Cl_2, rt.

Scheme 4.

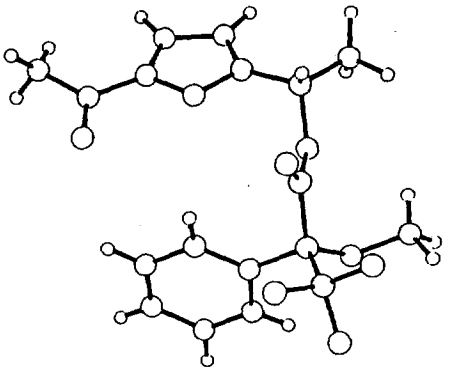


Figure 1. ORTEP drawing of (*R*)-MTPA ester of **2f**.

by chiral HPLC analysis. The DL-portions of **3d** and **3e** were shown to be enantiomerically pure (>99% ee) by chiral HPLC analysis. The absolute configuration of **3d** was considered to be *S,S* on the basis of the reduction of **1a** and **1b**, and that of **3e** was revealed to be *S,S* by the comparison of its specific rotation with the reported value.[9,15] From the facts presented above, it can be seen that the enantioselectivity of the second reductions of **1d** and **1e** are similar to that of the first.

In conclusion, baker's yeast reduction of diacetylaromatics **1a**, **1b**, and **1d–g** gave highly enantiomerically pure monoalcohols **2a**, **2b**, and **2d–g** selectively by using appropriate reaction conditions (method A or B). The absolute configurations of all alcohols obtained in this study were *S* (or *S,S*) in accordance with Prelog's rule.[16] This selective mono-reduction in a highly enantioselective manner is extremely interesting and valuable because such a reduction is generally considered to be difficult for chemical methods.

Experimental

General

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were measured with a JASCO A-100 spectrophotometer, mass spectra with a Hitachi M-80 mass spectrometer, optical rotations with a JASCO DIP-360 automatic polarimeter, ^{1}H-NMR spectra with a Varian Gemini 300 or a Brucker AM-400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. HPLC was carried out with a JASCO flow system PU-980 and JASCO UV detector UV-970 and JASCO integrator 807-IT using Daicel Chiralcel OB or OD, and Chiralpak AD (0.46 cmϕ×25 cm). CH_2Cl_2 was freshly distilled over P_2O_5, and THF from sodium diphenylketyl prior to use. Silica gel (Kieselgel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4. The substrate for baker's yeast reduction, **1c**,[6] **1g**,[7] and

1h[8] were prepared according to the procedures reported in literature. Fresh baker's yeast (Type II, Sigma Chem. Co.) and commercially available sucrose were used for baker's yeast reductions.

2,6-Bis(1-methoxymethoxyethyl)pyridine, DL-*and* meso-***4***

Methoxymethyl chloride (2.9 ml, 38.2 mmol) was added to a mixture of **3a** (synthesized according to literature procedure,[9] 1.27 g, 7.60 mmol, a mixture of DL and *meso*-compounds) and *N*-ethyldiisopropylamine (6.7 ml, 38.5 mmol) in $CHCl_3$ (10 ml) at 0°C. After being stirred at rt for 2 days, the reaction mixture was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=5:1) to give DL- and *meso*-**4** (1.91 g, 98%) as a colorless oil. MS *m/z* 254 (M^+-1); ^{1}H-NMR δ 1.51 (6H, dd, *J*=6.6, 2.1 Hz, Me×2), 3.38 (6H, s, OMe×2), 4.64 (2H, dd, *J*=1.6, 6.6, OCH_2O), 4.71 (2H, d, *J*=6.6 Hz, OCH_2O), 4.85 (2H, dq, *J*=1.3, 6.6 Hz, $CHCH_3$×2), 7.32 (2H, d, *J*=7.7 Hz, pyridine-H), 7.69 (1H, t, *J*=7.7 Hz, pyridine-H); *Anal.* Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.06; H, 8.27; N, 5.18.

2,6-Bis(methoxymethoxyethyl)pyridine 1-oxide, DL-*and* meso-***5***

A solution of **4** (1.91 g, 7.48 mmol) in CH_2Cl_2 (50 ml) was added to a solution of maleic acid (1.19 g, 12.1 mmol) and 60% H_2O_2 (0.68 g, 12 mmol) in CH_2Cl_2 (50 ml) at rt. After being stirred for 12 h, the reaction mixture was diluted with water and extracted with ethyl acetate. The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to give **5** (1.96 g, 97%) as a colorless oil. MS *m/z* 272 (M^++1); ^{1}H-NMR δ 1.54 (6H, d, *J*=6.4 Hz, $CHCH_3$×2), 3.39 (6H, s, OMe×2), 4.68 (4H, dd, *J*=6.6, 17 Hz, OCH_2O×2), 5.41 (2H, q, *J*=6.3 Hz, $CHCH_3$×2), 7.31 (1H, t, *J*=8.3 Hz, pyridine-H), 7.46 (2H, d, *J*=7.7 Hz, pyridine-H); *Anal.* Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.71; H, 7.69; N, 4.92.

2,6-Bis(1-hydroxyethyl)pyridine 1-oxide, DL-*and* meso-***3b***

A mixture of **5** (0.27 g, 1.0 mmol) and 5 N HCl (10 ml) was heated to 50°C. After being stirred for 30 min, the reaction mixture was diluted with water and neutralized with K_2CO_3. The resulting mixture was fixed on ion exchange resin (DIAION HP-20), washed with water and eluted with MeOH. The MeOH fraction was concentrated, and the residue was dissolved in ethyl acetate, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate → MeOH:ethyl acetate=1:10) to give DL- and *meso*-**3b** (0.18 g, 99%) as a colorless oil. IR and ^{1}H-NMR were in complete agreement with those reported in the literature.[16]

2,6-Diacetylpyridine 1-oxide ***1b***

To a solution of oxalyl chloride (1.5 ml, 15 mmol) was added dimethyl sulfoxide (2.4 ml, 35 mmol) at −78°C. After being stirred for 10 min, a solution of **3b** (1.29 g, 7.0 mmol) in CH_2Cl_2 (10 ml) was added and the reaction mixture was stirred at the same temperature for 15 min. Triethylamine (9.0 ml, 70 mmol) was added to the reaction mixture, which was stirred for 5 min at that temperature then gradually warmed to rt. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=1:1) to give **1b** (0.94 g, 75%) as colorless needles. mp 92–94°C (hexane); MS *m/z* 179 (M^+); IR (KBr) 1700 (CO) cm^{-1}; ^{1}H-NMR δ 2.78 (6H, s, acetyl×2), 7.35 (1H, t, *J*=7.6 Hz, pyridine-H), 7.74 (2H, d, *J*=7.8 Hz, pyridine-H); *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.43; H, 4.88; N, 7.82.

2-Methyl-2-(5-acetyl-2-furyl)dioxolane ***8***

To a solution of **7**[11] (310 mg, 2.0 mmol) in THF (15 ml) was added dropwise a solution of *n*-BuLi 1.4 ml, 2.2 mmol, 1.6 M in hexane) at −78°C. After being stirred for 1 h, *N*-methoxy-*N*-methylacetamide (230 mg, 2.2 mmol) was added dropwise to the reaction mixture at 0°C. The mixture was stirred

at rt for additional 1 h. The reaction was quenched with sat. NH_4Cl aqueous solution. The aqueous layer was extracted with ethyl acetate. The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=4:1) to give **8** (330 mg, 83%) as a colorless oil. MS *m/z* 196 (M^+); IR (neat) 1680, 1580, 1518 cm^{-1}; ^{1}H-NMR δ 1.77 (3H, s, Me), 2.48 (3H, s, acetyl), 3.98–4.12 (4H, br-m, OCH_2CH_2O), 6.46 (1H, d, *J*=3.5 Hz, furan-H), 7.11 (1H, d, *J*=3.5 Hz, furan-H); *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.12; H, 6.16. Found: C, 61.31; H, 6.19.

2,5-Diacetylfuran ***1f***

A mixture of **8** (155 mg, 0.79 mmol) and 75% AcOH (8 ml) was heated to 50°C. After being stirred for 2 h, the reaction mixture was diluted with water, neutralized with K_2CO_3 and extracted with CH_2Cl_2. The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate=3:1) to give **1f** (114 mg, 95%) as colorless plates. mp 137–138°C (ethyl acetate); MS *m/z* 152(M^+); IR (KBr) 1668 (CO) cm^{-1}; ^{1}H-NMR δ 2.57 (6H, s, acetyl×2), 7.21 (2H, s, furan-H); *Anal.* Calcd for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 62.83; H, 5.31.

General procedure for baker's yeast reduction

Method A: A mixture of sucrose (3 g), baker's yeast (0.1 g), phosphate buffer (0.1 M, pH 6.5, 20 ml) was stirred at 30°C for 2 h, at which time the diacetylaromatic compound (**1a**, **1c–h**: 0.6 mmol, **1b**: 1.0 mmol) was added. The resulting mixture was stirred at 30°C for 6 days with addition of sucrose (3 g) each day. Celite and acetone were then added, and the resulting mixture was filtered. The Celite cake was washed sequentially with water and acetone, and the filtrate was evaporated under reduced pressure. The residue was extracted with ethyl acetate. (The residue was successively extracted for 30 h in the reduction of **1b**.) The extracts were washed with brine, dried and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding alcohols. In the case of the reduction of **1a**, however, 180 g of sucrose, 6 g of baker's yeast, 1200 ml of phosphate buffer, and 37 mmol of **1a** were used. It should be noted that **1a** could not be successively reduced in the same scale as described for **1c–h** or **1b**.

Method B: To an aqueous solution of sucrose (25 g/40 ml) and diacetylaromatic compound (**1a**, **1c–h**: 0.6 mmol, **1b**: 1.0 mmol) was added baker's yeast (12.5 g). The resulting mixture was stirred at 30°C for 2 h, at which time an aqueous solution of sucrose (25 g/40 ml) was added. After stirring for 2 h, an additional aqueous solution of sucrose (25 g/40 ml) was added and stirred for 6 days under the same conditions. The subsequent procedure was the same as that described for method A. The yields, the enantiomeric purity and the absolute configuration of the products are listed in Table 1.

(S)-(−)-2-Acetyl-6-(1-hydroxyethyl)pyridine ***2a***

Colorless oil; 99% ee; $[\alpha]_D^{25}$ −4.1 (*c* 1.0, $CHCl_3$) {lit.[4c] $[\alpha]_D^{20}$ −7.5 (*c* 1.5, $CHCl_3$) for 99.8% ee (*S*)}; MS *m/z* 165 (M^+); IR (neat) 3400, 1700 cm^{-1}; ^{1}H-NMR δ 1.55 (3H, d, *J*=6.6 Hz, Me), 2.75 (3H, s, acetyl), 4.16 (1H, br-s, OH), 4.97 (1H, q, *J*=6.6 Hz, C*H*OH), 7.48 (1H, d, *J*=7.7 Hz, pyridine-H), 7.86 (1H, t, *J*=7.7 Hz, pyridine-H), 7.97 (1H, d, *J*=7.1 Hz, pyridine-H); *Anal.* Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.42. Found: C, 65.32; H, 6.79; N, 8.29. The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralcel OB (eluent, hexane:2-propanol=9:1).

(S,S)-(−)-2,6-Bis(hydroxyethyl)pyridine ***3a***

Colorless oil; 99% ee; $[\alpha]_D^{25}$ −26.6 (*c* 0.51, $CHCl_3$) {lit.[4c] $[\alpha]_D^{20}$ −26.84 (*c* 2.98, $CHCl_3$) for >99.92% ee (*S,S*)}. IR and ^{1}H-NMR spectra were in complete agreement with those reported in the literature.[9]

(S)-(+)-2-Acetyl-6-(1-hydroxyethyl)pyridine 1-oxide ***2b***

Colorless oil; >99% ee; $[\alpha]_D^{25}$ +18.5 (*c* 0.3, $CHCl_3$); MS *m/z* 181 (M^+); IR (neat) 3375, 1695 cm^{-1}; ^{1}H-NMR δ 1.65 (3H, d, *J*=6.7 Hz, Me), 2.78 (3H, s, acetyl), 5.15 (1H, q, *J*=6.7 Hz, C*H*OH), 5.31 (1H,

br-s, OH), 7.38 (1H, t, J=7.7 Hz, pyridine-H), 7.47 (1H, dd, J=2.2, 7.8 Hz, pyridine-H), 7.59 (1H, dd, J=2.2, 7.7 Hz, pyridine-H); *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.85; H, 5.96; N, 7.65. The absolute configuration of **2b** was determined by the chemical transformation shown in Scheme 3. The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralcel OD (eluent, hexane:2-propanol=9:1).

(S,S)-(+)-2,6-Bis(1-hydroxyethyl)pyridine 1-oxide ***3b***

Colorless oil; >99% ee; $[\alpha]_D^{25}$ +74.2 (c 0.3, $CHCl_3$). The absolute configuration of **3b** was determined by chemical transformation as shown in Scheme 4. The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralpak AD (eluent, hexane:2-propanol=9:1). IR and ^{1}H-NMR spectra were identical with those for the mixture of DL- and *meso*-**3b**.

(S)-(−)-1-Acetyl-3-(1-hydroxyethyl)benzene ***2d***

Colorless oil; 94% ee; $[\alpha]_D^{25}$ −39.1 (c 1.2, $CHCl_3$); MS m/z 164 (M^+); IR (neat) 3420, 1760, 1680 cm^{-1}; ^{1}H-NMR δ 1.53 (3H, d, J=6.8 Hz, Me), 2.62 (3H, s, acetyl), 4.99 (1H, q, J=6.3 Hz, C*H*OH), 7.46 (1H, t, J=7.7 Hz, benzene-H), 7.61 (1H, d, J=7.7 Hz, benzene-H), 7.87 (1H, d, J=7.7 Hz, benzene-H), 7.97 (1H, s, benzene-H); *Anal.* Calcd for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 72.93; H, 7.33. The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralcel OB (eluent, hexane:2-propanol=9:1). The absolute configuration was determined by the correlation of the corresponding (*R*)-MTPA ester by means of ^{1}H-NMR spectroscopy (Mosher's method).[13] The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralcel OB (eluent, hexane:2-propanol=9:1).

(S,S)-(−)-1,3-Bis(1-hydroxyethyl)benzene ***3d***

3d by method B (Table 1, entry 8) was a 94:6 mixture of DL- and *meso*-compounds. The DL-component was of >99% ee. The DL/*meso* ratio and the enantiomeric purity (ee) were determined by HPLC analysis using Daicel Chiralcel OD (eluent, hexane:2-propanol=9:1). The absolute configuration was considered to be *S,S* on the basis of the reduction of **1a** and **1b**. IR and ^{1}H-NMR spectra were in complete agreement with those reported in the literature.[9]

(S)-(−)-1-Acetyl-4-(1-hydroxyethyl)benzene ***2e***

Colorless solid; 98% ee; $[\alpha]_D^{25}$ −44.9 (c 1.2, $CHCl_3$) {lit.[14] $[\alpha]_D^{21}$ +37.4 (c not given, ethanol or $CHCl_3$) for 97% ee (*R*)}. The enantiomeric purity (ee) was determined by HPLC analysis using Daicel Chiralcel OB (eluent, hexane:2-propanol=9:1). IR and ^{1}H-NMR spectra were in complete agreement with those reported in the literature.[14]

(S,S)-(−)-1,4-Bis(1-hydroxyethyl)benzene ***3e***

Colorless needles; mp 127–130°C (benzene). **3e** by method B (Table 1, entry 10) was a 99:1 mixture of DL- and *meso*-compounds. The DL-component was of >99% ee. The DL/*meso* ratio and the enantiomeric purity (ee) were determined by HPLC analysis using Daicel Chiralcel OD (eluent, hexane:2-propanol=9:1). $[\alpha]_D^{25}$ −82.1 (c 0.56, acetone) {lit.[9] $[\alpha]_D^{25}$ −79.9 (c 2, acetone) for >97% ee (*S,S*)} {lit.[15] $[\alpha]_D^{25}$ −86.3 (c 1.7, acetone) for ≥99% ee (*S,S*)}. IR and ^{1}H-NMR spectra were in complete agreement with those reported in the literature.[9]

(S)-(−)-2-Acetyl-5-(1-hydroxyethyl)furan ***2f***

Colorless oil; 86% ee; $[\alpha]_D^{25}$ −7.0 (c 0.4, $CHCl_3$); MS m/z 154 (M^+); IR (neat) 3500, 1780, 1660 cm^{-1}; ^{1}H-NMR δ 1.58 (3H, d, J=6.6 Hz, Me), 2.46 (3H, s, acetyl), 4.94 (1H, q, J=6.9 Hz, C*H*OH), 6.41 (1H, d, J=3.5 Hz, furan-H), 7.13 (1H, d, J=3.6 Hz, furan-H); *Anal.* Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.18; H, 6.58. The absolute configuration of **2f** was established by X-ray analysis of the corresponding (*R*)-MTPA ester. The enantiomeric purity was determined by ^{1}H-NMR analysis of the (*R*)-MTPA ester.[13]

(S)-(−)-2-Acetyl-5-(1-hydroxyethyl)thiophene 2g

Orange oil; 95% ee; $[\alpha]_D^{25}$ −13.9 (*c* 1.1, $CHCl_3$); MS *m/z* 170(M^+); IR (neat) 3400, 1640 cm^{-1}; ^{1}H-NMR δ 1.61 (3H, d, *J*=6.5 Hz, Me), 2.54 (3H, s, acetyl), 5.13 (1H, q, *J*=6.5 Hz, C*H*OH), 7.00 (1H, dd, *J*=0.8, 3.8 Hz, thiophene-H), 7.58 (1H, d, *J*=3.8 Hz, thiophene-H); *Anal.* Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92. Found: C, 56.48; H, 6.02. The absolute configuration and enantiomeric purity of **2g** were determined by ^{1}H-NMR analysis of the corresponding (*R*)-MTPA ester (Mosher's method).[13]

X-ray crystallographic analysis of the (R)-MTPA ester of 2f

Crystal data: $C_{18}H_{17}O_5F_3$, M=370.32, orthorhombic, space group $P2_12_12_1$(#19), a=10.336(1), b=20.587(2), c=8.379(2) Å, V=1783.1(5) $Å^3$, Z=8, D_{calc}=1.38 g/cm^3, m(Cu–Kα)=10.10 cm^{-1}, number of observation 1267 (I>3.00σ(I)), R=0.039, Rw=0.050. Intensity data were collected on a Rigaku AFC5R diffractometer using Cu–Kα radiation (λ=1.54178 Å).

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