

COUMARIN-CONTAINING AMINO ACIDS AND OXY ACIDS AS CHIRAL DISCRIMINATING AGENTS. Part III. NOVEL CRYSTALLINE (*R*)-(+)- AND (*S*)-(-)-*O*-COUMARINYL LACTIC ACIDS AS CHIRAL DERIVATIZING AGENTS FOR ¹H NMR INSPECTION OF OPTICAL PURITIES OF ALCOHOLS AND AMINES^{1,2}

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Abstract- Commercially available (*S*)-(-)-ethyl lactate and (*R*)-(+)-methyl lactate were quite simply coupled with commercial 4-hydroxycoumarin by the Mitsunobu reaction followed by alkaline hydrolysis to furnish new crystalline optically pure (*R*)-(+)- and (*S*)-(-)-*O*-coumarinyl lactic acids [RCLOH and SCLOH] in good yields. Diastereomeric esters and amides derived easily and quantitatively from these acids were subjected to chiral shift ¹H NMR examination, revealing that these were efficient and reliable chiral derivatizing agents. Either racemization or kinetic resolution was not induced during derivatization.

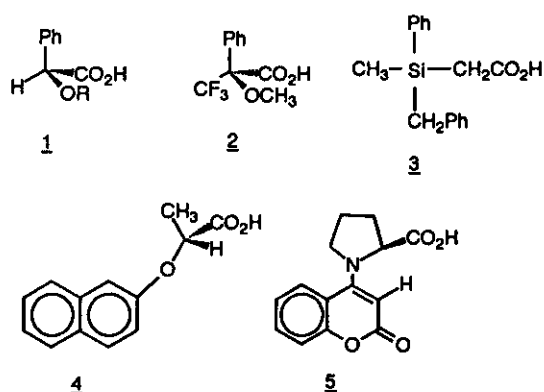
INTRODUCTION

The more rapid progress in the diverse protocols for asymmetric synthesis³ has been made for some time, the more growing interest in finding new methodologies for determination of enantiomeric excesses (ee's) in order to check the level of asymmetric induction is unabated. At present, there are commonly three instrumental methods available for this purpose. Optical rotation has been employed frequently, but is unreliable because of the variations of rotation with the measurement conditions in some cases^{4a} and chromatographic analyses (GC^{4b} and HPLC^{4c}) also meet with both a bottleneck to the necessity of quite expensive chiral stationary phases and the time-consuming difficulties in selection of the proper chiral column and solvent-combination. Under these circumstances, it appears that a simple and quick analysis by NMR spectroscopy occupies a leading position,⁵ where transformation of enantiomers into diastereomers and/or diastereomeric complexes with chiral derivatizing agents (CDAs),^{5a} chiral solvating agents (CSAs),^{5a, b} and chiral lanthanide shift agents (CLSAs)^{6a} is followed by an NMR inspection of diastereotopically nonequivalent signals of the resultants to directly reveal the precise enantiomeric composition of chiral compounds. Among three kinds

of aforementioned reagents, CDAs are now most widely used owing, mainly, to the greater magnitude of chemical shift nonequivalence usually observed. There have been reported so far a variety of nuclei (e.g. ^1H , ^{13}C , ^{19}F , ^{29}Si , ^{31}P , ^{77}Se , and ^{195}Pt)⁷ utilized in the NMR chiral analysis, but proton (^1H) appears to be still one of the best nuclei of choice because ^1H NMR is worldwide accessible to almost all chemists and besides, appearance of the new generation of high-field FT-NMR spectrometers makes even

better separation of the diastereomeric signals possible.^{5c, 7d} Selected examples of CDAs developed to date for alcohols and amines by ^1H NMR chiral analysis are shown in Chart 1. Mandelic acid derivatives ($\text{R}=\text{CH}_3$ - and CH_3CO -) (1)^{5b} were used frequently in the past but not now due to suffering from easy racemization, while usage of the broad methoxy quartet proton signal in the most well-known Mosher's acid (2)^{7b} often discourages an NMR inspection. CDAs such as 3^{7c} and 4^{7d} appear to have utility with a limited range of substrates. CDA (5)^{7e} disclosed recently by us offers the comparable and/or superior alternative, whose advantages are based on that a substrate-independent sharp singlet can be always verified and that no need of optical resolution is ascertained. However, the development of novel more effective and more powerful CDAs for NMR chiral analysis has remained a challenging objective.

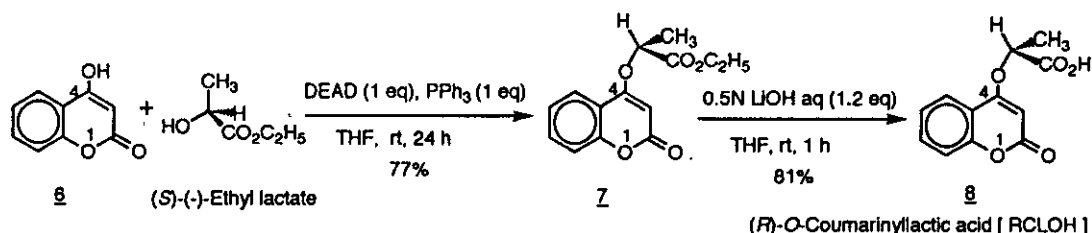
Chart 1



RESULTS AND DISCUSSION

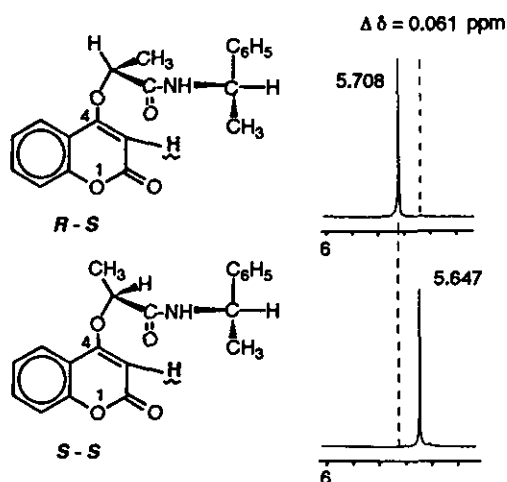
As illustrated in Scheme 1, the expected enantiopure (*R*)-(+)-*O*-coumarinyllactic acid [RCLOH] (8) was synthesized quite easily from both commercial (*S*)-(-)-ethyl lactate and

Scheme 1



4-hydroxycoumarin *via* a Mitsunobu reaction,⁸ which is known to proceed by an S_N2 mechanism. An antipodal modification[SCLOH], **9** was prepared in a similar fashion. Their optical purities were examined as follows. RCLOH (**8**) or SCLOH (**9**) reacted cleanly with ($\pm$)- α -phenethylamine by using 1,1'-carbonyldiimidazole as a condensing agent to afford a diastereomeric mixture of *N*- α -phenethyl-*O*-coumarinyllactamides whose ^1H NMR showed two diastereotopically nonequivalent singlet signals (coumarin C-3 protons) with equal integration to each other at 5.708 and 5.647 ppm, while only one singlet signal could be detected, as shown in Figure 1,

Figure 1 ^1H NMR Optical Purity Inspection of RCLOH and SCLOH Amides with (*S*)-(-)-Phenethylamine



in each of the ^1H NMR of the diastereomeric amides from the same reactions with optically pure (*S*)-(-)- α -phenethylamine, thus implying both RCLOH (**8**) and SCLOH (**9**) being 100% optically pure. Physical properties for both enantiomers are listed in Table 1.

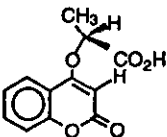
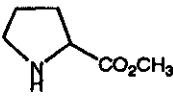
To strictly quantitate enantiomeric purity, a derivatization process does not definitely induce any kinetic resolution or racemization; otherwise diastereomeric ratio with ^1H NMR inspection never reflects the original enantiomeric ratio. Thus, in order to check this possibility, known enantiomeric ratios(% ee) of the weighed compositions of the three representative enantiopure methyl lactate, α -phenethylamine, and methyl prolinatate were compared with diastereomeric ratios (% de) from the ^1H NMR integration of their resultant ester and amides derived by SCLOH (**9**).

As a result, good to excellent agreement was found among these percentage values to evi-

Table 1 Physical Properties of Optically Pure RCLOH and SCLOH

RCLOH	SCLOH
mp 185.5-186°C (80% aq. MeOH) [α] _D ²⁰ + 13.52° (c=1.02, MeOH) IR (KBr): 3486, 1671 cm ⁻¹ ^1H -NMR (CDCl ₃) δ : 5.59 (1H, s) ^{13}C -NMR (CDCl ₃) δ : 162.51, 164.60, 171.51	mp 185-186°C (60% aq. MeOH) [α] _D ²⁰ - 13.13° (c=1.01, MeOH) IR (KBr): 3484, 1671 cm ⁻¹ ^1H -NMR (CDCl ₃) δ : 5.60 (1H, s) ^{13}C -NMR (CDCl ₃) δ : 162.68, 164.53, 171.45

Table 2 Comparison of Optical Purity Quantitation by
Optical Rotation and ^1H NMR Integration (270 MHz)

		A		B	C	A - B	A - C
		R : S mixture by weight		^1H NMR (CDCl_3) % d e	$[\alpha]_D^{20}$ (neat) % e e		
		R : S	% e e				
 (S)-(-)-CLOH	$\text{CH}_3\text{CHCOOCH}_3$	50 : 50	0	0.2	1.2	0.2	1.2
	$\text{CH}_3\text{CH(OH)COOCH}_3$	20 : 80	60	59.6	60.0	0.4	0
	Methyl lactate	5 : 95	90	89.9	90.3	0.1	0.3
	$\text{C}_6\text{H}_5\text{CHNH}_2$	50 : 50	0	0.1	1.1	0.1	1.1
	CH_3	75 : 25	50	51.1	48.8	1.1	1.2
	α -Phenethylamine	10 : 90	80	80.2	80.5	0.2	0.5
		50 : 50	0	1.3	1.9 ^{a)}	1.3	1.9
	Methyl prolinatate	30 : 70	40	38.0	40.0 ^{a)}	2.0	0
		15 : 85	70	68.9	72.0 ^{a)}	1.1	2.0

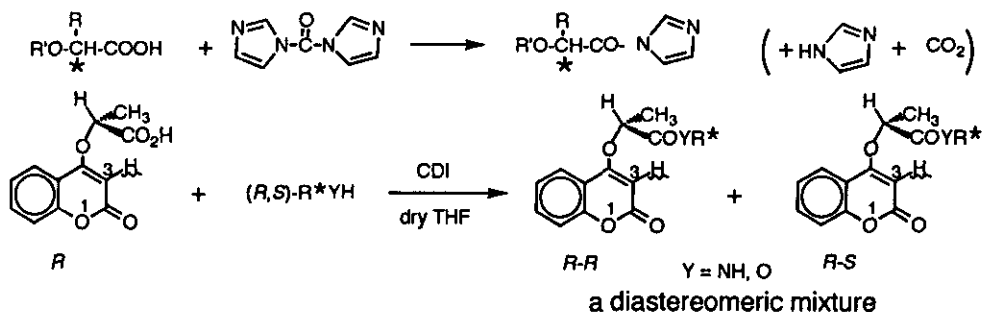
a) $[\alpha]_D^{20}$ (c = 1, CH_2Cl_2)

dence that either racemization or kinetic resolution was not observed at all as depicted in Table 2.

Then, the diastereomeric esters of RCLOH (8) and/or SCLOH (9) with a large variety of racemic alcohols including arylaliphatic, aliphatic, alicyclic, unsaturated aliphatic, α - and β -hydroxy esters function and so on were prepared by way of 1,1'-carbonyldiimidazole (CDI method in Scheme 2), and the chemical shift differences between two diastereomers by routinely examining each coumarin C-3 proton singlet signal (5-6 ppm) were investigated. Results obtained are summarized in Table 3. Generally in all cases screened, baseline resolution

Scheme 2

CDI (1,1'-Carbonyldiimidazole) Method



was ascertained and several remarkable observations should be pointed out. As can be seen in entries 2, 3, and 6, chiral recognition can be accomplished with not only secondary alcohols but primary aliphatic and alicyclic alcohols. Especially in the case of ($\pm$)-2,2-dimethyl-1,3-dioxolan-4-ylmethanol (trade name Solketal, entry 6) which is known as the extremely difficult case,⁹ chiral recognition *via* baseline resolution

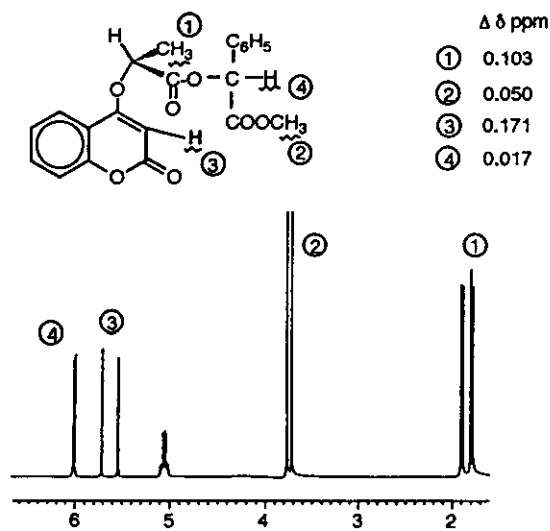
has never been performed by ^1H NMR to the best of our knowledge. It is, therefore, the first case that RCLOH (**8**) and/or SCLOH (**9**) produced a baseline resolution ($\Delta\delta$ 0.012 ppm). Moreover, α -hydroxy esters, the bifunctional compounds like mandelic, lactic, and leucic

Table 3 ^1H NMR Chemical Shift Difference, $\Delta\delta$ (in ppm) of Diastereomeric Esters with RCLOH^{a)}

entry	di-alcohol	$\Delta\delta$	entry	di-alcohol	$\Delta\delta$
1	<chem>C6H5CHOHCH3</chem>	0.029	6	<chem>C6H5CH(OH)C1OC(C1)CO</chem> ^{b)}	0.012
2	<chem>C6H5CH(OH)CH2OH</chem>	0.016	7	<chem>C6H5CH(OH)CH(COOCH3)2</chem>	0.171 (0.050) ^{c)}
3	<chem>C6H5CH(OH)CH2CH2OH</chem>	0.122	8	<chem>CH3CH(OH)CH(COOCH3)2</chem>	0.108 (0.053) ^{c)}
4	<chem>C6H5CH(OH)CH2CH2CH2OH</chem>	0.029	9	<chem>(CH3)2CHCH2CH(OH)CH(COOCH3)2</chem>	0.120
5	<chem>C6H5CH(OH)CH2CH2CH2CH2OH</chem>	0.010	10	<chem>(CH3)2CHCH2CH(OH)CH(COOCH3)2</chem> ^{b)}	0.106 (0.006) ^{c)}
			11	<chem>CH3CH(OH)CH2COOC2H5</chem>	0.034

a) Measured in CDCl_3 on a JEOL GX-270 spectrometer. b) ref. 10.
c) $\Delta\delta$ (in ppm) of $-\text{COOCH}_3$.

Figure 2 Comparison of Peak Separation for RCLOH Ester with ($\pm$)-Methyl Mandelate



acids (entries 7-10) generally gave the quite big magnitudes of the chemical shift nonequivalence, although less efficient resolution in methyl resonance of ester function derived from the substrate can be also observed. For instance, Figure 2 shows particularly how good is utilizing coumarin C-3 proton as a tool for ee determination compared to any other protons in the diastereomeric esters of RCLOH (**8**) with ($\pm$)-methyl mandelate which has been known as a CDA before. The diastereotopic nonequivalence of coumarin C-3 proton shows about 10 times greater than that of mandelic methine proton.

Next, the diastereomeric amides of RCLOH (8) and/or SCLOH (9) with many kinds of racemic amines as collected in Table 4 were prepared by the same method as before (Scheme 2) and, likewise, a ^1H NMR verification on the diastereomeric chemical shift differences was accomplished. Among ten chiral amines investigated in Table 4, baseline resolution by a 270 MHz machine was performed only for entries 1, 2, 4, 7, and 10 although the small dia-

stereomeric shift disper-

sion ($\Delta\delta$ values of less than 0.010 ppm) might be resolved when higher field strengths can be applied, in contrast to the results with chiral alcohols and, therefore, RCLOH (8) and/or SCLOH (9) unexpectedly appear not very suitable for the ^1H NMR ee determination of chiral amines. Fortunately, methyl ester resonances derived from the substrate rather than coumarin C-3 proton signal were, however, baseline-resolved for entries 8 and 9 in Table 4, which might be a better marker of the ee's.

In conclusion, novel and easily-handled crystalline chiral derivatizing agents (CDAs), RCLOH (8) and/or SCLOH (9) readily prepared from the commercial sources, have been developed for the ^1H NMR ee determination of chiral alcohols and amines by routinely checking coumarin C-3 proton signals of CDAs. These CDAs were demonstrated to be extremely useful for the former but not so effective to the latter. It seems that no straightforward relationship between the structure of the substrates and the magnitude of diastereotopic nonequivalence of the resultant esters and amides has been found, which implying nonequivalence is absolutely substrate-dependent.

EXPERIMENTAL

All the melting points by a Yanaco MP-S3 micromelting point apparatus are uncorrected. ^1H

Table 4 ^1H NMR Chemical Shift Difference, $\Delta\delta$ (in ppm) of Diastereomeric Amides with RCLOH^{a)}

entry	di-amine	$\Delta\delta$	entry	di-amine	$\Delta\delta$
1	<chem>Cc1ccccc1CN</chem>	0.061	6	<chem>CC(C)CC(C)N</chem>	0.009
2	<chem>Cc1ccccc1CCN</chem>	0.068	7	<chem>Cc1ccccc1CC(=O)OC</chem>	0.086 (0.044) ^{b)}
3	<chem>C1CCOC1CN</chem>	0.007	8	<chem>CC(C)CC(=O)OC</chem>	0.004 (0.057) ^{b)}
4	<chem>Cc1ccccc1CC(C)CN</chem>	0.024	9	<chem>CC(C)CC(C)CC(=O)OC</chem> ^{c)}	0.008 (0.062) ^{b)}
5	<chem>CC(C)CC(C)CN</chem>	0.004	10	<chem>C1CC(C)CC1C(=O)OC</chem>	0.026

a) Measured in CDCl_3 on a JEOL GX-270 spectrometer.
b) $\Delta\delta$ (in ppm) of $-\text{COOCH}_3$. c) ref. 10.

and ^{13}C NMRs were taken in the solvent indicated on a JEOL JNM-GX 270(270 and 67.8 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as 0.0 ppm and deuteriochloroform as 77.1 ppm(internal standard each), respectively. IR spectra were recorded with a Hitachi 215 grating spectrophotometer or with a JASCO FT/IR-7000 spectrophotometer. High-resolution mass spectral(HRMS) data were obtained by the electron impact method at 70 eV on a Hitachi M-2000 double focusing mass spectrometer employing a peak matching technique with known PFK peaks. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Microanalyses were performed on a Perkin Elmer PE 2400 II CHN/O/S analyzer. All research chemicals were obtained from commercial sources. Tetrahydrofuran(THF) was distilled first from lithium aluminum hydride and then from sodium/benzophenone, immediately before use. All chromatographic purifications were carried out on silica gel 60(230-400 mesh, Merck). NMR spectra for all diastereomeric esters and amides were assigned from mixture, except for spectra of the diastereomeric amides derived from optically pure (*S*)-(-)- α -phenethylamine.

(*R*)-(+)-*O*-Coumarinyllactic acid, RCLOH (8)

To a solution of (*S*)-(-)-ethyl lactate(10.9 g, 92.6 mmol), 4-hydroxycoumarin(15 g, 92.6 mmol) and triphenylphosphine(24.3 g, 92.6 mmol) in dry THF(150 mL) was added dropwise a solution of diethyl azodicarboxylate(DEAD)(18 mL, 92.6 mmol) in dry THF(60 mL)[somewhat exothermic] and then the whole was stirred for 24 h under argon. After removal of THF *in vacuo*, 225 mL of a 1/1 mixture of hexane and diethyl ether were added to the residue and then the resulting white solid $[(\text{Ph})_3\text{P}=\text{O}]$ was stripped off. Evaporation of the organic solvent yielded a crude yellow oil which was submitted to chromatography on silica gel with hexane-ethyl acetate(4:1) to give a yellow solid. Recrystallization of this solid from hexane-ethyl acetate (2:1) furnished (*R*)-(+)-ethyl *O*-coumarinyllactate(mp 68-69°C, 18.7 g, 77%). (*R*)-(+)-Ethyl *O*-coumarinyllactate(12 g, 46 mmol) was hydrolyzed with LiOH $\cdot$ H₂O(2.3 g, 55 mmol) in a mixture of THF(110 mL) and water(132 mL) at 5-20°C for 1 h and then the reaction mixture was acidified with 1M aqueous KHSO₄(25 mL) under cooling. Extraction with methylene chloride(3 $\times$ 60 mL) followed by washing(brine), drying(MgSO₄)and evaporation of the solvent *in vacuo* gave a white solid which was recrystallized from 60% aqueous MeOH to produce the title compound as colorless needles(mp 185.5-186°C, 8.6 g, 81%). $[\alpha]_{\text{D}}^{20} +13.52^\circ$ ($c=1.02$, MeOH); IR ν_{max} (KBr) cm^{-1} : 3486, 1750, 1671, 1628, 1257; ^1H NMR(270 MHz, CDCl₃) δ : 1.76(3 H, d, $J=6.93$ Hz, -CH₃), 4.88(1 H, q, $J=6.93$ Hz, -CH), 5.59(1 H, s), 7.29-7.32(2 H, m), 7.50-7.59(2 H, m), 7.90-7.93(1 H, m); ^{13}C NMR(67.8 MHz, CDCl₃) δ : 17.89, 73.19, 91.16, 115.44, 116.45, 123.34, 123.96, 132.53, 153.23, 162.51, 164.60, 171.51. *Anal.* Calcd for C₁₂H₁₀O₅: C, 61.54; H, 4.30. Found: C, 61.33; H, 4.31.

(S)-(-)-O-Coumarinyllactic acid, SCLOH (9)

This compound was prepared in a similar fashion described above. Colorless fluffy needles (mp 185-186°C from 60% aqueous MeOH, 60% yield based on 4-hydroxycoumarin). $[\alpha]_D^{25} -13.13^\circ$ (c=1.01, MeOH); IR $\nu_{\max}(\text{KBr}) \text{ cm}^{-1}$: 3484, 1750, 1671, 1628, 1257; $^1\text{H NMR}(270 \text{ MHz, CDCl}_3) \delta$: 1.76(3H, d, J=6.93 Hz, $-\text{CH}_3$), 4.87(1H, q, J=6.93 Hz, $-\text{CH}$), 5.60(1H, s), 7.25-7.33(2H, m), 7.52-7.59(2H, m), 7.90-7.94(1H, m); $^{13}\text{C NMR}(67.8 \text{ MHz, CDCl}_3) \delta$: 17.74, 73.04, 91.08, 115.32, 116.40, 123.21, 123.81, 132.36, 153.13, 162.88, 164.53, 171.45. *Anal.* Calcd for $\text{C}_{12}\text{H}_{10}\text{O}_5$: C, 61.54; H, 4.30. Found: C, 61.46; H, 4.30.

General Procedure for Preparation of RCLOH (8) and/or SCLOH (9) Esters and Amides

A solution of RCLOH or SCLOH(45 mg, 1.93 mmol) and 1,1'-carbonyldiimidazole(34.4 mg, 2.12 mmol) in dry THF(2 mL) was first stirred at rt for 1 h under dry argon and then to this was added a solution of racemic substrates(1.29 mmol) in dry THF(1 mL) *via* a syringe. After stirring of the whole at rt for an additional 2-24 h under argon, the reaction mixture was, under cooling, quenched with sat. aqueous NaHCO_3 (10 mL) and extracted with ether(10 mL). The extract was dried over MgSO_4 and concentrated to dryness to give crude diastereomeric esters or amides which were first subjected to a $^1\text{H NMR}$ inspection and then to silica gel preparative TLC for physical data.

(R,S)-1-Phenylethyl (R)-O-coumarinyllactate(entry 1, Table 3)

Colorless oil; IR $\nu_{\max}(\text{neat}) \text{ cm}^{-1}$: 1721, 1624, 1201, 932; $^1\text{H NMR}(270 \text{ MHz, CDCl}_3) \delta$: 1.57 and 1.60($\Delta \delta=0.03$)(3H, d, J=6.60 Hz, $-\text{CH}_3$ in alcohol), 1.70 and 1.73($\Delta \delta=0.03$)(3H, d, J=6.93 Hz, $-\text{CH}_3$ in CLOH), 4.86-4.94(1H, m), 5.480 and 5.509($\Delta \delta=0.029$)(1H, s, coumarin C-3 proton), 5.95(1H, q, J=6.93 Hz, $-\text{CH}$ in CLOH), 7.23-7.91(9H, m); HRMS Calcd for $\text{C}_{20}\text{H}_{18}\text{O}_5$ (M^+) m/z 338.1153. Found 338.1125.

(R,S)-2-Phenylpropyl (R)-O-coumarinyllactate(entry 2, Table 3)

Colorless solid, mp 128-136°C; IR $\nu_{\max}(\text{KBr}) \text{ cm}^{-1}$: 1752, 1717, 1671, 1624, 1185, 936; $^1\text{H NMR}(270 \text{ MHz, CDCl}_3) \delta$: 1.26 and 1.28($\Delta \delta=0.02$)(3H, d, J=7.26 Hz, $-\text{CH}_3$ in alcohol), 1.59 and 1.61($\Delta \delta=0.02$)(3H, d, J=6.93 Hz, $-\text{CH}_3$ in CLOH), 3.07-3.15(1H, m, $-\text{CH}$ in alcohol), 4.19-4.42(2H, m, $-\text{CH}_2$ in alcohol), 4.81(1H, quintet, J=6.93 Hz, $-\text{CH}$ in CLOH), 5.431 and 5.447($\Delta \delta=0.016$)(1H, s, coumarin C-3 proton), 7.11-7.86(9H, m); HRMS Calcd for $\text{C}_{21}\text{H}_{21}\text{O}_5$ ($\text{M}+1$) m/z 353.1209. Found 353.1239.

(R,S)-(2-Furfuryl)methyl (R)-O-coumarinyllactate(entry 3, Table 3)

Colorless oil; IR $\nu_{\max}(\text{neat}) \text{ cm}^{-1}$: 1729, 1624, 1570, 1189, 936; $^1\text{H NMR}(270 \text{ MHz, CDCl}_3) \delta$: 1.74 and 1.76($\Delta \delta=0.02$)(3H, d, J=6.93 Hz, $-\text{CH}_3$ in CLOH), 1.97-2.24(4H, m), 3.51-3.75(5H,

m), 4.60(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.472 and 5.594($\Delta\delta=0.122$)(1H, s, coumarin C-3 proton), 7.24-7.93(4H, m); HRMS Calcd for $C_{17}H_{19}O_6$ ($M+1$) m/z 319.1180. Found 319.1174.

(*R,S*)-3-Butyn-2-yl (*R*)-*O*-coumarinyllactate(entry 4, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 2126, 1717, 1624, 1189, 1114; 1H NMR(270 MHz, $CDCl_3$) δ : 1.56 and 1.57($\Delta\delta=0.01$)(3H, d, $J=6.60$ Hz, $-CH_3$ in alcohol), 1.76 and 1.77($\Delta\delta=0.01$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 4.26-4.29(1H, m), 4.90(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.50-5.53(1H, m), 5.522 and 5.551($\Delta\delta=0.029$)(1H, s, coumarin C-3 proton), 7.30-7.93(4H, m); HRMS Calcd for $C_{16}H_{14}O_5$ (M^+) m/z 286.0840. Found 286.0843.

(*R,S*)-3-Buten-2-yl (*R*)-*O*-coumarinyllactate(entry 5, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 2934, 1725, 1624, 1400, 1241; 1H NMR(270 MHz, $CDCl_3$) δ : 1.38 and 1.39($\Delta\delta=0.01$)(3H, d, $J=6.60$ Hz, $-CH_3$ in alcohol), 1.74 and 1.75($\Delta\delta=0.01$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 4.87(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.15-5.44(3H, m), 5.530 and 5.540($\Delta\delta=0.010$)(1H, s, coumarin C-3 proton), 5.67-5.90(1H, m, alcohol), 7.29-7.93(4H, m); HRMS Calcd for $C_{16}H_{16}O_5$ (M^+) m/z 288.0997. Found 288.0999.

(*R,S*)-2,2-Dimethyl-1,3-dioxolan-4-ylmethyl (*R*)-*O*-coumarinyllactate(entry 6, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1734, 1626, 1609, 1570, 1243, 1191; 1H NMR(270 MHz, $CDCl_3$) δ : 1.34(3H, s, $-CH_3$ in alcohol), 1.40(3H, s, $-CH_3$ in alcohol), 1.77 and 1.78($\Delta\delta=0.01$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 3.67-3.77(2H, m), 4.62-4.92(2H, m), 4.23-4.36(1H, m), 4.95(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.540-5.552($\Delta\delta=0.012$)(1H, s, coumarin C-3 proton), 7.30-7.92(4H, m); HRMS Calcd for $C_{18}H_{21}O_7$ ($M+1$) m/z 349.1286. Found 349.1262.

(*R,S*)-(Methoxycarbonyl)phenylmethyl (*R*)-*O*-coumarinyllactate(entry 7, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1750, 1626, 1189; 1H NMR(270 MHz, $CDCl_3$) δ : 1.800 and 1.903($\Delta\delta=0.103$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 3.720 and 3.770($\Delta\delta=0.050$)(3H, s, $-COOCH_3$ in alcohol), 5.052 and 5.072($\Delta\delta=0.020$)(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.556 and 5.727($\Delta\delta=0.171$)(1H, s, coumarin C-3 proton), 6.003 and 6.020($\Delta\delta=0.017$)(1H, s, -CH in alcohol), 7.25-7.93(9H, m); HRMS Calcd for $C_{21}H_{18}O_7$ (M^+) m/z 382.1051. Found 382.1077.

(*R,S*)-1-Methoxycarbonylethyl (*R*)-*O*-coumarinyllactate(entry 8, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1717, 1624, 1570, 1191, 1112, 1048; 1H NMR(270 MHz, $CDCl_3$) δ : 1.53 and 1.57($\Delta\delta=0.04$)(3H, d, $J=7.26$ Hz, $-CH_3$ in alcohol), 1.80 and 1.84($\Delta\delta=0.04$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 3.75 and 3.80($\Delta\delta=0.05$)(3H, s, $-COOCH_3$ in alcohol), 4.96 and 4.97($\Delta\delta=0.01$)(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.21 and 5.22($\Delta\delta=0.01$)(1H, q, $J=7.26$ Hz, -CH in alcohol), 5.552 and 5.660($\Delta\delta=0.108$)(1H, s, coumarin C-3 proton), 7.27-7.92

(4H, m). HRMS Calcd for $C_{16}H_{16}O_7$ (M^+) m/z 320.0895. Found 320.0879.

(R,S)-1-Isopropoxycarbonyl-3-methylbutyl (R)-O-coumarinyllactate(entry 9, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1734, 1626, 1570, 1191; 1H NMR(270 MHz, $CDCl_3$) δ : 0.85 and 0.95($\Delta\delta=0.10$)(6H, d, $J=6.27$ Hz, $(CH_3)_2-C$ in alcohol), 1.22-1.26(7H, m), 1.43-1.77(2H, m), 1.81 and 1.83($\Delta\delta=0.02$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 4.97-5.12(3H, m), 5.542 and 5.662($\Delta\delta=0.120$)(1H, s, coumarin C-3 proton), 7.25-7.93(4H, m); HRMS Calcd for $C_{21}H_{26}O_7$ (M^+) m/z 390.1677. Found 390.1657.

(R,S)-1-Methoxycarbonyl-3-methylbutyl (R)-O-coumarinyllactate(entry 10, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1734, 1626, 1570, 1191; 1H NMR(270 MHz, $CDCl_3$) δ : 0.87 and 0.88($\Delta\delta=0.01$)(6H, d, $J=6.60$ Hz, $(CH_3)_2-C$ in alcohol), 1.73 and 1.76($\Delta\delta=0.03$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 3.71 and 3.72($\Delta\delta=0.01$)(3H, s, $-COOCH_3$ in alcohol), 4.04-4.17(1H, m), 4.90 and 4.91($\Delta\delta=0.01$)(1H, q, $J=6.93$ Hz, $-CH$ in CLOH), 5.07-5.57(1H, m), 5.576 and 5.686($\Delta\delta=0.110$)(1H, s, coumarin C-3 proton), 7.20-7.82(4H, m); HRMS Calcd for $C_{19}H_{22}O_7$ (M^+) m/z 362.1364. Found 362.1384.

(R,S)-1-Ethoxycarbonyl-2-propyl (R)-O-coumarinyllactate(entry 11, Table 3)

Colorless oil; IR ν_{max} (neat) cm^{-1} : 1734, 1624, 1570, 1243, 1189; 1H NMR(270 MHz, $CDCl_3$) δ : 1.16 and 1.18($\Delta\delta=0.02$)(3H, t, $J=7.26$ Hz, $-CH_3$ of ester ethyl in alcohol), 1.24 and 1.26($\Delta\delta=0.02$)(3H, d, $J=6.27$ Hz, CH_3-C in alcohol), 1.63 and 1.66($\Delta\delta=0.03$)(3H, d, $J=6.93$ Hz, $-CH_3$ in CLOH), 2.43-2.64(2H, m), 4.03 and 4.06($\Delta\delta=0.03$)(2H, q, $J=7.26$ Hz, $-OCH_2$ of ester ethyl in alcohol), 4.78 and 4.79($\Delta\delta=0.01$)(1H, q, $J=6.93$ Hz, $-CH$ in CLOH), 5.29-5.36(1H, m), 5.446 and 5.480($\Delta\delta=0.034$)(1H, s, coumarin C-3 proton), 7.20-7.85(4H, m); HRMS Calcd for $C_{19}H_{20}O_7$ (M^+) m/z 348.1208. Found 348.1215.

(R,S)-N-(1-Phenylethyl) (R)-O-coumarinyllactamide(entry 1, Table 4)

Colorless solid, mp 160-163°C; IR ν_{max} (KBr) cm^{-1} : 3454, 1725, 1657, 1626, 1560, 1243, 1110; 1H NMR(270 MHz, $CDCl_3$) δ : 1.45 and 1.50($\Delta\delta=0.05$)(3H, d, $J=8.90$ Hz, $-CH_3$ in amine), 1.68 and 1.70($\Delta\delta=0.02$)(3H, d, $J=6.60$ Hz, $-CH_3$ in CLOH), 4.84 and 4.87($\Delta\delta=0.03$)(1H, q, $J=6.60$ Hz, $-CH$ in CLOH), 5.15 and 5.17($\Delta\delta=0.02$)(1H, quintet, $J=7.26$ Hz, $-CH$ in amine), 5.640 and 5.701($\Delta\delta=0.061$)(1H, s, coumarin C-3 proton), 7.20-7.83(9H, m); HRMS Calcd for $C_{20}H_{19}NO_4$ ($M+1$) m/z 338.1391. Found 338.1415.

(S)-N-(1-Phenylethyl) (R)-O-coumarinyllactamide

Colorless plates, mp 160-161°C; IR ν_{max} (KBr) cm^{-1} : 3453, 1725, 1655, 1625, 1560, 1240, 1115; 1H NMR(270 MHz, $CDCl_3$) δ : 1.45(3H, d, $J=8.90$ Hz, $-CH_3$ in amine), 1.65(3H, d, $J=6.63$ Hz, $-CH_3$

in CLOH), 4.84(1H, q, $J=6.63$ Hz, -CH in CLOH), 5.15(1H, quintet, $J=7.26$ Hz, -CH in amine), 5.70(1H, s, coumarin C-3 proton), 7.20-7.83(9H, m). *Anal.* Calcd for $C_{20}H_{13}NO_4$: C, 71.42; H, 5.39; N, 4.16. Found: C, 71.59; H, 5.37; N, 4.28.

(*R,S*)-*N*-(2-Phenylpropyl) (*R*)-*O*-coumarinyllactamide(entry 2, Table 4)

Colorless solid, mp 118-123°C; IR $\nu_{\max}$ (KBr) cm^{-1} : 3490, 1736, 1655, 1628, 1570, 1238, 1185; ^1H NMR(270 MHz, CDCl_3) δ : 1.25 and 1.26($\Delta\delta=0.01$)(3H, d, $J=7.26$ Hz, -CH₃ in amine), 1.59 and 1.63($\Delta\delta=0.04$)(3H, d, $J=6.60$ Hz, -CH₃ in CLOH), 2.85-3.06(1H, m), 3.16-3.37(1H, m), 3.62-3.86(1H, m), 4.74 and 4.76($\Delta\delta=0.02$)(1H, q, $J=6.60$ Hz, -CH in CLOH), 5.540 and 5.608($\Delta\delta=0.068$)(1H, s, coumarin C-3 proton), 6.00(1H, s), 7.02-7.60(9H, m); HRMS Calcd for $C_{21}H_{21}NO_4$ (M^+) m/z 351.1469. Found 351.1468.

(*R,S*)-*N*-(2-Furfuryl)methyl (*R*)-*O*-coumarinyllactamide(entry 3, Table 4)

Colorless solid, mp 140-142°C; IR $\nu_{\max}$ (KBr) cm^{-1} : 3400, 1736, 1657, 1626, 1560, 1238, 1178, 1081; ^1H NMR(270 MHz, CDCl_3) δ : 1.24-1.42(4H, m), 1.72 and 1.74($\Delta\delta=0.02$)(3H, d, $J=6.93$ Hz, -CH₃ in CLOH), 3.20-3.32(1H, m), 3.54-4.00(5H, m), 4.88(1H, q, $J=6.93$ Hz, -CH in CLOH), 5.693 and 5.700($\Delta\delta=0.007$)(1H, s, coumarin C-3 proton), 7.39-7.89(4H, m); HRMS Calcd for $C_{17}H_{20}NO_5$ ($M+1$) m/z 318.1405. Found 318.1382.

(*R,S*)-*N*-(4-Phenyl)but-2-yl (*R*)-*O*-coumarinyllactamide(entry 4, Table 4)

Colorless solid, mp 197-199°C; IR $\nu_{\max}$ (KBr) cm^{-1} : 3452, 1736, 1657, 1628, 1560, 1185; ^1H NMR(270 MHz, CDCl_3) δ : 1.20 and 1.22($\Delta\delta=0.02$)(3H, d, $J=6.60$ Hz, -CH₃ in amine), 1.68 and 1.69($\Delta\delta=0.01$)(3H, d, $J=6.60$ Hz, -CH₃ in CLOH), 1.73-1.86(2H, m), 2.57(1H, t, $J=7.25$ Hz), 2.67(1H, t, $J=7.92$ Hz), 4.05-4.12(1H, m), 4.80(1H, q, $J=6.60$ Hz, -CH in CLOH), 5.680 and 5.704($\Delta\delta=0.024$)(1H, s, coumarin C-3 proton), 6.22(1H, d, $J=8.58$ Hz), 7.05-7.85(9H, m); HRMS Calcd for $C_{22}H_{23}NO_4$ (M^+) m/z 365.1626. Found 365.1603.

(*R,S*)-*N*-Pent-2-yl (*R*)-*O*-coumarinyllactamide(entry 5, Table 4)

Colorless semisolid; IR $\nu_{\max}$ (neat) cm^{-1} : 1734, 1655, 1560; ^1H NMR(270 MHz, CDCl_3) δ : 0.84 and 0.94($\Delta\delta=0.10$)(3H, t, $J=7.26$ Hz, -CH₂CH₃ in amine), 1.10 and 1.17($\Delta\delta=0.07$)(3H, d, $J=6.60$ Hz, -CHCH₃ in amine), 1.20-1.49(4H, m), 1.71(3H, d, $J=6.60$ Hz, -CH₃ in CLOH), 4.00-4.07(1H, m), 4.82(1H, q, $J=6.60$ Hz, -CH in CLOH), 5.697 and 5.701($\Delta\delta=0.004$)(1H, s, coumarin C-3 proton), 5.83(1H, d, $J=7.26$ Hz), 7.30-7.85(4H, m); HRMS Calcd for $C_{17}H_{21}NO_4$ (M^+) m/z 303.1469. Found 303.1476.

(*R,S*)-*N*-Oct-2-yl (*R*)-*O*-coumarinyllactamide(entry 6, Table 4)

Colorless solid, mp 115-118°C; IR $\nu_{\max}$ (KBr) cm^{-1} : 3278, 1736, 1655, 1528, 1570, 1238, 1185;

^1H NMR(270 MHz, CDCl_3) δ : 0.82 and 0.88($\Delta\delta=0.06$)(3H, t, $J=6.93$ Hz, $-\text{CH}_2\text{CH}_3$ in amine), 1.10 and 1.17($\Delta\delta=0.03$)(3H, d, $J=6.60$ Hz, $-\text{CHCH}_3$ in amine), 1.10-1.48(10H, m), 1.71(3H, d, $J=6.93$ Hz, $-\text{CH}_3$ in CLOH), 3.97-4.05(1H, m), 4.82(1H, q, $J=6.93$ Hz, $-\text{CH}$ in CLOH), 5.694 and 5.703($\Delta\delta=0.009$)(1H, s, coumarin C-3 proton), 6.83(1H, d, $J=7.92$ Hz), 7.28-7.87(4H, m); HRMS Calcd for $\text{C}_{28}\text{H}_{27}\text{NO}_4$ (M^+) m/z 345.1938. Found 345.1941.

(*R,S*)-*N*-[(Methoxycarbonyl)phenylmethyl] (*R*)-*O*-coumarinyllactamide(entry 7, Table 4)

Colorless solid, mp 109-113°C; IR ν_{max} (KBr) cm^{-1} : 3280, 1736, 1669, 1626, 1560, 1241, 1187; ^1H NMR(270 MHz, CDCl_3) δ : 1.69 and 1.73($\Delta\delta=0.04$)(3H, d, $J=6.93$ Hz, $-\text{CH}_3$ in CLOH), 3.714 and 3.758($\Delta\delta=0.044$)(3H, s, $-\text{COOCH}_3$ in amine), 4.91(1H, quintet, $J=6.60$ Hz), 5.57 and 5.59($\Delta\delta=0.02$)(1H, d, $J=6.93$ Hz, $-\text{CH}$ in CLOH), 5.643 and 5.729($\Delta\delta=0.086$)(1H, s, coumarin C-3 proton), 7.13-7.92(10H, m); HRMS Calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_6$ (M^+) m/z 381.1211. Found 381.1187.

(*R,S*)-*N*-[1-(Methoxycarbonyl)ethyl] (*R*)-*O*-coumarinyllactamide(entry 8, Table 4)

Colorless solid, mp 143-144.5°C; IR ν_{max} (KBr) cm^{-1} : 3290, 1736, 1717, 1560, 1189, 1112; ^1H NMR(270 MHz, CDCl_3) δ : 1.42 and 1.48($\Delta\delta=0.06$)(3H, d, $J=7.26$ Hz, $-\text{CH}_3$ in amine), 1.72 and 1.74($\Delta\delta=0.06$)(3H, d, $J=6.60$ Hz, $-\text{CH}_3$ in CLOH), 3.733 and 3.790($\Delta\delta=0.057$)(3H, s, $-\text{COOCH}_3$ in amine), 4.61 and 4.63($\Delta\delta=0.02$)(1H, quintet, $J=7.26$ Hz, $-\text{CH}$ in amine), 4.88 and 4.89($\Delta\delta=0.01$)(1H, q, $J=6.60$ Hz, $-\text{CH}$ in CLOH), 5.700 and 5.704($\Delta\delta=0.004$)(1H, s, coumarin C-3 proton), 7.30-7.92(5H, m); HRMS Calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_6$ (M^+) m/z 319.1055. Found 319.1079.

(*R,S*)-*N*-[1-(Methoxycarbonyl)-3-methylbutyl] (*R*)-*O*-coumarinyllactamide(entry 9, Table 4)

Colorless solid, mp 80-83°C; IR ν_{max} (KBr) cm^{-1} : 3280, 1736, 1686, 1669, 1626, 1560, 1243, 1187, 1110; ^1H NMR(270 MHz, CDCl_3) δ : 0.86 and 0.90($\Delta\delta=0.04$)(3H, d, $J=6.27$ Hz, $-\text{CH}_3$ of i-Pr in amine), 0.96 and 0.97($\Delta\delta=0.01$)(3H, d, $J=6.27$ Hz, $-\text{CH}_3$ of i-Pr in amine), 1.73(3H, d, $J=6.60$ Hz, $-\text{CH}_3$ in CLOH), 1.59-1.77(2H, m), 1.83-1.88(1H, m), 3.700 and 3.762($\Delta\delta=0.062$)(3H, s, $-\text{COOCH}_3$ in amine), 4.65(1H, m), 4.90(1H, quintet, $J=6.60$ Hz, $-\text{CH}$ in CLOH), 5.712 and 5.720($\Delta\delta=0.008$)(1H, s, coumarin C-3 proton), 6.86(1H, d, $J=7.92$ Hz), 7.18-7.93(4H, m); HRMS Calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_6$ (M^+) m/z 361.1524. Found 361.1495.

(*R,S*)-*N*-(2-Methoxycarbonylpyrrolidinyl) (*R*)-*O*-coumarinyllactamide(entry 10, Table 4)

Colorless semisolid; IR ν_{max} (neat) cm^{-1} : 3450, 1754, 1661, 1624, 1195; ^1H NMR(270 MHz, CDCl_3) δ : 1.52-1.56(2H, m), 1.77 and 1.78($\Delta\delta=0.01$)(3H, d, $J=6.93$ Hz, $-\text{CH}_3$ in CLOH), 1.82-2.03(3H, m), 3.76-3.89(2H, m), 4.10-4.30(3H, m), 4.94(1H, q, $J=6.93$ Hz, $-\text{CH}$ in CLOH), 5.552 and 5.578($\Delta\delta=0.026$)(1H, s, coumarin C-3 proton), 7.29-7.93(4H, m); HRMS Calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_6$ (M^+) m/z 345.1211. Found 345.1237.

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1. Dedicated in memory of Professor Dr. Shun-ichi Yamada.
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