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Chemoenzymatic synthesis of chiral 1-benzyl-5-(hydroxymethyl)-2-piperidone enabled by lipase AK desymmetrization of prochiral 1,3-diol and its diacetate

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Abstract: The synthesis of (*R*)-1-benzyl-5-(hydroxymethyl)-2-piperidone **1** from key synthon monoacetate (*R*)-**3** has been accomplished conveniently in 6 steps with 93% *ee* and in 44% overall yield. The key step involved lipase AK desymmetrization of diol **4** to produce monoacetate (*R*)-**3** in 93% *ee* and 93% yield. Lipase AK desymmetrization of diacetate **5** provided ready access to monoacetate (*S*)-**3** in 93% *ee* and 54% yield.

Introduction

Chiral piperidines are embedded in many natural products and lead drug candidates.[1] Several chiral approaches have been developed for their syntheses, many of which directly start from chiral piperidones.[1] 2-Piperidones are key subclass of piperidones and are embedded in many bioactive compounds such as cytisine,[2] deplancheine,[3] tacamonine,[4] strynuxlines,[5] leuconoxine[6] and yaequinolone.[7] Cytisine (Figure 1) has attracted much attention as it demonstrates potent nicotinic agonist activity behaving as a partial agonist at α4β2 and a full agonist at α7.[8] Gallagher *et. al.* have described an efficient and highly convergent synthetic approach to cytisine and its derivatives/analogues using key synthon 1-benzyl-5-(hydroxymethyl)-2-piperidone **1** (Figure 1).[9] This piperidine synthon is critical for cytisine activity.[10]

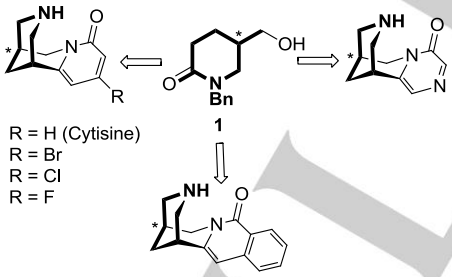
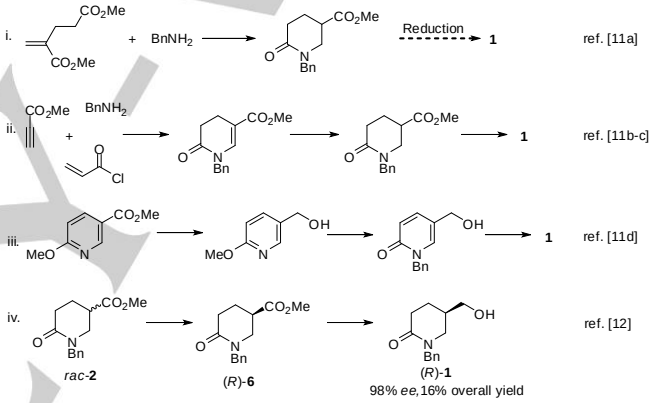


Figure 1.
Cytisine and derivatives/analogues highlighting the 2-piperidone **1** skeleton

Syntheses of *rac*-2-piperidone **1** have been conveniently achieved by three approaches as depicted in i-iii, scheme 1.[11] However, access to the enantiopure version of 2-piperidone **1** was more challenging. Gallagher *et al*.[12] synthesis of (*R*)-2-piperidone **1** relied on kinetic resolution of lactam ester **2** using α-chymotrypsin to give an overall 16% yield after 6 steps (iv, Scheme 1). The major disadvantage of this approach is that kinetic resolution only offer up to 50% of the theoretical possible yield. It is evident that efficient construction of 2-piperidone **1** is highly desirable and ideally involving an approach that provides access to both enantiomers.

Scheme 1. Synthesis of *racemic* and (*R*)-2-piperidone **1**



Reagents and conditions for iv: (a) α-chymotrypsin, 0.1 m phosphate buffer, acetone, pH 7.4; (b) $LiAlH_4$, THF

Our retrosynthetic analysis of 2-piperidone **1** by disconnecting N1-C6 bond resulted in monoacetate **3** (Figure 2). Synthesis of chiral monoacetate **3** could be envisioned to proceed through asymmetric enzymatic desymmetrization of diol **4** and its diacetate **5**. This approach is challenging and unpredictable since we learned from the literature that the success of the desymmetrization is very dependent on the nature of the diol/diacetate bulky groups (acidic, basic, neutral, aliphatic, aromatic etc)[13] and the distance between the prochiral hydroxyls/acetates and the bulky groups.[14] Generally, the greater the distance, the lower is the enantioselectivity. Lipases have been successfully used for enantioselective acetylation of diols and hydrolysis of the corresponding *meso*-diacetates to give the two complementary enantiomeric forms of monoacetates.[13-14]

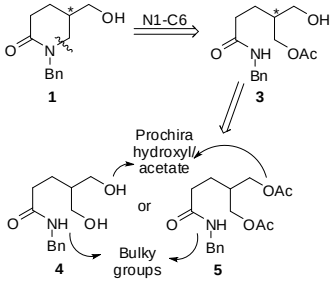


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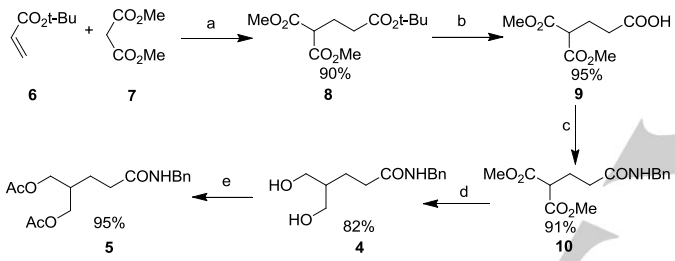
Figure 2. Retrosynthetic analysis of 2-piperidone **1**

Herein, we report an efficient asymmetric synthesis of 2-piperidone **1** and key synthons monoacetates (*S*)- and (*R*)-**3** using enzymatic desymmetrization approach using commercially available lipases.

Results and Discussion

Synthesis of diol 4 and its diacetate 5

We synthesized diol **4** and its diacetate **5** in 64% and 60% overall yields, respectively, as featured in scheme 2. Michael addition of dimethyl malonate **7** to *tert*-butyl acrylate **6** provided triester **8**[15] in 90% yield. Chemoselective hydrolysis of the *tert*-butyl ester group of triester **8** using trifluoroacetic acid produced acid **9**[16] in 95% yield. Reaction of acid **9** with benzylamine provided amide **10** in 91% yield. Reduction of amide **10** using $LiBH_4$ provided diol **4** as white solid in 82% yield. Acetylation of diol **4** using acetyl chloride produced diacetate **5** in 95% yield.



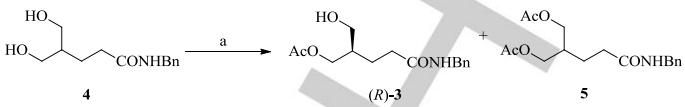
Reagents and conditions: (a) NaH, THF, 0 °C-rt, 21 h; (b) TFA, DCM, 12 h; (c) $(COCl)_2$, DCM, DMF, 0 °C-rt, 1.5 h then $BnNH_2$, TEA, THF, 0 °C-rt, 1 h; (d) LiBH4, THF, MeOH, 0 °C-rt, 2 h; (e) AcCl, Et_3N, CH_2Cl_2, rt, 12 h

Scheme 2. Synthesis of diol **4** and diacetate **5**

Desymmetrization of diol 4 through acetylation

Lipase PS was reported as the optimal lipase for asymmetric desymmetrization of several 1,3-diol substrates.[17-18] We attempted acetylation of diol **4** with vinyl acetate in THF using lipase PS (from *Burkholderia cepacia*), lipase AK (from *Pseudomonas fluorescens*), lipase A (from *Aspergillus niger*), lipase G (from *Penicillium camemberti*), lipase M (from *Mucor javanicus*), CAL-B (from *Candida antartica*), CCL (from *Candida rugosa*) and PPL (porcine pancreatic lipase) (Table 1).[17] Interestingly, only lipases PS and AK catalyzed the formation of monoacetate **3** in excellent isolated yields (85% and 91%, respectively) and enantioselectivities (75% *ee* and 87% *ee*, respectively) (Table 1, entries 1-2). CAL-B and CCL gave poor yield and *ee* (Table 1, entries 3-4) while other lipases gave back the starting material unchanged. Monoacetate **3** was confirmed to have the (*R*)-configuration based on its optical rotation sign (section 2.4).[12] Reaction optimization was examined using Lipase AK because of its superior catalytic activity.

Table 1. Screening of lipases. Enantioselective acetylation of diol **4**[a]



Reagents and condition: (a) lipase, vinyl acetate, MS 4Å, THF, rt

Entry	Lipase	Time (h)	Monoacetate (*R*)-**3**		Diacetate **5**
			Yield[b] (%)	Ee[c] (%)	Yield[b] (%)
1	Lipase PS	21	91	75	4
2	Lipase AK	1	85	87	10
3	CAL-B	21	46	0	4
4	CCL	21	17	14	0

a: Conditions: diol **4** (0.2 mmol), lipases (150 mg/ mmol diol **4**), vinyl acetate (10.0 equiv), molecular sieve 4Å (10 mg), THF (3.125 mL), rt.

b: Isolated yield

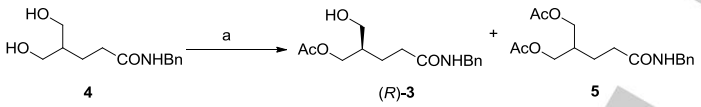
c: Measured by HPLC: Chiralpak AD-H (hexane: *i*-PrOH, 95: 5), 0.9 ml/ min, 254 nm, t1: 46.3 min, t2: 49.8 min

The effect of organic solvents such as THF, MTBE, *i*-Pr_2O, toluene, $CHCl_3$, CH_2Cl_2, acetone and MeCN was examined (Table 2). In all cases, the desymmetrization proceeded smoothly under heterogeneous condition to give monoacetate (*R*)-**3** in excellent yields and enantioselectivities after 1-2 h (Table 2, entries 1-8). However, ether-type solvents THF, MTBE and *i*-Pr_2O produced mixtures of monoacetate (*R*)-**3** and diacetate **5** Table 2, entry 1-3).

In comparison, nonpolar and non-coordinating solvents toluene, $CHCl_3$ and CH_2Cl_2 provided only the desired monoacetate (*R*)-**3** in excellent yields and comparable ees (Table 2, entries 4-6 vs 1-3). Polar aprotic solvents acetone and MeCN also provided only monoacetate (*R*)-**3** in excellent yield (91% and 96%, respectively) and enantioselectivity (82% and 88%, respectively) within 1 h (Table 2, entries 7-8). Intramolecular acyl group migration did not happen. HPLC analysis of monoacetate (*R*)-**3** showed no racemization after storing at room temperature for 7 days.

Next, effects of lipase loading, equivalents of vinyl acetate and temperature were examined using MeCN (Table 2, entries 9-16). Interestingly, no significant changes on the yield or ee were observed by varying lipase loading (Table 2, entries 8-10) or vinyl acetate equivalents (Table 2, entries 11-14). However, a decrease in the reaction temperature to 4 °C (ice-bath) and to 0 °C, improved the *ee* to 93% and 91% without compromising the excellent yield of 93% and 94%, respectively (Table 2, entries 15-16). Further temperature reduction to -25 °C lead to decreased yield and ee as it affected lipase AK activity. In conclusion, enantioselective desymmetrization of diol **4** using lipase AK provided monoacetate (*R*)-**3** in excellent 93% yield and 93% *ee* (Table 2, entry 15).

Table 2. Optimization of the enantioselective acetylation of diol **4**[a] using lipase AK



4 (*R*)-**3** **5**

Reagents and conditions: (a) lipase AK, vinyl acetate, MS 4Å, solvent, rt

Entry	Solvent	Enzyme ratio (mg/mmol)	Vinyl acetate (equiv)	Temp. (°C)	Time (min)	Monoacetate (*R*)-**3**[b]	Diacetate **5**[b]	*Ee*[c] (%)
1	THF	150	10	25	60	80	17	87
2	MTBE	150	10	25	60	75	20	91
3	*i*-Pr_2O	150	10	25	60	65	20	78
4	Toluene	150	10	25	120	88	0	85
5	$CHCl_3$	150	10	25	120	99	0	85
6	CH_2Cl_2	150	10	25	100	99	0	85
7	Acetone	150	10	25	60	91	0	82
8	MeCN	150	10	25	45	96	0	88
9	MeCN	250	10	25	30	95	0	87
10	MeCN	100	10	25	120	96	0	86
11	MeCN	150	20	25	40	96	0	87
12	MeCN	150	15	25	60	95	0	88
13	MeCN	150	5	25	90	94	0	88
14	MeCN	150	3	25	120	94	0	86
15	MeCN	150	10	4	300	93	0	93
16	MeCN	150	10	0	360	94	0	91

[a]: Conditions: diol **4** (0.2 mmol), lipase AK, vinyl acetate, molecular sieve 4Å (10 mg), solvent (3.125 mL).

[b]: Isolated yield

[c]: Measured by HPLC: Chiralpak AD-H (hexane: *i*-PrOH, 95: 5), 0.9 ml/ min, 254 nm, t_1: 46.3 min, t_2: 49.8 min.

We carried a time-based study of desymmetrization of diol **4** to examine the progress of the reaction and the possibility of undesired racemization of monoacetate **3** under the optimal conditions (Table 1, entry 15). HPLC analysis of the reaction mixture was carried out at different time intervals and the results are summarized in Figure 3. It can be seen that within the first 5 hours, the fast decrease in the amount of the starting material diol **4** corresponded to the fast formation of monoacetate 3. No formation of diacetae **5** was detected during this time. However, as time progressed, some of the monoacetate **3** and diol **4** converted to diacetate **5** which was obtained in 27% yield after 18 h. The enantioselectivity of monoacetate **3** was well maintained at 91-93% *ee* during the first five hours and slightly dropped to 90% *ee* after 18 h. This indicated that there was no significant racemisation or intramolecular acyl migration.

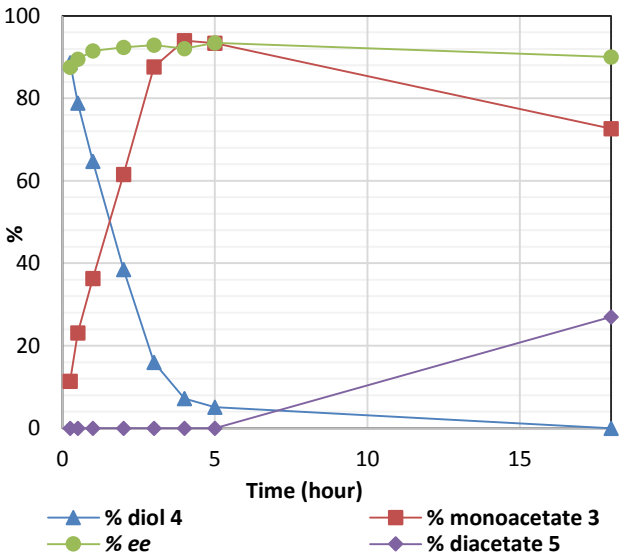


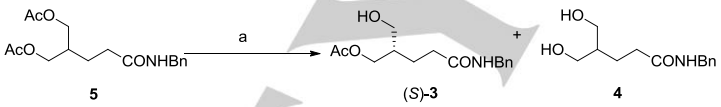
Figure 3. Time-based study of desymmetrization of diol **4** at optimal condition

Desymmetrization of diacetate 5 through hydrolysis

Enantioselective hydrolysis (or deacetylation) of diacetate **5** using lipase AK should give monoacetate (*S*)-**3** since lipases display the same prochiral selectivity for acetylation and hydrolysis.[19] Initial hydrolysis experiments in phosphate buffer solution (pH 7) at different lipase AK loadings produced a mixture of unreacted starting diacetate **5**, monoacetate (*S*)-**3** and diol **4** (Table 3, entries 1-3). The configuration of monoacetate (*S*)-**3** was confirmed by comparing its HPLC trace with monoacetate (*R*)-**3** and monoacetate *rac*-**3**. While reaction at lipase loading of 150 mg/ mmol of diacetate **5** were sluggish, loading of 300 mg/ mmol or 600 mg/ mmol enhanced the reaction rate but still produced a mixture of monoacetate (*S*)-**3** and diol **4** with low enantioselectivity (Table 3, entry 1-3). This reduction in selectivity may be attributed to the conformational mobility of lipase structure in aqueous media.[20] However, in organic solvents, the conformation of lipase is more rigid since hydrogen bonding caused by water is very minimal. Therefore, the use of organic co-solvents (Table 3, entries 4-9) was expected to increase the discrimination ability of lipase AK between the substrates.[21] Initial screening established the optimal volumetric ratio between the buffer solution and cosolvents to be 10:1 since higher amount of the co-solvent lead to lipase inactivation because of denaturation.[22] Cosolvents exerted strong effect on the enantioselectivity and produced mixtures of monoacetate (*S*)-**3** and diol **4**. While MeCN, toluene and THF improved the *ee* of monoacetate (*S*)-**3** (87%, 82% and 93%, respectively), acetone and *i*-Pr_2O diminished the *ee* to 24% and 9%, respectively (Table 3, entries 4-9). Attempts to improve the yield of monoacetate (*S*)-**3** on the account of diol **4** by conducting the reaction at buffer pH of 6.0, 6.5 and 7.5 (optimal working pH range of lipase AK is pH 6.0-7.5[23]) were not very successful (Table 3, entries 9-12). The optimal condition for enzymatic hydrolysis of diacetate **5** is given in table 3, entry 9.

We attempted to improve the enantiopurity of monoacetate (*S*)-**3** by selective hydrolysis of an enantioenriched mixture of monoacetate (*S*)-**3** (93% *ee*) using the optimal condition in table 2, entry 15. However, no enantioselective hydrolysis was obtained. Instead, 50% of monoacetate (*S*)-**3** was hydrolysed to diol **4** and the remaining 50% was recovered unchanged with 93% *ee*.

Table 3: Screening of enzymatic hydrolysis of diacetate **5**[a]



5 (*S*)-**3** **4**

Reagents and conditions: (a) lipase AK, phosphate buffer pH 7

Entry	Solvent	pH	Enzyme (mg/mmol **5**)	Temp. (°C)	Time (h)	Monoacetate (*S*)-**3**[b] (%)	Diol **4**[b] (%)	*Ee*[c] (%)
1	H_2O	7.0	150	rt	24	36	42	66
2	H_2O	7.0	300	rt	5	63	25	72
3	H_2O	7.0	600	rt	3	60	10	59
4	H_2O:MeCN	7.0	300	rt	24	46	38	87
5	H_2O:acetone	7.0	300	rt	24	56	35	24
6	H_2O:toluene	7.0	300	rt	24	49	41	82
7	H_2O:*i*-Pr_2O	7.0	300	rt	24	56	7	9
8	H_2O:MTBE	7.0	300	rt	24	60	19	63
9	H_2O:THF	7.0	300	rt	24	54	39	93
10	H_2O:THF	6.0	300	0	24	55	33	90
11	H_2O:THF	6.5	300	0	24	53	37	90
12	H_2O:THF	7.5	300	0	24	54	32	91

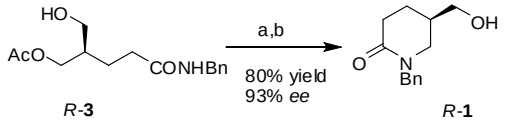
[a]: Conditions: diol **4** (0.2 mmol), lipase AK, vinyl acetate (10.0 equiv), molecular sieve 4Å (10 mg), solvent (3.125 mL, H_2O:solvent is 10:1, v:v).

[b]: Isolated yield

[c]: Measured by HPLC: Chiralpak AD-H (hexane: *i*-PrOH, 95: 5), 0.9 ml/ min, 254 nm, t_1: 46.3 min, t_2: 49.8 min.

Synthesis of chiral 1-benzyl-5-(hydroxymethyl)-2-piperidone 1

Tosylation of monoacetate (*R*)-**3** followed by intramolecular amide alkylation using *n*-Bu_4NHSO_4 as phase transfer catalyst produced (*R*)-1-benzyl-5-(hydroxymethyl)-2-piperidone **1** in 80% yield and 93% *ee* (Scheme 3). It showed optical rotation value of $\alpha_D^{22} = +42.5$ (c, 1.0, CH_2Cl_2) and therefore confirming the *R*-configuration assignment as (*R*)-**1.**[12]



R-**3** *R*-**1**

Reagents and conditions: (a) TsCl, DMAP, Et_3N, DCM, 0 ^oC -rt; 12 h; (b) *n*-Bu_4NHSO_4, NaOH, K_2CO_3, PhMe, reflux, 2-3 h

Scheme 3. Synthesis of chiral 1-benzyl-5-(hydroxymethyl)-2-piperidone **1**

Conclusions

We have achieved a practical chemoenzymatic synthesis of (*R*)-1-benzyl-5-(hydroxymethyl)-2-piperidone **1** with the highest ever reported 44% overall yield and 93% *ee* in 6 steps. The synthesis involved intramolecular amide alkylation of the tosylated monoacetate (*R*)-**3**. Lipase AK desymmetrization of diol **4** produced monoacetate (*R*)-**3** in excellent 93% *ee* and 93% yield. Lipase AK desymmetrization of diacetate **5** produced the corresponding monoacetate (*S*)-**3** in 91% *ee* and moderate 54% yield. With the availability of (*R*)- and (*S*)-piperidone **1** and (*R*)- and (*S*)- monoacetate **3**, we anticipate their use in the synthesis of numerous biologically active products and chiral intermediates.

Experimental Section

Chemicals were purchased from Sigma-Aldrich or Alfa Aesar and used as received without further purification. All lipases used are in free powder form. Lipase PS, Lipase AK, Lipase A, Lipase G, Lipase M are from Amano Enzyme Inc. Lipase PPL was purchased from Sigma while CAL-B and CCL were purchased from Fluka. ^1H NMR spectra were recorded at 300 MHz on a Bruker Avance DPX 300. Unless stated otherwise, data refer to solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C NMR spectra were recorded at 75.47 MHz on a Bruker Advanced DPX 300. High resolution mass spectra were recorded on Qstar XL MS/MS system. FTIR were recorded on Perkin Elmer FTIR system Spectrum BX. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 precoated silica gel plate (0.2 mm thickness) and visualized using UV radiation (254 nm). Flash chromatography was performed using Merck silica gel 60 (230-400 mesh). Optical rotation values were measured on JASCO P-1020 polarimeter.

Dimethyl 2-(3-(benzylamino)-3-oxopropyl)malonate 10

Oxalyl chloride (6.25 mL, 71.7 mmol) was added drop-wise to a solution of carboxylic acid **9** (9.75 g, 47.8 mmol) in CH_2Cl_2 (60 mL) and DMF (50 µL) at 0 ^oC under inert condition. After that, the solution was allowed to warm up to room temperature and stirred for 1 h before removal of CH_2Cl_2 under reduced pressure. The reaction mixture was then diluted with THF (50 mL) and Et_3N (13 mL, 95.6 mmol) and cooled to 0 ^oC. A solution of $BnNH_2$ (5.74 mL, 52 mmol) in THF (25 mL) was added drop-wise to the above solution under inert condition and the resulting slurry was warmed up to room temperature and stirred for additional 1 h. H_2O (50 mL) was then added slowly to the slurry and the biphasic mixture produced was separated. The aqueous phase was extracted with CH_2Cl_2 (40 mL x 3). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc: hexane, 1:3) to give compound **10** (12.86 g, yield 91%) as light yellow oil**.** (FTIR (KBr) ν_{max}: 1741, 1661, 1556, 1442, 1268, 1035, 699. ^1H NMR δ: 2.23-2.35 (m, 4H), 3.53 (t, *J*= 6.75 Hz, 1H), 3.75 (s, 6H), 4.44 (d, *J*= 15 Hz, 2H, d, J= 15 Hz, PhC*H*$_2$NH), 5.83 (br s, 1H), 7.28-7.38 (m, 5H). ^{13}C NMR δ: 24.5, 33.3, 43.5, 50.5, 52.6, 127.4, 127.7, 128.6, 138.3, 169.6, 171.5.HRMS (ESI-positive mode): *m/z* calcd. for $C_{15}H_{19}NO_5$ 293.1263; found 316.1174 $[M+Na]^+$.

***N*-Benzyl-5-hydroxy-4-(hydroxymethyl)pentanamide 4**

To a solution of amide **10** (5.87 g, 20 mmol) in anhydrous THF (200 mL) and MeOH (3.8 mL) was added drop-wise a solution of $LiBH_4$ 2M in THF (40 mL, 80 mmol) under inert atmosphere at 0 ^oC. The reaction was allowed to warm up to room temperature, stirred for additional 1 h (TLC), cooled to 0 ^oC and was quenched by drop-wise addition of saturated aqueous NH_4Cl solution (50 mL). The biphasic mixture was separated and the aqueous phase was extracted with a co-solvent of *i*-PrOH/$CHCl_3$ (1/4, v/v) (3 x 100 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude yellow oil was triturated with EtOAc to give diol **4** (4.03 g, 85% yield) as white solid, mp 90-91 ^oC. FTIR (KBr) ν_{max}: 1646, 1558, 1457, 1265, 1052, 700 cm^{-1}. ^1H NMR (CD_3OD) δ: 1.56-1.67 (m, 3H), 2.28 (t, *J*= 7.65 Hz, 2H), 3.53 (d, *J*= 5.1 Hz, 4H), 4.32 (s, 2H), 7.16-7.29 (m, 5H). ^{13}C NMR (CD_3OD) δ: 26.9, 36.2, 45.7, 45.8, 64.8, 129.8, 130.1, 131.2, 141.6, 177.6. HRMS (ESI-positive mode): *m/z* calcd. for $C_{13}H_{19}NO_3$ 237.1365; found 260.1261 $[M+Na]^+$.

***N*-Benzyl-5-acetoxy-4-(acetoxymethyl)pentanamide 5**

To a suspension of diol **4** (1.2 g, 5 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (2.0 mL, 15 mmol) followed by acetyl chloride (1.1 mL, 15 mmol) at the ice-bath temperature. The reaction was slowly allowed to warm up to room temperature and stirred for 24 h (TLC). The reaction was concentrated and the crude residue obtained was diluted with a mixture of EtOAc and H_2O (50 mL, 1:1 volumetric ratio). The aqueous phase was further extracted with EtOAc (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated. The residue obtained was purified by column chromatography (hexane: EtOAc, 1:1) to give diacetate **5** (1.48 g, 92% yield) as yellow oil. FTIR (KBr) ν_{max}: 1741, 1655, 1558, 1248, 1045. ^1H NMR δ: 1.70-1.78 (m, 2H), 1.97-2.08 (m, 1H), 2.04 (s, 6H), 2.27-2.33 (t, *J*= 7.95 Hz, 2H), 4.05-4.07 (d, *J*= 6Hz, 4H), 4.41-4.43 (d, *J*= 5.4 Hz, 2H), 6.08 (br s, 1H), 7.26-7.37 (m, 5H). ^{13}C NMR δ: 21.0, 24.4, 33.6, 37.1, 43.8, 63.9, 127.6, 127.8, 128.7, 138.2, 171.2, 172.1. HRMS (ESI-positive mode): *m/z* calcd. for $C_{17}H_{23}NO_5$ 321.1576; found 344.1481 $[M+Na]^+$.

Enantioselective acetylation of diol 4 under optimal condition

Lipase AK (30 mg, 150 mg/ mmol) was added to a suspension of diol **4** (48 mg, 0.2 mmol) and molecular sieve 4Å (10 mg) in MeCN (3.1 mL) at 4 ^oC under inert condition. The mixture was stirred for 15 min, vinyl acetate (190 µL, 2 mmol) was added and then further stirred for 4-5 h at 4 ^oC. The reaction mixture was filtrated, evaporated and purified by column chromatography (EtOAc: hexane, 5:1) to give monoacetate (*R*)-**3** (52 mg, 93% yield) as colorless oil, $[\alpha]_D^{22} - 2.1$ (c, 0.11, CH_2Cl_2). FTIR (KBr) ν_{max}: 1737, 1659, 1556, 1269, 1037, 702 cm^{-1}. ^1H NMR δ: 1.53-1.79 (m, 3H), 1.96 (s, 3H), 2.12-2.32 (m, 2H), 3.47-3.49 (d, *J*= 4.5 Hz, 2H), 4.00-4.02 (d, *J*= 4.8 Hz, 2H), 4.35 (d, *J*= 5.7 Hz, 2H), 6.17 (br s, 1H), 7.17-7.28 (m, 5H). ^{13}C NMR δ: 20.9, 23.3, 33.6, 40.2, 43.7, 61.7, 64.5, 127.6, 127.8, 128.7, 138.1, 171.6, 173. HRMS (ESI-positive mode): *m/z* calcd. for $C_{15}H_{21}NO_4$ 279.1471; found 302.1373 $[M+Na]^+$. HPLC: Chiralpak AD-H (hexane: *i*PrOH, 95: 5), 0.9 ml/ min, 254 nm, t_1: 46.3 min, t_2: 49.8 min (93% *ee*).

Enantioselective hydrolysis of diacetate 5 under optimal condition

To a solution of diacetate **5** (64 mg, 0.2 mmol) in buffer pH 7 (12.5 mL) and THF (1.25 mL) was added lipase AK (90 mg, 450 mg/ mmol) at room temperature. The reaction was stirred for 11 h and then extracted with CH_2Cl_2 (10 mL x 3). The organic phase was washed with brine, dried over $MgSO_4$, filtrated and evaporated under reduced pressure. The crude mixture was purified by column chromatography (hexane: EtOAc, 1:1) to give diol **4** (18 mg, 39% yield) and monoacetate (*S*)-**3** (48 mg, 51% yield) as colorless oils. $[\alpha]_D^{22} + 2.3$ (c, 0.15, CH_2Cl_2). HPLC: Chiralpak AD-H (hexane: *i*PrOH, 95: 5), 0.9 ml/ min, 254 nm, t_1: 46.3 min, t_2: 49.8 min (93% *ee*).

(*R*)-1-benzyl-4-(hydroxymethyl)piperidin-2-one 1

To a solution of (*R*)-**3** (280 mg, 1 mmol) in CH_2Cl_2 (10 mL) was added consecutively Et_3N (270 µL, 2 mmol) and DMAP (12.2 mg, 0.1 mmol) at 0 °C. A solution of *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) in CH_2Cl_2 (5 mL) was then added drop-wise to the above solution while maintaining the temperature at 0 °C. The reaction mixture was stirred for 12 h while allowed to warm up to room temperature. It was then washed with H_2O (2 x 25 mL) and brine solution (25 mL). The CH_2Cl_2 phase was dried over MgSO4, filtered, concentrated and the crude residue was re-dissolved in toluene (10 mL). *n*-Bu_4NHSO_4 (34 mg, 0.1 mmol), NaOH (40 mg, 1.0 mmol), and K_2CO_3 (415 mg, 3.0 mmol) were consecutively added to the toluene solution and the resulting mixture was heated at 90 °C for 2 h until the complete consumption of the tosylate starting material. The mixture was then filtered, diluted with EtOAc and the organic layer was washed with H_2O (25 mL x 2), brine (25 mL), dried over MgSO4, filtered and concentrated. The crude residue obtained was purified by column chromatography (EtOAc: Hexane = 3:1) to give 2-piperidone **1** (186 mg, 85% yield) as viscous oil. $\alpha_D^{22} + 43$ (c, 1.0, CH_2Cl_2). ^{1}H NMR δ: 1.46-1.52 (m,1H), 1.79-1.89 (m, 1H), 1.90-2.05 (m, 1H), 2.39-2.51 (m, 2H), 2.99 (t, *J*= 11.25 Hz, 1H), 3.27-3.33 (m, 1H), 3.40-3.46 (m, 1H), 3.51-3.56 (m, 1H), 4.56 (q, *J*= 14.7 Hz, 2H), 7.20-7.33 (m, 5H). ^{13}C NMR δ: 23.8, 31.2, 36.4, 49.9, 50.4, 64.3, 127.5, 128.0, 136.9, 170.2. HRMS (ESI, positive mode) *m/z* calcd. for $C_{13}H_{17}NO_2$ 219.1259, found 220.1329 $[M+H]^+$.[12, 24] Literature values for (*R*)-**1**[12]: ^{1}H NMR: (400 MHz, $CDCl_3$) δ: 1.51 – 1.61 (1H, m), 1.87–1.93 (1H, m), 2.00 – 2.09 (1H, m), 2.45 (1H, ddd, J = 18.0, 11.0, 6.5), 2.58 (1H, ddd, J = 18.0, 6.5, 3.5), 3.02 (1H, dd, J = 12.0, 9.5), 3.30 (1H, ddd, J = 12.0, 5.5, 1.5), 3.46 – 3.53 (2H, m), 4.60 (2H, s), 7.23 – 7.35 (5H, m, ArCH x 5). ^{13}C NMR: (100 MHz, $CDCl_3$) δ: 23.8 (CH_2), 31.2 (CH_2), 36.5 (CH), 49.7 (CH_2), 50.4 (CH_2), 64.5 (CH_2), 127.4, 128.3, 128.7 (ArCH x 5), 137.1 (ipso-Ph), 170.0 (C=O).

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Keywords: Chiral piperidones • Desymmetrization • 1,3-diols • Lipase • Cytisine

[1] *For reviews in the synthesis of chiral piperidines and piperidones*: a) D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435-446; b) H. Yoda, *Curr. Org. Chem.* **2002**, *6*, 223-243; c) P. M. Weintraub, J. S. Sabol, J. M. Kane, D. R. Borcherding, *Tetrahedron* **2003**, *59*, 2953-2989; d) B. Maxime G.P, *Tetrahedron* **2004**, *60*, 1701-1729; e) M. S. M. Pearson, M. Mathé-Allainmat, V. Fargeas, J. Lebreton, *Eur. J. Org. Chem.* **2005**, *2005*, 2159-2191; f) P. Kittakoop, C. Mahidol, S. Ruchirawat, *Curr. Top. Med. Chem.* **2014**, *14*, 239-252.

[2] D. Stead, P. O'Brien, *Tetrahedron* **2007**, *63*, 1885-1897.

[3] M. Amat, M. Pérez, J. Bosch, *Synlett* **2011**, *2011*, 143-160.

[4] A. Deiters, M. Pettersson, S. F. Martin, *J. Org. Chem.* **2006**, *71*, 6547-6561.

[5] Y. Fu, Y. Zhang, H. He, L. Hou, Y. Di, S. Li, X. Luo, X. Hao, *J. Nat. Prod.* **2012**, *75*, 1987-1990.

[6] C.-Y. Gan, Y.-Y. Low, N. F. Thomas, T.-S. Kam, *J. Nat. Prod.* **2013**, *76*, 957-964.

[7] R. Uchida, R. Imasato, K. Shiomi, H. Tomoda, S. Ōmura, *Org. Lett.* **2005**, *7*, 5701-5704.

[8] J. Rouden, M.-C. Lasne, J. Blanchet, J. Baudoux, *Chem. Rev.* **2014**, *114*, 712-778.

[9] P. Durkin, P. Magrone, S. Matthews, C. Dallanoce, T. Gallagher, *Synlett* **2010**, *2010*, 2789-2791.

[10] C. Hirschhäuser, C. A. Haseler, T. Gallagher, *Angew. Chem. Int. Ed.* **2011**, *50*, 5162-5165.

[11] a) A. Samarat, J. Ben Kraïem, T. Ben Ayed, H. Amri, *Tetrahedron* **2008**, *64*, 9540-9543; b) G. R. Cook, L. G. Beholz, J. R. Stille, *J. Org. Chem.* **1994**, *59*, 3575-3584; c) A. Lerchner, E. M. Carreira, *Chem. Eur. J.* **2006**, *12*, 8208-8219; d) A. A. Bisset, A. Shiibashi, J. L. Desmond, A. Dishington, T. Jones, G. J. Clarkson, T. Ikariya, M. Wills, *Chem. Commun.* **2012**, *48*, 11978-11980.

[12] D. Gray, T. Gallagher, *Angew. Chem. Int. Ed.* **2006**, *45*, 2419-2423.

[13] a) E. García-Urdiales, I. Alfonso, V. Gotor, *Chem. Rev.* **2011**, *111*, PR110-PR180; b) J. M. Palomo, Z. Cabrera, *Curr. Org. Synth.* **2012**, *9*, 791-805.

[14] a) S. Mizuta, T. Tsuzuki, T. Fujimoto, I. Yamamoto, *Org. Lett.* **2005**, *7*, 3633-3635; b) B. Jung, M. S. Hong, S. H. Kang, *Angew. Chem. Int. Ed.* **2007**, *46*, 2616-2618; c) B. M. Trost, S. Malhotra, T. Mino, N. S. Rajapaksa, *Chem. Eur. J.* **2008**, *14*, 7648-7657; d) M. Candy, G. r. Audran, H. Bienaymé, C. Bressy, J.-M. Pons, *Org. Lett.* **2009**, *11*, 4950-4953.

[15] H. Quast, R. Janiak, *Liebigs Ann. Chem.* **1991**, *1991*, 1305-1308.

[16] K. R. Prabhu, N. Pillarsetty, H. Gali, K. V. Katti, *J. Am. Chem. Soc.* **2000**, *122*, 1554-1555.

[17] L. Banfi, A. Basso, G. Guanti, M. T. Zannetti, *Tetrahedron: Asymmetry* **1997**, *8*, 4079-4088.

[18] K. Takabe, Y. Iida, H. Hiyoshi, M. Ono, Y. Hirose, Y. Fukui, H. Yoda, N. Mase, *Tetrahedron: Asymmetry* **2000**, *11*, 4825-4829.

[19] B. Morgan, D. R. Dodds, A. Zaks, D. R. Andrews, R. Klesse, *J. Org. Chem.* **1997**, *62*, 7736-7743.

[20] A. M. Klibanov, *Trends Biotechnol.* **1997**, *15*, 97-101.

[21] A. M. Klibanov, *Nature* **2001**, *409*, 241-246.

[22] W. Kauzmann, in *Adv. Protein Chem., Vol. Volume 14* (Eds.: M. L. A. K. B. C.B. Anfinsen, T. E. John), Academic Press, **1959**, pp. 1-63.

[23] Lipase AK "Amano", http://www.amano-enzyme.co.jp/pdf/synthe_e/cat_synthe_LAK_e.pdf, **2008**.

[24] C. Botuha, C. M. S. Galley, T. Gallagher, *Org. Biomol. Chem.* **2004**, *2*, 1825-1826.

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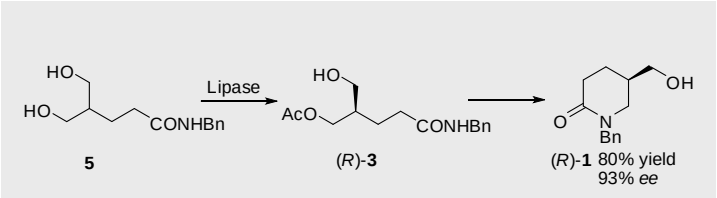

Chemoenzymatic synthesis of chiral 1-benzyl-5-(hydroxymethyl)-2-piperidone enabled by lipase AK desymmetrization of prochiral 1,3-diol and its diacetate

Key Topic* Asymmetric synthesis

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*Desymmetrization, chiral 2-piperidones