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SYNTHESIS OF CHIRAL α-ACETOXY-N-ACETYLAMIDES FROM CHIRAL PYRIMIDYLALKANOLS BY THE OXIDATIVE CLEAVAGE OF PYRIMIDINE RING

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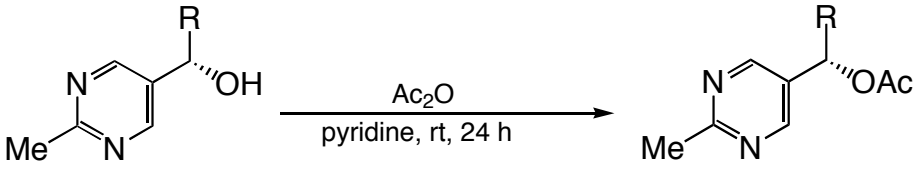
Abstract - Acetates of chiral 5-pyrimidylalkanols are transformed into chiral α-acetoxy-N-acetylamides and α-acetoxyamides without racemization in high total yields by the oxidative cleavage of pyrimidine ring using ruthenium tetroxide.

Benzene ring is known to undergo oxidative cleavage to afford carboxylic acid by the use of ruthenium tetroxide.[1] The oxidative cleavage of benzene ring has been utilized for the transformation of chiral secondary phenylalkanols into the corresponding chiral hydroxy carboxylic acids.[2] On the other hand, in the course of our continuing study on the catalytic enantioselective alkylation of aldehydes,[3] we have reported the synthesis of various chiral 5-pyrimidylalkanols by the enantioselective alkylation of pyrimidine-5-carbaldehyde using dialkylzincs.[4] Moreover we have reported that certain chiral 5-pyrimidylalkanols operate as asymmetric autocatalysts with amplification of enantiomeric excess (e.e.) in the addition of diisopropylzinc to pyrimidine-5-carbaldehyde.[5]

To the best of our knowledge, however, no example of the oxidative cleavage of pyrimidine ring has been reported. Thus, the development of the method for the oxidative cleavage of pyrimidine ring of chiral 5-pyrimidylalkanols may provide a new synthetic tool for the preparation of various chiral α-hydroxy-carboxylic acid derivatives.

Chiral pyrimidylalkanols (**1a-d**)[4] were protected as acetates (**2a-d**) in 87-96% by the reaction with acetic anhydride in pyridine (Eq.1).



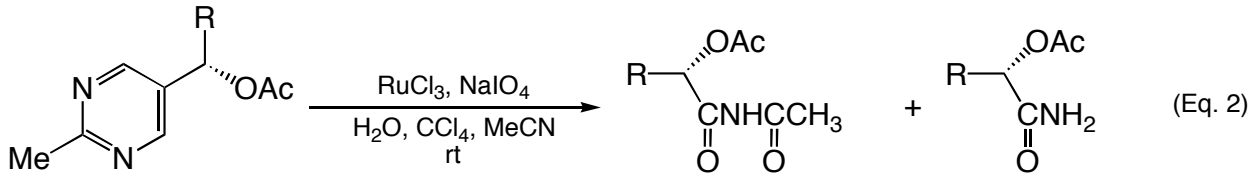
(Eq. 1)

1a-d **2a-d**

a; R=i-Pr, **b**; R=Et, **c**; R=n-Bu, **d**; R=n-Pentyl

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

Then they were submitted to the oxidative cleavage of pyrimidine ring (Eq. 2, Table 1): In a mixed solvent of water, carbon tetrachloride and acetonitrile, chiral acetate ((S)-**2a**) (R=i-Pr) was treated with ruthenium tetroxide (RuO_4),[2] which was prepared in situ from 15 mol% of ruthenium trichloride hydrate and 20 equivalents of sodium metaperiodate. The reaction smoothly proceeded at room temperature to afford chiral α-acetoxy-N-acetylamide ((S)-**3a**) (95% e.e.) and α-acetoxy amide ((S)-**4a**) (95% e.e.) in high total yield of 91% and it is ascertained that the optical purity of **2a** (95% e.e.) was completely retained (Entry 1). Under the same reaction conditions, other acetates ((S)-**2b**-**d** (R=Et, n-Bu, n-Pentyl)) were also transformed into the corresponding N-acetylamides (**3b**-**d**) (89-93% e.e.) and amides (**4b**-**d**) (91-93% e.e.) in the total yields of 76-89% with complete retention of configuration. As far as we know, these results are the first example of the oxidative cleavage of pyrimidine ring to give chiral carboxylic acid derivatives.[6]



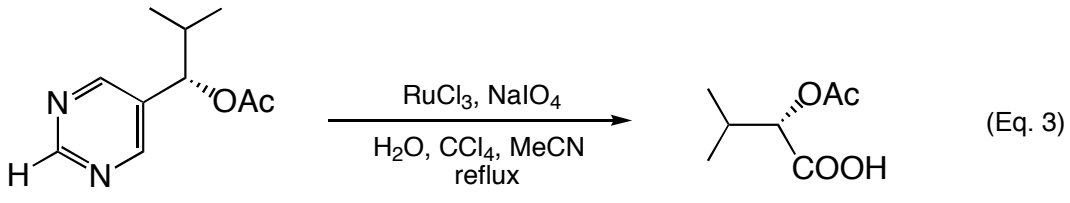
2a-d **3a-d** **4a-d** (Eq. 2)

Table 1. Oxidative cleavage of pyrimidine ring of **2a-d** using RuO_4.

Entry	Acetate **2**			N-Acetylamides **3**		Amide **4**		Total yield
	R		E.e. (%)[a]	Yield(%)	E.e.(%)[a]	Yield(%)	E.e.(%)[a]	**3**+**4** (%)
1	i-Pr	**2a**	95 (S)[b]	**3a** 80	95 (S)	**4a** 11	95 (S)	91
2	Et	**2b**	90 (S)[b]	**3b** 75	89 (S)	**4b** 13	91 (S)	88
3	n-Bu	**2c**	93 (S)[c]	**3c** 75	92 (S)	**4c** 14	92 (S)	89
4	n-Pentyl	**2d**	94 (S)[c]	**3d** 59	93 (S)	**4d** 17	93 (S)	76

[a] Determined by HPLC analysis using a chiral column. [b] Absolute configuration is already determined.[4, 5b]
[c] Absolute configuration was estimated by the analogy with **2a** and **2b**.

Next, we examined the oxidative cleavage of chiral acetate ((S)-**2e**) (89% e.e.) possessing 5-pyrimidyl group instead of 2-methyl-5-pyrimidyl group (Eq. 3). The reaction proceeded under the same conditions with those of **2a-d** except that higher reaction temperature was needed. As a result, instead of the corresponding N-acetylamide (**3a**) and amide (**4a**), chiral α-acetoxy carboxylic acid ((S)-**5**) was obtained in 41% with 86% e.e.



2e
89% e.e.

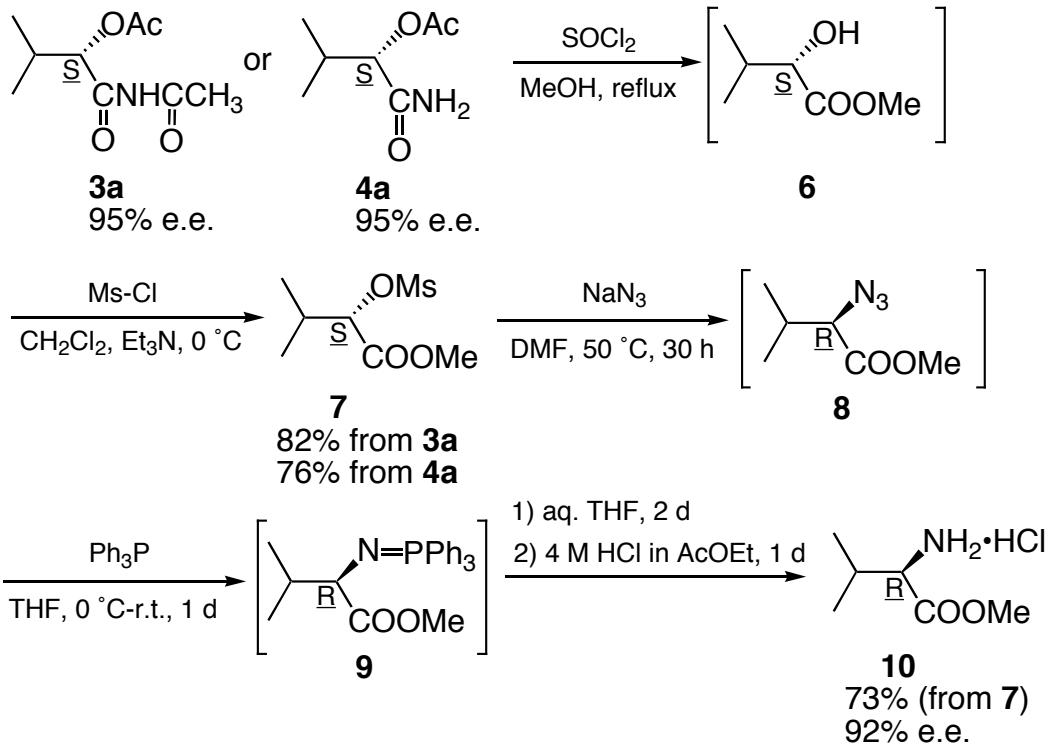
5 41%
86% e.e.

(Eq. 3)

These results imply that 1) acetylamino moiety of **3a-d** is derived from 1- and 2-positions of 2-

methylpyrimidine ring of acetates (**2a**-**d**), 2) chiral α-acetoxy carboxylic acids may be firstly formed, then they were transformed into N-acetylamides (**3a-d**) and amides (**4a-d**).

Synthetic utility of chiral α-acetoxy-N-acetylamide (**3a**) and α-acetoxyamide (**4a**) is exemplified by the transformation into chiral valine (α-amino acid) ester with almost no racemization (Scheme 1). Both (S)-**3a** (95% e.e.) and (S)-**4a** (95% e.e.) were readily converted into α-hydroxy methyl ester ((S)-**6**) by the removal of the acetyl group and esterification using thionyl chloride in refluxing methanol.[7] Then α-hydroxy methyl ester (**6**) was isolated as its mesylate ((S)-**7**) in the total yield of 82% from **3a** and in the total yield of 76% from **4a**. Mesylate ((S)-**7**) reacted with sodium azide in DMF at 50 ℃ to provide azide ((R)-**8**) with a stereogenic inversion.[8] Then the azide group was reduced to the corresponding amine by Staudinger reaction.[9] Azide ((R)-**8**) was treated with triphenylphosphine to give the corresponding iminophosphorane ((R)-**9**). The subsequent hydrolysis of iminophosphorane (**9**) in aqueous THF followed by the treatment with 4 M HCl in ethyl acetate gave (R)-valine methyl ester hydrochloride (**10**) [$[\alpha]^{24}_{D}$ -22.0° (*c* 2.0, MeOH)] in the total yield of 73% from mesylate (**7**). The optical purity of **10** was determined to be 92% e.e. as its p-toluenesulfonamide by HPLC analysis using a chiral column. Thus, chiral N-acetylamide ((S)-**3a**) and amide ((S)-**4a**) were derived into valine derivative ((R)-**10**) with almost no loss of the optical purity.



Scheme 1.

As described, oxidative cleavage of pyrimidine ring by RuO_4 provides a new route for the transformation of acetates of chiral pyrimidylalkanols into chiral α-acetoxy-N-acetylamides and α-acetoxyamides, which are synthetic equivalents of chiral α-hydroxy carboxylic acids, without racemization.

EXPERIMENTAL

General. Optical rotation was measured by Jasco DIP-1000 polarimeter. IR spectra were recorded with

Horiba FT210 spectrophotometer. ^{1}H NMR spectra (300 MHz) were measured with Bruker DPX300 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ was used as solvent. HRMS were obtained with JEOL JMS-SX102A mass spectrometer.

Methanol was distilled from calcium hydride and dried over molecular sieves 3A (MS 3A).THF was distilled from lithium aluminium hydride and dried over molecular sieves 4A (MS 4A). DMF was distilled and dried over molecular sieves 4A (MS 4A). Dichloromethane and chloroform were distilled from calcium hydride and dried over molecular sieves 4A (MS 4A). Chiral pyrimidylalkanols (**1a**, **1b** and **1c**) were prepared according to the literature procedure.[4]

(S)-(-)-1-(2-Methyl-5-pyrimidyl)-1-hexanol (1d). A mixture of a toluene solution (10 mL) of (1S,2R)-N,N-dibutylnorephedrine (316.1 mg, 1.2 mmol) and 1 M toluene solution of dipentylzinc (3.6 mmol, 3.6 mL) was stirred for 20 min at 0 ℃. Then 2-methylpyrimidine-5-carbaldehyde[10] (146.5 mg, 1.2 mmol) in a toluene solution (3 mL) was added. The reaction mixture was stirred at 0 ℃ for 36 h. The reaction was quenched by the successive addition of 1 M HCl (5 mL) and sat. aq. $NaHCO_3$ (15 mL) at 0 ℃. The mixture was filtered using celite and the filtrate was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated under reduced pressures. Purification of the residue by TLC on silica gel gave the pyrimidylalkanol (**1d**). 189.9 mg. Yield 82%. Colorless oil. Optical purity was determined to be 94% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 0.5 mL/min, retention time: 13 min for the minor isomer and 16 min for the major isomer). $[\alpha]^{29}_D$ -33.12° (*c* 9.5, MeOH); IR (neat) 1450.2, 3382.5 cm^{-1}; ^{1}H NMR δ= 0.89-0.90 (m, 3H), 1.29-1.47 (m, 2H+2H+2H), 1.64-1.87 (m, 2H), 2.66 (s, 3H) 4.71 (br s, 1H) 4.85 (t, J= 3.5 Hz, 1H) 8.55 (s, 2H); HRMS Found m/z 194.1412. Calcd for $C_{11}H_{18}N_2O$: M, 194.1419.

Typical procedure for the preparation of (S)-(-)-2-methyl-1-(2-methyl-5-pyrimidyl)-1-alkyl acetates (2a-2d). To a stirred solution of pyrimidylalkanol (**1a**)[5] (0.94 g, 5.7 mmol) in pyridine (6.0 mL) was added dropwise acetic anhydride (2.3 g, 22.6 mmol, 2.1 mL) at 0 ℃. After 24 h the reaction mixture was concentrated in vacuo, diluted with H_2O (20 mL) and extracted three times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered and evaporated. The residue was purified by column chromatography on silica gel to give the acetates (**2a**).

(S)-(-)-2-Methyl-1-(2-methyl-5-pyrimidyl)-1-propyl acetate (2a). Colorless oil. 1.07 g. Yield 91%. $[\alpha]^{24}_D$ -87.60° (*c* 2.1, MeOH); IR (neat) 1743.3 cm^{-1}; ^{1}H NMR δ= 0.84 (d, J= 6.8 Hz, 3H), 1.00 (d, J=6.8, 3H), 2.10 (s, 3H), 2.13 (dqq, J= 7.3, 6.8, 6.8 Hz, 1H), 2.74 (s, 3H), 5.43 (d, J= 7.3 Hz, 1H), 8.57 (s, 2H); HRMS Found m/z 208.1202. Calcd for $C_{11}H_{16}N_2O_2$: M, 208.1213.

(S)-(-)-1-(2-Methyl-5-pyrimidyl)-1-propyl acetate (2b). Pyrimidylalkanol (**1b**) (0.16 g, 1.06 mmol) was used as a starting material. Colorless oil. 0.18 g. Yield 87%. $[\alpha]^{30}_D$ -88.17° (*c* 1.9, MeOH); IR (neat) 1743.3 cm^{-1}; ^{1}H NMR δ= 0.94 (dd, J= 7.2, 7.2 Hz, 3H), 1.86 (dq, J=7.0, 7.2, 1H), 1.99 (dq, J= 7.0, 7.2 Hz, 1H), 2.10 (s, 3H), 2.74 (s, 3H), 5.66 (dd, J= 7.0, 7.0 Hz, 1H), 8.63 (s, 2H); HRMS Found m/z 194.1048. Calcd for $C_{10}H_{14}N_2O_2$: M, 194.1055.

(S)-(-)-1-(2-Methyl-5-pyrimidyl)-1-pentyl acetate (2c). Pyrimidylalkanol (**1c**) (0.17 g, 0.93 mmol) was used as a starting material. Colorless oil. 0.20 g. Yield 96%. $[\alpha]^{31}_D$ -68.52° (*c* 1.03, MeOH);

IR (neat) 1739.5 cm^{-1}; ^1H NMR δ= 0.89 (t, J= 7.0, 7.0 Hz, 3H), 1.20-1.41 (m, 2H+2H), 1.74-1.87 (m, 1H), 1.92-2.04 (m, 1H), 2.08 (s, 3H), 2.74 (s, 3H), 5.71 (dd, J= 7.6, 7.6 Hz, 1H), 8.62 (s, 2H); HRMS Found m/z 222.1380. Calcd for $C_{12}H_{18}N_2O_2$: M, 222.1368.

(S)-(-)-1-(2-Methyl-5-pyrimidyl)-1-hexyl acetate (2d). Pyrimidylalkanol (**1d**) (0.18 g, 0.93 mmol) was used as a starting material. Colorless oil. 0.20 g. Yield 92%. $[\alpha]^{29}_D$ -67.56° (*c* 1.87, MeOH); IR (neat) 1743.3 cm^{-1}; ^1H NMR δ= 0.85-0.90 (m, 3H), 1.23-1.42 (m, 2H+2H+2H), 1.73-1.87 (m, 1H), 1.93-2.03 (m, 1H), 2.08 (s, 3H), 2.74 (s, 3H), 5.71 (dd, J= 6.6, 7.6 Hz, 1H), 8.63 (s, 2H); HRMS Found m/z 236.1498. Calcd for $C_{13}H_{20}N_2O_2$: M, 236.1525.

Preparation of chiral N-acetylamides (3a-3d) and amides (4a-4d) by the oxidative cleavage of 1-(2-methyl-5-pyrimidyl)-1-alkyl acetates (2a-2d) with ruthenium tetroxide. To a solution of chiral acetate (**2a**) (1.07 g, 5.15 mmol) in carbon tetrachloride (7.8 mL) was added sodium metaperiodate (22.0 g, 103 mmol). After injecting acetonitrile (7.8 mL) and water (19.5 mL), ruthenium trichloride hydrate (0.160 g, 0.77 mmol, 15 mol%) was added. The reaction mixture was vigorously stirred for 12 h at rt. To the reaction mixture, water (100 mL) and dichloromethane (50 mL) were added and organic layer was separated. Aqueous layer was extracted two times with ethyl acetate. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo . Purification of the residue by flash column chromatography on silica gel (hexane : ethyl acetate = 10 : 1 to 3 : 1) afforded the chiral N-acetylamide (**3a**) and chiral amide (**4a**).

(S)-(-)-N-Acetyl-2-acetoxy-3-methylbutanamide (3a). Plate crystal. 0.82 g. Yield 80%. mp 55-56 ℃. Optical purity was determined to be 95% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 254 nm UV detector, rt, eluent: 3% i-propanol in hexane, flow rate: 0.3 mL/min, retention time: 51 min for minor isomer and 65 min for major isomer). $[\alpha]^{24}_D$ -2.92° (*c* 1.3, MeOH); IR (KBr) 1712.5, 1724.1, 1747.2 cm^{-1}; ^1H NMR δ= 0.99 (d, J= 6.8 Hz, 3H), 1.02 (d, J= 6.8 Hz, 3H), 2.19 (s, 3H), 2.33 (dqq, J= 4.6, 6.8, 6.8 Hz, 1H), 2.44 (s, 3H), 5.05 (d, J= 4.6 Hz, 1H), 9.24 (br s, 1H).; HRMS Found m/z 202.1078. Calcd for $C_9H_{16}NO_4$: M+1, 202.1079.

(S)-(-)-N-Acetyl-2-acetoxybutanamide (3b). Acetate (**2b**) (0.14 g, 0.74 mmol) was used as a starting material. Colorless oil. 0.10 g. Yield 75%. Optical purity was determined to be 89% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 9 min for minor isomer and 12 min for major isomer). $[\alpha]^{31}_D$ -23.8° (*c* 2.51, MeOH); IR (neat) 1712.5, 1743.3 cm^{-1}; ^1H NMR δ= 0.98 (dd, J= 7.4, 7.4 Hz, 3H), 1.89 (ddq, J= 4.9, 7.4, 7.4 Hz, 2H), 2.19 (s, 3H), 2.46 (s, 3H), 5.17 (dd, J= 4.9, 7.4 Hz, 1H), 8.46 (br s, 1H), ; HRMS Found m/z 188.0918. Calcd for $C_8H_{14}NO_4$: M+1, 188.0923.

(S)-(-)-N-Acetyl-2-acetoxyhexanamide (3c). Acetate (**2c**) (0.17 g, 0.78 mmol) was used as a starting material. Colorless oil. 0.13 g. Yield 75%. Optical purity was determined to be 92% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 6 min for minor isomer and 9 min for major isomer). $[\alpha]^{27}_D$ -26.45° (*c* 2.18, MeOH); IR (neat) 1673.9, 1739.5 cm^{-1}; ^1H NMR δ= 0.92 (t, J= 7.1 Hz, 3H), 1.29-1.45 (m, 2H+2H), 1.80-1.89 (m, 2H), 2.18 (s, 3H), 2.43 (s, 3H), 5.19 (dd, J= 5.2, 7.2 Hz, 1H), 9.09 (br s, 1H); HRMS Found m/z 216.1222. Calcd for $C_{10}H_{18}NO_4$: M+1, 216.1236.

(S)-(-)-N-Acetyl-2-acetoxyheptanamide (3d). Acetate (**2d**) (0.18 g, 0.74 mmol) was used as a starting material. Colorless oil. 0.091 g. Yield 59%. Optical purity was determined to be 93% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 0.8 mL/min, retention time: 7 min for minor isomer and 11 min for major isomer). $[\alpha]^{31}_{D}$ -23.09° (*c* 2.84, MeOH); IR (neat) 1708.6, 1747.2 cm^{-1}; ^{1}H NMR δ= 0.87-0.92 (m, 3H), 1.31-1.44 (m, 2H+2H+2H), 1.74-1.92 (m, 2H), 2.17 (s, 3H), 2.43 (s, 3H), 5.17-5.21 (m, 1H), 9.28 (br s, 1H); HRMS Found m/z 230.1347. Calcd for $C_{11}H_{20}NO_4$: M+1, 230.1347.

(S)-(-)-2-Acetoxy-3-methylbutanamide (4a). Colorless oil. 0.091 g. Yield 11%. Optical purity was determined to be 95% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 210 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 14 min for minor isomer and 26 min for major isomer). $[\alpha]^{24}_{D}$ -15.7° (*c* 3.52, MeOH); IR (neat) 1677.8, 1739.5 cm^{-1}; ^{1}H NMR δ= 0.98 (d, J =6.9 Hz, 6H), 2.17 (s, 3H), 2.25 (dseptet, J= 4.6, 6.9 Hz, 1H), 5.00 (d, J= 4.6 Hz, 1H), 6.27 (br s, 1H), 6.63 (br s, 1H); HRMS Found m/z 159.0894. Calcd for $C_7H_{13}NO_3$: M, 159.0896.

(S)-(-)-2-Acetoxybutanamide (4b). Acetate (**2b**) (0.14 g, 0.74 mmol) was used as a starting material. Colorless oil. 0.014 g. Yield 13%. Optical purity was determined to be 95% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 210 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for minor isomer and 15 min for major isomer). $[\alpha]^{31}_{D}$ -22.35° (*c* 0.69, MeOH); IR (neat) 1712.5, 1747.2 cm^{-1}; ^{1}H NMR δ= 0.98 (dd, J= 7.4, 7.4 Hz, 3H), 1.89 (dq, J= 6.3, 7.4 Hz, 1H+1H), 2.17 (s, 3H), 5.15 (dd, J= 6.3, 6.3 Hz, 1H), 6.11 (br s, 2H); HRMS Found m/z 145.0771. Calcd for $C_6H_{11}NO_3$: M, 145.0739.

(S)-(-)-2-Acetoxyhexanamide (4c). Acetate (**2c**) (0.17 g, 0.78 mmol) was used as a starting material. Colorless oil. 0.019 g. Yield 14%. Optical purity was determined to be 92% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 210 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 15 min for minor isomer and 28 min for major isomer). $[\alpha]^{31}_{D}$ -12.98° (*c* 0.9, MeOH); IR (neat) 1685.5, 1739.5 cm^{-1}; ^{1}H NMR δ= 0.90 (t, J= 7.1 Hz, 3H), 1.28-1.41 (m, 2H+2H), 1.79-1.94 (m, 2H), 2.16 (s, 3H), 5.15 (dd, J= 5.1, 7.0 Hz, 1H), 6.10 (br s, 2H); HRMS Found m/z 173.1051. Calcd for $C_8H_{15}NO_3$: M, 173.1052.

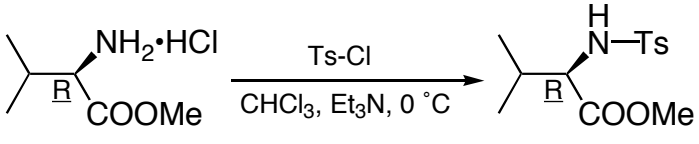
(S)-(-)-2-Acetoxyheptanamide (4d). Acetate (**2d**) (0.18 g, 0.74 mmol) was used as a starting material. Colorless oil. 0.024 g. Yield 17%. Optical purity was determined to be 93% e.e. by HPLC analysis using a chiral column (Daicel Chiralcel OD: 4 x 250 mm, 210 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 0.7 mL/min, retention time: 13 min for minor isomer and 18 min for major isomer). $[\alpha]^{31}_{D}$ -11.63° (*c* 0.92, MeOH); IR (neat) 1677.8, 1739.5 cm^{-1}; ^{1}H NMR δ= 0.86-0.91 (m, 3H), 1.27-1.42 (m, 2H+2H+2H), 1.78-1.94 (m, 2H), 2.16 (s, 3H), 5.15 (t, J= 6.0 Hz, 1H), 6.15 (br s, 2H); HRMS Found m/z 188.1279. Calcd for $C_9H_{18}NO_3$: M+1, 188.1287.

(S)-(-)-2-Acetoxy-3-methylbutanoicacid (5). Colorless oil. 0.066 g. Yield 40.9%. Optical purity was determined to be 86% e.e. by comparison of the optical rotation with that in the literature. $[\alpha]^{27.7}_{D}$ -24.18° (*c* 1.26, CH_2Cl_2) (lit.,[7] $[\alpha]_{D}$ -28.2° (*c* 1.5, CH_2Cl_2) for optical pure (S)-isomer). ^{1}H nmr spectra accorded with those in literature.[7]

(S)-(-)-Methyl 2-methanesulfonyloxy-3-methylbutanoate (7). To a vigorously stirred solution of **3a** (0.93 g, 4.1 mmol) in methanol (5.0 mL) was added dropwise thionyl chloride (1.63 g, 1.0 mL, 13.7 mmol) at 0 ℃, and the reaction mixture was refluxed for 3 h. Further twice additions of a pair of methanol (2 mL) and thionyl chloride (1.63 g, 1.0 mL, 13.7 mmol) following refluxing for 2 h were performed, then the reaction was quenched by water (5 mL) at 0 ℃. The mixture was extracted three times with ether. The extracts were dried over anhydrous sodium sulfate and the most part of the solvent was evaporated under reduced pressures at 10 ℃ to give crude **6**. Triethylamine (1.45 g, 2.0 mL, 14.4 mmol) and methanesulfonyl chloride (0.92 g, 0.62 mL, 8.0 mmol) was added at 0 ℃ to the solution of crude **6** in dichloromethane (3.0 mL). After the mixture was stirred for 10 min, the reaction was quenched by water (5 mL). The aqueous layer was extracted three times with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and evaporated in vacuo to give the crude compound (**7**). Purification by flash column chromatography on silica gel (hexane : dichloro methane = 4:1) afforded methanesulfonate ((S)-**7**). 0.69 g. Yield 82%. Colorless oil. Optical purity was determined to be 94% e.e. by ^{1}H-NMR using (+)-Eu(hfc)$_3$. $[\alpha]^{24}_D$ -39.6° (*c* 1.2, MeOH); IR (neat) 1180.2, 1357.6, 1754.9 cm^{-1}; ^{1}H NMR δ= 0.97 (d, J= 6.9 Hz, 3H), 1.07 (d, J= 6.9 Hz, 3H), 2.33 (dqq, J= 4.1, 6.9, 6.9 Hz, 1H), 3.15 (s, 3H), 3.81 (s, 3H), 4.88 (d, J= 4.1 Hz, 1H); HRMS Found m/z 211.0647. Calcd for $C_7H_{15}O_5S$: M+1, 211.0641.

The procedure for the transformation of (S)-methanesulfonate (7) into (R)-valine methyl ester hydrochloride (10). To a solution of **7** (0.69 g, 3.3 mmol) in DMF (10 mL), sodium azide (0.73 g, 11.2 mmol) was added. After stirring 30 h at 50 ℃, water (5.0 mL) was added to the reaction mixture. Organic layer was extracted three times with ether. The extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo at 10 ℃. The resulting residue was dissolved in THF (5.0 mL) and the solution of triphenylphosphine (1.72 g, 6.6 mmol) in THF (3.0 mL) was added dropwise at 0 ℃ and the reaction mixture was stirred for 24 h. Water (0.1 mL) was added and the reaction mixture was stirred for another 48 h. The solution of 4 M hydrochloric acid in ethyl acetate (1.6 mL) was added. After the mixture was stirred for further 24 h, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (ethyl acetate : methanol = 10 : 1) to afford valine methyl ester hydrochloride (**10**) (0.40 g, 2.4 mmol) as colorless needle. Yield 73%. mp 161-162 ℃. Optical purity was determined to be 92% e.e. as its tosylate by HPLC analysis using a chiral column. $[\alpha]^{24}_D$ -22.0° (*c* 2.0, MeOH), lit.,[11] $[\alpha]^{21}_D$ +23.6° (*c* 2, MeOH) for optically pure (S)-isomer; IR (KBr) 1747 cm^{-1}; ^{1}H NMR δ= 1.14 (d, J=7.0 Hz, 3H), 1.16 (d, J=7.0 Hz, 3H), 2.47 (dqq, J=4.3, 7.0, 7.0 Hz, 1H), 3.83 (s, 3H), 3.96 (d, J=4.3 Hz, 1H), 7.5-10.5 (br s, 3H); HRMS Found m/z 132.1008. Calcd for $C_6H_{14}N\ O_2$: M-35, 132.1025.

(R)-(-)-Methyl 2-p-toluenesulfonylamino-3-methylbutanoate.



10

To a solution of valine methyl ester hydrochloride (**10**) (0.084 g, 0.5 mmol) in $CHCl_3$ (3 mL), triethylamine (0.14 g, 0.19 mL, 1.5 mmol) and a chloroform solution (1 mL) of p-toluenesulfonyl chloride

(0.19 g, 1.0 mmol) was added dropwise at 0 ℃, then the reaction mixture was stirred at rt for 1 h. Water (5.0 mL) was added to the reaction mixture and organic layer was extracted three times with dichloromethane. The extracts were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was purified by thin layer chromatography (TLC) on silica gel (developing solvent. hexane : acetone = 3 : 1, then hexane : 2-propanol = 10 : 1). p-Toluenesulfonamide was obtained. 0.14 g. Yield 94%. Colorless needle. mp 74-75 ℃. Optical purity was determined to be 92% e.e. by HPLC analysis using a chiral column (Daicel Chiralpak AS: 4 x 250 mm, 254 nm UV detector, rt, eluent: 10% i-propanol in hexane, flow rate: 1.0 mL/min, retention time: 13 min for major isomer and 20 min for minor isomer). $[\alpha]^{24}_{D}$ -3.2° (*c* 3.3, MeOH); IR (KBr) 1164.8, 1334.5, 1743.3, 3282.3 cm^{-1}; ^{1}H NMR δ= 0.87 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H), 2.03 (dqq, J=5.2, 6.8, 6.8 Hz, 1H), 2.42 (s, 3H), 3.44 (s, 3H),3.73 (dd, J=5.2, 10.1 Hz, 1H), 5.06 (d, J=10.1 Hz, 1H), 7.27-7.30 (m, 2H), 7.70-7.72 (m, 2H); HRMS Found m/z 285.1044. Calcd for $C_{13}H_{19}O_4NS$: M, 285.1036.

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