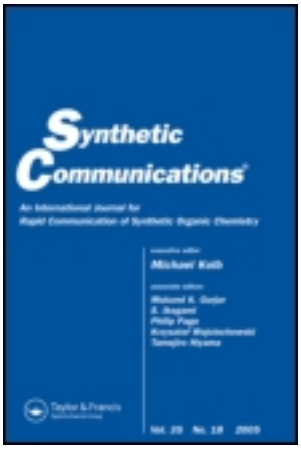

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Novel Synthesis of Optically Active 2-Ethylhexanoic Acid, 2-Ethylhexanol, and 2-Ethylhexylamine via the Asymmetric Favorskii Rearrangement

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Abstract: The asymmetric Favorskii rearrangement of optically active α-haloketones, which are easily prepared from chiral menthyl-4-toluenesulfoxide in several steps using primary or secondary amines, yields their corresponding secondary or tertiary chiral amides. The secondary chiral amides were converted to acids or amines using acylation followed by hydrolysis or reduction. In addition, the tertiary amides were directly reduced to alcohol with Super-Hydride®.

Keywords: Asymmetric Favorskii rearrangement, enantioselective reactions, optically active amide

The Favorskii rearrangement is a well-known organic reaction that uses α-haloketones. These α-haloketones, when treated with a base such as hydroxide, alkoxide, or amine, can undergo a rearrangement reaction to give carboxylic acids or carboxylic acid derivatives.[1,2]

We have previously reported that this rearrangement is applicable to the asymmetric reaction, and that this reaction may be followed by the formation of cyclopropanone intermediated via the six-membered cyclic transition state.[3]

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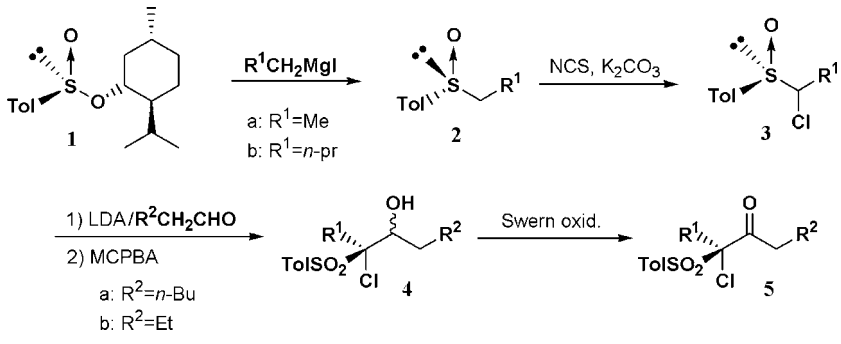


Figure 1. Synthesis of (*R*)-2-chloro-2-tosyl ketone **5**.

2-Ethylhexanoic acid and 2-ethylhexanol, each of which has a chiral center in its alkyl branch, are biologically active substances,[4] and these compounds are useful building blocks for novel functionalized optically active surfactants.[5]

Therefore, we attempted a synthesis of enantiomers and 2-ethylhexylamine as a corresponding amine using the asymmetric Favorskii rearrangement.

First, optically active α-haloketones **5** (75–99% ee) were easily prepared from (−)-(*1R, 2S, 5R*)-menthyl-4-toluenesulfoxide **1** in six steps (Figure 1 and Table 1).[6]

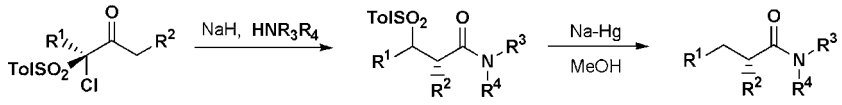
Next, in the asymmetric Favorskii rearrangement, optically active α-haloketones **5** were treated with NaH in dry THF with benzylamine or piperidine at 0°C for 2.5 h[3] (Scheme 1).

A clean reaction took place, and chiral amides **6** were obtained in good yield. The sulfonyl group of **6** was reduced with a Na-Hg amalgam in absolute methanol[7] at 0°C for 2 h to give optically active amides **7** (Table 2).

Table 1. Synthesis of (*R*)-2-chloro-2-tosyl ketone **5** from (*l*)-menthyl sulfoxide **1**

R^1	R^2	Product	Yield	$[\alpha]_D{}^a$	ee (%)^b
Me	*n*-Bu	2a	99	—	—
n-Pr	Et	2b	94	—	—
Me	*n*-Bu	3a	93	—	—
n-Pr	Et	3b	85^c	—	—
Me	*n*-Bu	4a	97	—	—
n-Pr	Et	4b	98	—	—
Me	*n*-Bu	5a	92	−33.9	75
n-Pr	Et	5b	96	−30.6	99

[a]Measured in acetone at room temperature.
[b]Calculated from HPLC using Daicel OD-H column.
[c]Recrystallization from petroleum ether.



Scheme 1.

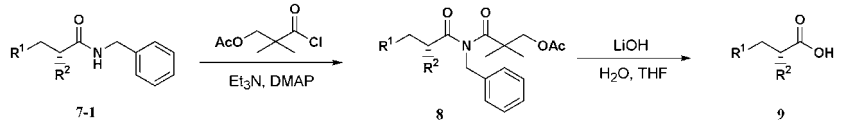
Optically active 2-ethylhexanoic acid was easily converted from **7a-1** and **7b-1**.[8] **7a-1** was treated with an excess of 3-acetoxy-2,2-dimethylpropionyl chloride in the presence of triethylamine and a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) in CH_2Cl_2 at room temperature. The product, **8a**, was hydrolyzed by LiOH aqueous solution under mild conditions (Scheme 2).

As a result of the acylation/hydrolysis, (*S*)-2-ethylhexanoic acid **9a** was obtained in 72% yield (two steps) and 96% ee. Through the same procedure, (*R*)-2-ethylhexanoic acid **9b** was synthesized from **7b-1** (Table 3).

Table 2. Synthesis of optically active amides **7** via the asymmetric Favorskii rearrangements of **5**

	HNR^3R^4				
Compound	R_3	R_4	Product	Yield (%)	ee (%)[a]
5a	$PhCH_2$	H	**6a-1**	93	—
	$-(CH_2)_5-$		**6a-2**	88	—
5b	$PhCH_2$	H	**6b-1**	97	—
	$-(CH_2)_5-$		**6b-2**	82	—
5a	$PhCH_2$	H	**7a-1**	85[b]	99
	$-(CH_2)_5-$		**7a-2**	90	—
5b	$PhCH_2$	H	**7b-1**	90[b]	99
	$-(CH_2)_5-$		**7b-2**	85	—

[a]Calculated from HPLC using Daicel OJ-H column.
[b]Recrystallization from petroleum ether.



Scheme 2.

Table 3. Synthesis of 2-ethylhexanoic acid enantiomer **9** from optically active amide **7**

Compound	Product	Yield (%)	$[\alpha]_D{}^a$	ee (%)^b
7a-1	**8a**	92	—	—
7b-1	**8b**	92	—	—
7a-1	**9a** (*S*)	83	+11.2	96
7b-1	**9b** (*R*)	81	−10.6	92

[a]Measured in acetone at room temperature.

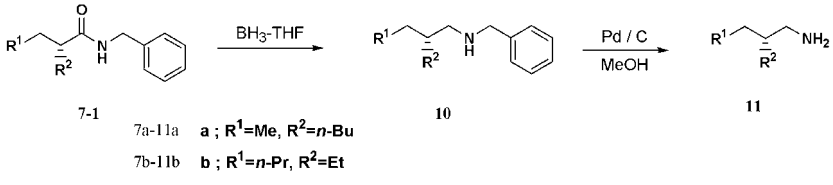
[b]The ee of **9** was derived for its 2-nitro benzyl amide derivative, which calculated from HPLC using Waters Opti Pak-TA column.

(*S*)-2-Ethylhexylamine **11a** was prepared as shown in Scheme 3.

Chiral amide **7a-1** was reduced with BH_3-THF solution at room temperature for 2 h, which gave the (*S*)-benzylamine derivative, **10a**, in good yield. The **10a** was treated with a 10% Pd/C catalytic reduction for (*S*)-2-ethylhexyl amine **11a**, which was produced in good enantiomeric excess[9] and yield (Table 4).

(*S*)-2-Ethylhexanol **12a** was synthesized from a tertiary amide of **7a-2**. The tertiary amide, **7a-2**, was treated with a 2.5 eq. Super-Hydride® in THF at 0°C for 40 min.[10] The reduction occurred immediately, and (*S*)-2-ethylhexanol **12a** was obtained (Scheme 4).

The enantiomeric excess of **12a** was determined and calculated by HPLC analysis of its 4-nitro benzoyl ester derivative (Table 5).

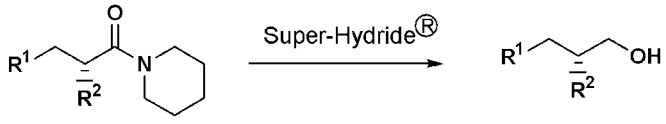


Scheme 3.

Table 4. Synthesis of 2-ethylhexylamine enantiomer **11** from optically active amide **7**

Compound	Product	Yield (%)	$[\alpha]_D{}^a$	ee (%)
7a-1	**10a**	92	—	—
7b-1	**10b**	90	—	—
7a-1	**11a** (*S*)	94	+1.16	99
7b-1	**11b** (*R*)	92	−1.17	99

[a]Measured in acetone at room temperature.



7-2 12

7a-12a **a ; R^1=Me, R^2=*n*-Bu**

7b-12b **b ; R^1=*n*-Pr, R^2=Et**

Scheme 4.

Table 5. Synthesis of 2-ethylhexanol enantiomer **12** from optically active amide **7**

Compound	Product	Yield (%)	$[\alpha]_D$[a]	ee (%)[b]
7a-2	**12a** (*S*)	85	+2.6	75
7b-2	**12b** (*R*)	94	−3.3	91

[a]Measured in acetone at room temperature.

[b]The ee of **12** was derived for its 4-nitro benzoyl ester derivative, which was calculated from HPLC using Daicel AS-H column.

In conclusion, we succeeded in synthesizing the optically active enantiomers of 2-ethylhexanoic acid, 2-ethylhexanol, and 2-ethylhexylamine. We were able to synthesize only a small amount of the (*R*)-enantiomer of (*S*)-2-ethylhexanol.

As far as we know, this is the first report of the synthesis of these compounds using asymmetric Favorskii rearrangement. The reaction can be used widely for the synthesis of various optically active compounds that have functional groups.

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