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NOVEL CHIRAL DERIVATIZING AGENTS FOR ^{1}H NMR DETERMINATION OF ENANTIOMERIC PURITIES OF CARBOXYLIC ACIDS

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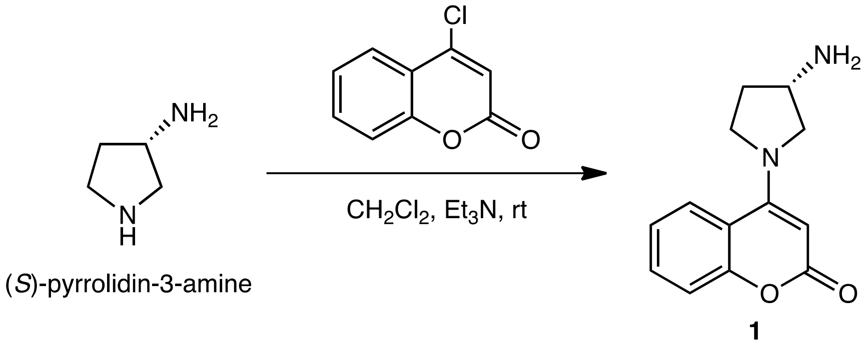
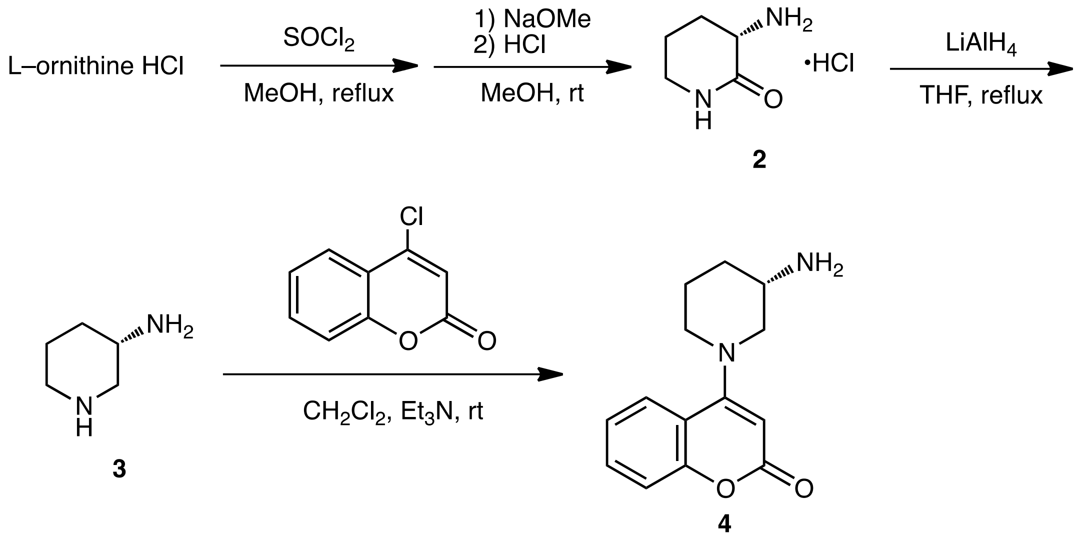
Abstract – (*S*)-4-(3-Aminopyrrolidin-1-yl)coumarin (**1**), (*S*)-4-(3-aminopiperidin-1-yl)coumarin (**4**), and (*S*)-4-(3-aminoazepan-1-yl)coumarin (**7**), prepared from 4-chlorocoumarin and (*S*)-pyrrolidin-3-amine, (*S*)-piperidin-3-amine, and (*S*)-azepan-3-amine, respectively, were proven to be versatile and reliable ^{1}H NMR optical purity determination agents for chiral carboxylic acids.

With the recent explosive progress in diverse asymmetric synthesis protocols, a constant need remains for the design and development of new chiral derivatizing agents (CDAs) to provide accurate, reliable, and convenient ^{1}H NMR enantiomeric excess (e.e.) determination. Such agents would argue the currently available methods, such as polarimetry, GLC, and HPLC.[1] During our studies on coumarin chemistry,[2] we frequently found that, in addition to remarkable solidity enhancement by coumarin nuclei, the proton on C-3 of coumarin always appears as a sharp singlet at 6.0-7.0 ppm.[2,3] This signal is more distinct than the methoxy protons in Mosher's acid,[4] the most well-known CDA, and less prone to overlap with other protons present in a substance. Thus, the development of coumarin-containing CDAs for ^{1}H NMR e.e. determination is quite attractive, and prior papers[5,6] have reported the preparation of such compounds for use with chiral alcohols and amines. Our newly prepared *N*-heterocyclo-coumarins might prove to be promising candidates as CDAs for ^{1}H NMR e.e. determination of chiral carboxylic acids.

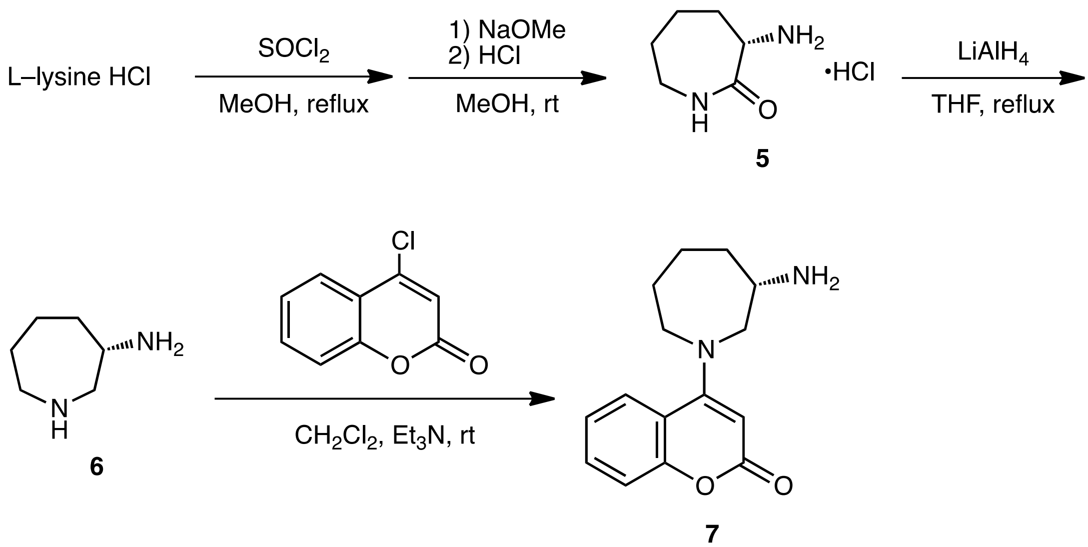
The first new coumarin-containing CDA, (*S*)-4-(3-aminopyrrolidin-1-yl)coumarin (**1**: 5-CDA), was prepared from (*S*)-pyrrolidin-3-amine and 4-chlorocoumarin in a 63% yield (Scheme 1). As seen in Scheme 2, following the preparation of (*S*)-3-aminopiperidin-2-one hydrochloride (**2**) from L-ornitine hydrochloride, the reduction of compound **2** gave (*S*)-piperidin-3-amine (**3**). Condensation of **3** and 4-chlorocoumarin produced (*S*)-4-(3-aminopiperidin-1-yl)coumarin (**4**: 6-CDA) in 61% yield. Similarly, following the preparation of (*S*)-3-aminoazepan-2-one hydrochloride (**5**) from L-lysine hydrochloride, the reduction of compound **5** gave (*S*)-azepan-3-amine (**6**), and condensation of **6** and 4-chlorocoumarin



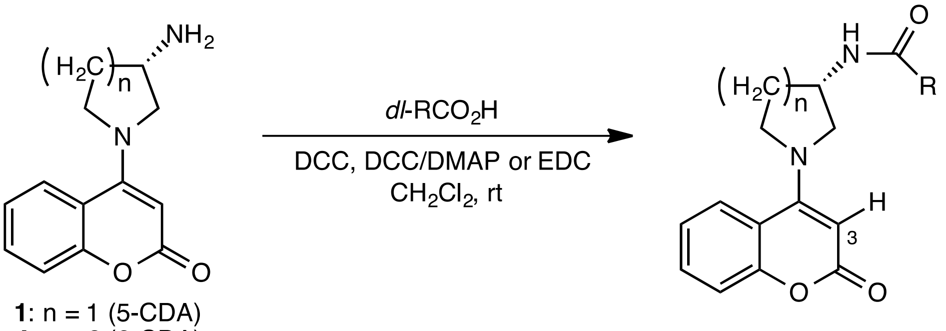
Scheme 1



Scheme 2



Scheme 3



1: n = 1 (5-CDA)
4: n = 2 (6-CDA)
7: n = 3 (7-CDA)

Scheme 4

provided (*S*)-4-(3-aminoazepan-1-yl)coumarin (**7**: 7-CDA) in 59% yield (Scheme 3). The target diastereomeric amides were prepared from the reaction of the new coumarin-containing CDA (**1**, **4**, or **7**) and carboxylic acid in the presence of *N*,*N'*-dicyclohexylcarbodiimide (DCC), DCC and 4-dimethylaminopyridine (DMAP), or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (Scheme 4). Each new coumarin-containing CDA (**1**, **4**, or **7**) was reacted with (*S*)-(+)-ketoprofen in the presence of DCC and DMAP to afford the desired amide. In the ^{1}H NMR spectrum of the product, the proton on C-3 of the coumarin appeared as a sharp singlet at ca. 5.10-5.66. The results suggested that the new coumarin-containing CDA (**1**, **4**, or **7**) was optically pure.

Table 1 lists the results for the observed diastereotopic nonequivalence (Δ δ ppm) of the sharp singlet found for the coumarin H-3 in the amide products resulting from the reactions of CDAs **1** (5-CDA), **4** (6-CDA), and **7** (7-CDA) with various chiral carboxylic acids. Generally, base-line resolution was observed with most of the racemic acid substrates in Table 1. For example, the ^{1}H NMR spectrum of a representative amide with 7-CDA (entry 2) is shown in Figure 1. However, with some racemic acids, particularly where the chiral center was not immediately adjacent to the carbonyl, chiral recognition did not occur as efficiently. For example, 4-phenylpentanoic acid (entry 3) had low Δ δ ppm values (ca. 0.015) with all three CDAs. Also, no chemical shift differences were found for the coumarin H-3 of

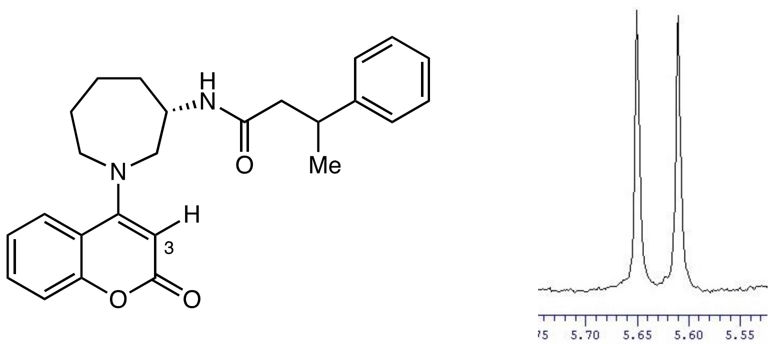
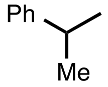
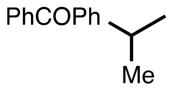
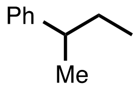
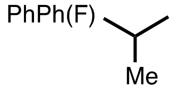
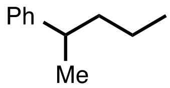
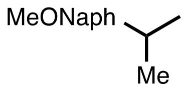
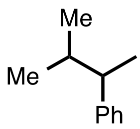
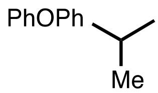
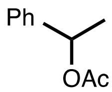
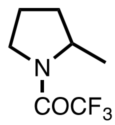
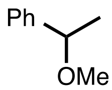
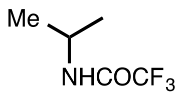
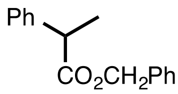
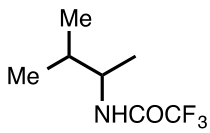
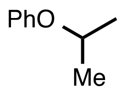
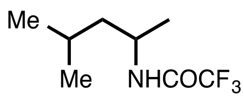
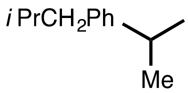


Figure 1. ^{1}H NMR spectrum of representative amide with 7-CDA (entry 2)

Table 1. ^{1}H NMR Chemical Shifts Difference of Proton at C-3 of Coumarin of CDAs, Δ δ ppm of Diastereomeric Amides with CDAs[a)]

entry	*dl*-R-CO_2H	5-CDA	6-CDA	7-CDA	entry	*dl*-R-CO_2H	5-CDA	6-CDA	7-CDA
1		0	0.032	0.028	10		0.016	0.033	0.040
2		0.017	0.040	0.039	11		0.020	0.018	0.026
3		0.015	0.015	0.014	12		0.018	0.119	0.034
4		0.008	0.061	0.098	13		0	0.016	0.022
5		0.023	0.012	0.006	14		0.056	0.009	0.048
6		0.011	0.029	0.080	15		0.010	0.048	0.036
7		0	0.026	0.064	16		0.011	0	0.025
8		0.078	0.116	0.108	17		0	0.034	0.041
9		0.009	0.019	0.024					

a) Measured in $CDCl_3$ on a 270 MHz spectrometer unless otherwise specified.

certain diastereomeric amides, including entries 1, 7, 13, and 17 with 5-CDA and 16 with 6-CDA. With 5-CDA, the largest observed diastereotopic nonequivalence (Δ δ ppm) values (> 0.05) were found for entries 8 (2-phenoxypropanoic acid) and 14 (*N*-trifluoroacetyl-DL-proline), while the remaining entries had much lower values (≤ 0.023). With 6-CDA, the Δ δ ppm values were less than 0.02 for seven entries (3, 5, 9, 11, 13, 14, 16), between 0.02 and 0.05 for seven entries (1, 2, 6, 7, 10, 15, 17), and greater than 0.05 for three entries (4, 8, 12). With 7-CDA, the entries with the lowest Δ δ ppm values were 3 and 5 (< 0.02), the entries with intermediate values were 1, 2, and 9-17 (between 0.02 and 0.05), and the entries with the largest values were 4 and 6-8 (> 0.05). Notably, among all acid-CDA combinations, the largest Δ δ ppm values occurred for entry 8 with 5-CDA, entries 8 and 12 (naproxen) with 6-CDA, and entries 4

(3-methyl-2-phenylbutanoic acid), 6 (*O*-methylmandelic acid), and 8 with 7-CDA. With most carboxylic acids, the Δ δ ppm values with 6-CDA were larger than or equivalent to those with 5-CDA; exceptions were entries 5, 14, and 16. Comparison of the Δ δ ppm values of 7-CDA and 6-CDA showed that one entry (12) showed a much larger value with 6-CDA, one entry (15) showed a slightly higher value with 6-CDA, ten entries (1, 2, 3, 5, 8-11, 13, 17) showed similar values with 6-CDA and 7-CDA, and five entries (4, 6, 7, 14, 16) showed larger values with 7-CDA. These results suggested that both 6-CDA and 7-CDA gave better chemical shift differences than those with 5-CDA; exceptions were entries 5, 14, and 16. Both 6-CDA and 7-CDA were considered to be near between the proton on C-3 of coumarin and the chiral center of carboxylic acid than 5-CDA. Also, with some racemic acids, particularly where the chiral center was not immediately adjacent to the carbonyl (e.g. entries 2 and 3), chemical shift differences were present as low Δ δ ppm values.

The known enantiomeric ratios (%e.e.) of weighed compositions of (*R*)- and (*S*)-enantiopure ketoprofen were compared with the diastereomeric ratios (%d.e.) calculated from ^{1}H NMR integration of the resultant amides derived with the CDAs (**1**, **4**, and **7**). Neither racemization nor kinetic discrimination was induced by the derivatization, as depicted in Table 2.

Table 2. Comparison of Optical Purity Determination by ^{1}H NMR Integration[a)]

	(*R*)- and (*S*)-Ketoprofen by weight	%e.e.	Diastereomeric ratio of CDAs amide by ^{1}H NMR	%d.e.
5-CDA	80 : 20	60.0	79.4 : 20.6	58.8
	60 : 40	20.0	59.5 : 40.5	19.0
	50 : 50	0	50.3 : 49.7	0.6
6-CDA	80 : 20	60.0	80.6 : 19.4	61.2
	60 : 40	20.0	61.0 : 39.0	22.0
	50 : 50	0	48.8 : 51.2	2.4
7-CDA	80 : 20	60.0	78.7 : 21.3	57.4
	60 : 40	20.0	60.6 : 39.4	21.2
	50 : 50	0	51.0 : 49.0	2.0

a) A sharp-singlet proton originated from the CDA was used for the analysis. It was independent of the spectroscopic properties of the substrate. CDAs were stable crystalline solids.

EXPERIMENTAL

Melting points were measured using a Yanaco micro-melting point apparatus. IR spectra were recorded using JASCO FT-7000 and Perkin-Elmer Model Spectrum100 spectrometers. NMR spectra were recorded in $CDCl_3$ on a JEOL Model GX-270 spectrometer with TMS as an internal standard. Chemical shifts are given in ppm. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. MS and HRMS were recorded on a Hitachi M-2000 mass spectrometer.

(*S*)-4-(3-Aminopyrrolidin-1-yl)coumarin (1). 4-Chlorocoumarin (5.0 g, 27.7 mmol) dissolved in dichloromethane (DCM) (100 mL) was stirred at 0 ºC under Ar and triethylamine (4.4 mL, 31.7 mmol) was added dropwise at 0 ºC. (*S*)-Pyrrolidin-3-amine (5.0 g, 58.0 mmol) dissolved in DCM (50 mL) was added dropwise over 30 min at 0 ºC, and the mixture was stirred for 27 h at room temperature. After removal of the solvent in vacuo, the crude product was purified by alumina column chromatography eluting with EtOAc-MeOH (2:1) to give (*S*)-4-(3-aminopyrrolidin-1-yl)coumarin (**1**: 4.02 g, yield 63%).

1: mp 154-155 °C, $[\alpha]_D^{20}$ –5.5 (*c* 1, CH_2Cl_2). *Anal.* Calcd for $C_{13}H_{14}N_2O_2$: C, 67.83; H, 6.09; N, 12.17. Found: C, 67.55; H, 6.08; N, 12.05. IR (KBr) cm^{-1}: 3350, 1660, 1530, 1440, 1420, 1360, 1260, 1200. ^{1}H NMR (δ): 1.42 (2H, bs), 1.87 (1H, m), 2.21 (1H, m), 3.43 (1H, dd, *J* = 10.2, 4.3 Hz), 3.67-3.94 (4H, m), 5.29 (1H, s, coumarin 3-H), 7.20 (1H, t, *J* = 8.2 Hz, Ar-H), 7.33 (1H, d, *J* = 8.2 Hz, Ar-H), 7.48 (1H, t, *J* = 8.2 Hz, Ar-H), 7.93 (1H, d, *J* = 8.2 Hz, Ar-H). ^{13}C NMR (δ): 34.3, 50.1, 50.9, 60.0, 87.0, 116.2, 118.1, 122.7, 125.4, 131.2, 154.3, 155.4, 162.8.

(*S*)-3-Aminopiperidin-2-one hydrochloride (2). L-Ornithine hydrochloride (180 g, 1.07 mol) dissolved in MeOH (1800 mL) was stirred for 30 min at 0 ºC under Ar. Thionyl chloride (160 mL, 2.19 mol) was added dropwise over 40 min at 0 ºC. The solution was stirred for 30 min at 0 ºC and refluxed for 6 h, and then solvent was removed in vacuo to give methyl L-ornithinate dihydrochloride (232.1 g). Methyl L-ornithinate dihydrochloride (223 g, 1.02 mol) dissolved in MeOH (2500 mL) was stirred at 0 ºC under Ar. NaOMe (116 g, 2.15 mol) was added, and the solution was stirred for 2 h at room temperature. After removal of the solvent in vacuo, the residue dissolved in Et_2O (600 mL) was stirred at room temperature. After filtration through celite, the solvent was removed in vacuo. The residue was dissolved in MeOH (400 mL), and then MeOH saturated with HCl (100 mL) was added to give the crude product. Recrystallization from MeOH-isopropyl alcohol (1:1) provided (*S*)-3-aminopiperidin-2-one hydrochloride (**2**: 131.2 g, yield 86%).

2: mp 204-206 °C, $[\alpha]_D^{25}$ +17.3 (*c* 0.6, MeOH). HRMS *m/z*: 114.0789 (Calcd. for $C_5H_{10}N_2O$: 114.0792). IR (ATR) cm^{-1}: 2867, 1646, 1586, 1262. ^{1}H NMR (δ, CD_3OD): 1.72-2.10 (3H, m), 2.29 (1H, m), 3.32 (2H, m), 3.86 (1H, dd, *J* = 11.9, 6.1 Hz).

(*S*)-Piperidin-3-amine (3). Lithium aluminum hydride (21.0 g, 553 mmol) dissolved in THF (500 mL) was stirred for 15 min at 0 ºC under Ar. Compound **2** (28.0 g, 186 mmol) was added and the solution was stirred for 15 min at 0 ºC, and then refluxed for 15 h. Then, water (21 mL), 15% sodium hydroxide solution (21 mL), and water (63 mL) were added sequentially. After vacuum filtration, the solvent was removed in vacuo. The crude product was purified by distillation at 75 ºC in vacuo (20 Torr) to give (*S*)-piperidin-3-amine (**3**: 11.8 g, yield 63%).

3: $[\alpha]_D^{20}$ -1.8 (*c* 10, $CHCl_3$). HRMS *m/z*: 100.1017 (Calcd. for $C_5H_{12}N_2$: 100.1000). IR (ATR) cm^{-1}: 3273, 2936, 1646, 1262. ^{1}H NMR (δ): 1.20 (1H, m), 1.30 (3H, s), 1.45 (1H, m), 1.69 (1H, m), 1.92 (1H, m), 2.31 (1H, dd, J = 11.5, 8.9 Hz), 2.53 (1H, dt, J = 3.2, 11.3 Hz), 2.73 (1H, m), 2.91 (1H, d, J = 12.1 Hz), 3.06 (1H, d, J = 11.5 Hz). ^{13}C NMR (ppm): 25.3, 34.6, 46.2, 48.6, 55.6.

(*S*)-4-(3-Aminopiperidin-1-yl)coumarin (4). 4-Chlorocoumarin (4.5 g, 25.9 mmol) dissolved in DCM (150 mL) was stirred at 0 ºC under Ar and triethylamine (4.4 mL, 31.7 mmol) was added dropwise at 0 ºC. Compound **3** (5.0 g, 49.9 mmol) dissolved in DCM (50 mL) was added dropwise over 15 min at 0 ºC, and the mixture was stirred for 18 h at room temperature. After removal of the solvent in vacuo, the crude product was purified by silica gel column chromatography eluting with $CHCl_3$-MeOH (4:1) to give (*S*)-4-(3-aminopiperidin-1-yl)coumarin (**4**: 3.71 g, yield 61%).

4: mp 163.5-165 °C, $[\alpha]_D^{20}$ –25.4 (*c* 1, MeOH). HRMS *m/z*: 244.1196 (Calcd. for $C_{14}H_{16}N_2O_2$: 244.1210). IR (KBr) cm^{-1}: 3422, 2942, 2870, 1669, 1630, 1605, 1549, 1419. ^{1}H NMR (δ): 1.79-2.12 (4H, m), 2.72 (1H, dd, J = 11.9, 8.9 Hz), 2.90 (1H, t, J = 9.5 Hz), 3.14 (1H, m), 3.43 (1H, d, J = 12.2 Hz), 3.53 (1H, d, J = 11.9 Hz), 5.71 (1H, s, coumarin 3-H), 7.24 (1H, t, J = 7.9 Hz, Ar-H), 7.31 (1H, d, J = 7.9 Hz, Ar-H), 7.48 (1H, t, J = 7.9 Hz, Ar-H), 7.64 (1H, d, J = 7.9 Hz, Ar-H). ^{13}C NMR (δ): 23.3, 33.8, 47.5, 51.3, 59.4, 97.5, 116.4, 117.6, 123.3, 124.8, 131.3, 154.0, 161.3, 162.5.

(S)-3-Aminoazepan-2-one hydrochloride (5). L-Lysine hydrochloride (100.0 g, 547 mmol) dissolved in MeOH (1200 mL) was stirred for 30 min at 0 ºC under Ar. Thionyl chloride (80 mL, 1.10 mol) was added dropwise over 20 min at 0 ºC. The solution was stirred for 1 h at room temperature, and refluxed for overnight. After removal of the solvent in vacuo, the crude product was recrystallized from MeOH to give methyl L-lysinate dihydrochloride (124.1 g, yield 97%). Methyl L-lysinate dihydrochloride (60.0 g, 257 mmol) dissolved in MeOH (1200 mL) was stirred at room temperature under Ar. NaOMe (48.0 g, 889 mmol) was added, and the solution was refluxed for 4 h. The mixture was hydrolyzed by adding ammonium chloride (20.0 g), and the solution was filtered, and then the solvent was removed in vacuo. The residue was dissolved in dimethoxyethane (80 mL), and the solution was filtered, and then the solvent was removed in vacuo. The residue was dissolved in EtOH (100 mL), and EtOH saturated with HCl (20 mL) was added to give the crude product. The crude product was recrystallized from MeOH to give (*S*)-3-aminozepan-2-one hydrochloride (**5**: 27.8 g, yield 66%).

5: mp >280 °C (dec.), $[\alpha]_D^{25}$ –26.4 (*c* 1.03, 1N HCl). *Anal.* Calcd for $C_6H_{12}N_2O$•HCl: C, 43.77; H, 7.96; N, 17.02. Found: C, 43.89; H, 8.02; N, 16.76. IR (KBr) cm^{-1}: 3192, 2940, 1667, 1491.

(*S*)-Azepan-3-amine (6). Lithium aluminum hydride (18.0 g, 474 mmol) dissolved in THF (400 mL) was stirred at 0 ºC. Compound **5** (26.0 g, 158 mmol) was added and the solution was refluxed for 12 h. Then, water (18 mL), 15% sodium hydroxide solution (18 mL), and water (54 mL) were added sequentially. The mixture was filtered in vacuo, and then the solvent was removed in vacuo. The crude product was purified by distillation at 75 ºC in vacuo (10 Torr) to give (*S*)-azepan-3-amine (**6**: 11.7 g, yield 65%).

6: $[\alpha]_D^{20}$ -9.1 (*c* 5.0, $CHCl_3$). HRMS *m/z*: 114.1160 (Calcd. for $C_6H_{14}N_2$: 114.1157). IR (neat) cm^{-1}: 2924, 2856, 1597, 1156. ^{1}H NMR (δ): 1.28-1.90 (9H, m), 2.54-2.62 (1H, m), 2.82-3.19 (4H, m). ^{13}C NMR (ppm): 21.8, 30.4, 37.1, 49.2, 52.6, 56.9.

(*S*)-4-(3-Aminoazepan-1-yl)coumarin (7). 4-Chlorocoumarin (5.0 g, 27.7 mmol) dissolved in DCM (100 mL) was stirred at 0 ºC and triethylamine (4 mL) was added dropwise at 0 ºC. Compound **6** (6.3 g, 55.2 mmol) dissolved in DCM (50 mL) was added dropwise at 0 ºC, and the mixture was stirred for 20 h at room temperature. After removal of the solvent in vacuo, the crude product was purified by alumina column chromatography eluting with EtOAc-MeOH (1:1) to give (*S*)-4-(3-aminoazepan-1-yl)coumarin (**7**: 4.25 g, yield 59%).

7: mp 172-174 °C, $[\alpha]_D^{20}$ –9.1 (*c* 1, MeOH). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$•HCl: C, 61.02; H, 6.50; N, 9.21. Found: C, 60.74; H, 6.55; N, 9.21. HRMS *m/z*: 258.1366 (Calcd. for $C_{15}H_{18}N_2O_2$: 258.1368). IR (KBr) cm^{-1}: 3320, 3236, 1717, 1661. ^{1}H NMR (δ): 1.47-2.02 (8H, m), 3.23-3.72 (5H, m), 5.60 (1H, s, coumarin 3-H), 7.22 (1H, t, *J* = 7.9 Hz, Ar-H), 7.33 (1H, d, *J* = 7.9 Hz, Ar-H), 7.48 (1H, t, *J* = 7.9 Hz, Ar-H), 7.76 (1H, d, *J* = 7.9 Hz, Ar-H). ^{13}C NMR (δ): 23.2, 27.8, 37.7, 51.6, 53.5, 59.4, 92.7, 116.4, 118.1, 122.9, 125.4, 131.1, 154.2, 156.0, 162.8.

General procedure for synthesis of coumarin analogues

Method A: CDA (**1**, **4**, or **7**) and carboxylic acid dissolved in DCM were stirred for 15 min at room temperature. *N,N′*-Dicyclohexylcarbodiimide (DCC) was then added, and the mixture was stirred for 30 min at room temperature.

Method B: CDA, carboxylic acid, and DMAP dissolved in DCM were stirred for 15 min at room temperature. DCC was added, and the mixture was stirred for 30 min at room temperature.

Method C: CDA and carboxylic acid dissolved in DCM were stirred for 10 min at room temperature. EDC was added, and the mixture was stirred for 30 min at room temperature.

Then, additional DCM was added, and the solution was washed with 10% aq. HCl, saturated aq. Na_2CO_3, and brine, and then dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by silica gel preparative thin layer chromatography eluting with EtOAc to give the desired product.

(*S*)-(+)-Ketoprofen + 5-CDA. Method B (yield 56%). $[\alpha]_D^{22}$ +10.4 (*c* 1, DCM). ^{1}H NMR (δ): 1.537 (3H, d, 2”-CH_3), 5.102 (1H, s, coumarin 3-H).

(*S*)-(+)-Ketoprofen + 6-CDA. Method B (yield 54%). $[\alpha]_D^{22}$ +2.4 (*c* 1, DCM). ^{1}H NMR (δ): 1.556 (3H, d, 2”-CH_3), 4.24 (1H), 5.664 (1H, s, coumarin 3-H).

(*S*)-(+)-Ketoprofen + 7-CDA. Method B (yield 73%). $[\alpha]_D^{22}$ -14.6 (*c* 1, DCM). ^{1}H NMR (δ): 1.495 (3H, d, 2”-CH_3), 4.33 (1H), 5.651 (1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenylpropanoic acid + 5-CDA (entry 1). Method A (yield 84%). HRMS *m/z*: 362.1615

(Calcd. for $C_{22}H_{22}N_2O_3$: 362.1629). IR (ATR) cm^{-1}: 3317, 2930, 1652, 1626, 1536, 1259, 1244. ^{1}H NMR (δ): 1.478 and 1.502 (Δδ = 0.024, each 3H, CH_3), 4.69 (1H), 5.116 (Δδ = 0, 1H, s, coumarin 3-H).

(*R*)- and (*S*)-3-Phenylbutanoic acid + 5-CDA (entry 2). Method A (yield 89%). HRMS *m/z*: 376.1762 (Calcd. for $C_{23}H_{24}N_2O_3$: 376.1785). IR (neat) cm^{-1}: 3296, 2932, 1663, 1541, 1446, 1365, 1261, 1199. ^{1}H NMR (δ): 1.297 and 1.308 (Δδ = 0.011, each 3H, CH_3), 4.63 (1H), 5.118 and 5.135 (Δδ = 0.017, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-4-Phenylpentanoic acid + 5-CDA (entry 3). Method A (yield 82%). HRMS *m/z*: 390.1971 (Calcd. for $C_{24}H_{26}N_2O_3$: 390.1942). IR (ATR) cm^{-1}: 3280, 2933, 1659, 1594, 1536, 1259. ^{1}H NMR (δ): 1.208 and 1.213 (Δδ = 0.005, each 3H, CH_3), 4.72 (1H), 5.127 and 5.142 (Δδ = 0.015, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-3-Methyl-2-phenylbutanoic acid + 5-CDA (entry 4). Method A (yield 86%). HRMS *m/z*: 390.1959 (Calcd. for $C_{24}H_{26}N_2O_3$: 390.1942). IR (ATR) cm^{-1}: 3274, 2932, 1649, 1595, 1537, 1258. ^{1}H NMR (δ): 1.013 and 1.095 (Δδ = 0.082, each 6H, CH_3), 4.75 (1H), 5.147 and 5.155 (Δδ = 0.008, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-*O*-Acetylmandelic acid + 5-CDA (entry 5). Method B (yield 96%). HRMS *m/z*: 406.1507 (Calcd. for $C_{23}H_{22}N_2O_5$: 406.1527). IR (neat) cm^{-1}: 3272, 3016, 1742, 1667, 1611, 1541, 1423, 1236, 1048. ^{1}H NMR (δ): 2.146 and 2.152 (Δδ = 0.006, each 3H, s, OAc), 5.160 and 5.183 (Δδ = 0.023, each 1H, s, coumarin 3-H), 5.993 and 6.015 (Δδ = 0.022, each 1H, s, mandelyl 2-H).

(*R*)- and (*S*)-*O*-Methylmandelic acid + 5-CDA (entry 6). Method A (yield 88%). HRMS *m/z*: 378.1600 (Calcd. for $C_{22}H_{22}N_2O_4$: 378.1579). IR (KBr) cm^{-1}: 3246, 2932, 1709, 1665, 1539, 1444, 1259, 1197. ^{1}H NMR (δ): 3.343 and 3.348 (Δδ = 0.005, each 3H, s, OCH_3), 5.292 and 5.303 (Δδ = 0.011, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Phenylmalonic acid monobenzyl ester + 5-CDA (entry 7). Method A (yield 92%). HRMS *m/z*: 482.1861 (Calcd. for $C_{29}H_{26}N_2O_5$: 482.1842). IR (neat) cm^{-1}: 3301, 2986, 1670, 1601, 1415, 1160. ^{1}H NMR (δ): 4.654 and 4.670 (Δδ = 0.016, each 1H, s, 2"-H), 5.11 and 5.16 (each 1H, s, Bzl-H), 5.181 (Δδ = 0, 1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenoxypropanoic acid + 5-CDA (entry 8). Method A (yield 73%). HRMS *m/z*: 378.1575 (Calcd. for $C_{22}H_{22}N_2O_4$: 378.1579). IR (neat) cm^{-1}: 3371, 3096, 2874, 1701, 1609, 1554, 1223. ^{1}H NMR (δ): 1.583 and 1.586 (Δδ = 0.003, each 3H, d, CH_3), 4.62 (1H), 5.145 and 5.223 (Δδ = 0.078, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Ibuprofen + 5-CDA (entry 9). Method B (yield 62%). HRMS *m/z*: 418.2239 (Calcd. for $C_{26}H_{30}N_2O_3$: 418.2254). IR (KBr) cm^{-1}: 3326, 3264, 2930, 1692, 1665, 1539, 1359, 1197. ^{1}H NMR (δ): 0.83 and 0.89 (each 3H, d, isobutyl-CH_3), 1.463 and 1.490 (Δδ = 0.027, each 3H, d, 2"-CH_3), 5.125 and

5.134 ($\Delta\delta$ = 0.009, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Ketoprofen + 5-CDA (entry 10). Method A (yield 88%). HRMS *m/z*: 466.1904 (Calcd. for $C_{29}H_{26}N_2O_4$: 466.1891). IR (ATR) cm^{-1}: 3270, 1650, 1594, 1535, 1258. ^{1}H NMR (δ): 1.508 and 1.536 ($\Delta\delta$ = 0.028, each 3H, d, 2”-CH_3), 5.094 and 5.110 ($\Delta\delta$ = 0.016, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Flurbiprofen + 5-CDA (entry 11). Method B (yield 83%). HRMS *m/z*: 456.1829 (Calcd. for $C_{28}H_{25}FN_2O_3$: 456.1849). IR (KBr) cm^{-1}: 3274, 3062, 2932, 1669, 1611, 1541, 1261, 1197. ^{1}H NMR (δ): 1.492 and 1.525 ($\Delta\delta$ = 0.033, each 3H, d, 2”-CH_3), 5.118 and 5.138 ($\Delta\delta$ = 0.020, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Naproxen + 5-CDA (entry 12). Method C (yield 89%). HRMS *m/z*: 442.1907 (Calcd. for $C_{27}H_{26}N_2O_4$: 442.1891). IR (ATR) cm^{-1}: 3317, 2930, 1624, 1606, 1575, 1537, 1263, 1243, 1196. ^{1}H NMR (δ): 1.525 and 1.563 ($\Delta\delta$ = 0.038, each 3H, d, 2”-CH_3), 3.92 (3H, s, OCH_3), 4.999 and 5.017 ($\Delta\delta$ = 0.018, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Fenoprofen + 5-CDA (entry 13). Method A (yield 85%). HRMS *m/z*: 451.1682 (Calcd. for $C_{28}H_{23}N_2O_4$: 451.1667). IR (ATR) cm^{-1}: 3274, 2932, 1659, 1593, 1536, 1244, 1199. ^{1}H NMR (δ): 1.466 and 1.493 ($\Delta\delta$ = 0.027, each 3H, d, 2”-CH_3), 5.141 ($\Delta\delta$ = 0, 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-proline + 5-CDA (entry 14).** Method A (yield 86%). HR-SIMS *m/z*: 424.1501 ($[M+H]^+$, Calcd. for $C_{20}H_{21}F_3N_3O_4$: 424.1483). IR (neat) cm^{-1}: 3278, 3018, 1671, 1613, 1541, 1446, 1216, 1152. ^{1}H NMR (δ): 5.177 and 5.233 ($\Delta\delta$ = 0.056, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-alanine + 5-CDA (entry 15).** Method A (yield 84%). HR-SIMS *m/z*: 398.1328 ($[M+H]^+$, Calcd. for $C_{18}H_{19}F_3N_3O_4$: 398.1327). IR (ATR) cm^{-1}: 3319, 2928, 1626, 1572, 1537, 1243 1185, 1155. ^{1}H NMR (δ): 1.457 and 1.509 ($\Delta\delta$ = 0.052, each 3H, 2”-CH_3), 4.82 (1H), 5.161 and 5.171 ($\Delta\delta$ = 0.010, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-valine + 5-CDA (entry 16).** Method A (yield 80%). HR-MS *m/z*: 425.1582 (Calcd. for $C_{20}H_{22}F_3N_3O_4$:425.1561). IR (ATR) cm^{-1}: 3319, 2928, 1623, 1570, 1537, 1242, 1185. ^{1}H NMR (δ): 5.191 and 5.202 ($\Delta\delta$ = 0.011, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-leucine + 5-CDA (entry 17).** Method A (crude). HR-SIMS *m/z*: 440.1789 ($[M+H]^+$, Calcd. for $C_{21}H_{25}F_3N_3O_4$: 440.1795). IR (ATR) cm^{-1}: 3316, 2932, 1662, 1624, 1539, 1243, 1185. ^{1}H NMR (δ): 1.01 and 1.02 (each 3H, d, CH_3), 4.54 (1H), 5.290 ($\Delta\delta$ = 0, 1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenylpropanoic acid + 6-CDA (entry 1). Method A (yield 80%). HRMS *m/z*: 376.1811 (Calcd. for $C_{23}H_{24}N_2O_3$: 376.1786). IR (ATR) cm^{-1}: 3316, 2928, 1623, 1573, 1242. ^{1}H NMR (δ): 1.448 and 1.463 ($\Delta\delta$ = 0.015, each 3H, CH_3), 4.29 (1H), 5.31 (1H), 5.609 and 5.641 ($\Delta\delta$ = 0.032, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-3-Phenylbutanoic acid + 6-CDA (entry 2). Method A (yield 80%). HRMS *m/z*: 390.1951

(Calcd. for $C_{24}H_{26}N_2O_3$: 390.1942). IR (neat) cm^{-1}: 3308, 2936, 1669, 1607, 1543, 1373. ^{1}H NMR (δ): 5.31 (1H), 5.608 and 5.648 (Δδ = 0.040, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-4-Phenylpentanoic acid + 6-CDA (entry 3). Method A (crude). HRMS *m/z*: 404.2115 (Calcd. for $C_{25}H_{28}N_2O_3$: 404.2099). IR (neat) cm^{-1}: 3310, 3030, 1711, 1607, 1553, 1493, 1274, 1193. ^{1}H NMR (δ): 1.263 and 1.270 (Δδ = 0.007, each 3H, CH_3), 4.19 (1H), 5.673 and 5.688 (Δδ = 0.015, each 1H, s, coumarin 3-H), 5.92 (1H, d).

(*R*)- and (*S*)-3-Methyl-2-phenylbutanoic acid + 6-CDA (entry 4). Method A (yield 94%). HRMS *m/z*: 404.2110 (Calcd. for $C_{25}H_{28}N_2O_3$: 404.2099). IR (ATR) cm^{-1}: 3317, 2930, 1605, 1550, 1230. ^{1}H NMR (δ): 0.71 (3H, CH_3), 1.000 and 1.064 (Δδ = 0.064, each 3H, CH_3), 4.25 (1H), 5.648 and 5.709 (Δδ = 0.061, each 1H, s, coumarin 3-H), 5.90 (1H, dd).

(*R*)- and (*S*)-*O*-Acetylmandelic acid + 6-CDA (entry 5). Method A (crude). HRMS *m/z*: 420.1663 (Calcd. for $C_{24}H_{24}N_2O_5$: 420.1683). IR (ATR) cm^{-1}: 3294, 2938, 1667, 1605, 1548, 1225, 1189. ^{1}H NMR (δ): 2.143 and 2.182 (Δδ = 0.039, each 3H, s, OAc), 4.28 (1H), 5.722 and 5.734 (Δδ = 0.012, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-*O*-Methylmandelic acid + 6-CDA (entry 6). Method A (yield 90%). HRMS *m/z*: 392.1744 (Calcd. for $C_{23}H_{24}N_2O_4$: 392.1735). IR (neat) cm^{-1}: 3410, 3058, 1711, 1609, 1555, 1518, 1470, 1232, 1195. ^{1}H NMR (δ): 3.337 and 3.367 (Δδ = 0.030, each 3H, s, OCH_3), 4.23 (1H), 4.613 and 4.633 (Δδ = 0.020, each 1H, s, 2”-H), 5.722 and 5.751 (Δδ = 0.029, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Phenylmalonic acid monobenzyl ester + 6-CDA (entry 7). Method A (yield 86%). HRMS *m/z*: 496.2013 (Calcd. for $C_{30}H_{28}N_2O_5$: 496.1997). IR (neat) cm^{-1}: 3316, 2938, 1676, 1607, 1551, 1456, 1160. ^{1}H NMR (δ): 4.24 (1H, bs), 4.695 and 4.707 (Δδ = 0.012, each 1H, s, 2”-H), 5.14 and 5.22 (each 1H, Bzl-H), 5.680 and 5.706 (Δδ = 0.026, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenoxypropanoic acid + 6-CDA (entry 8). Method A (yield 90%). HRMS *m/z*: 392.1733 (Calcd. for $C_{23}H_{24}N_2O_4$: 392.1734). IR (KBr) cm^{-1}: 3330, 2932, 2854, 1692, 1659, 1524, 1493, 1234, 1199. ^{1}H NMR (δ): 1.575 and 1.600 (Δδ = 0.025, each 3H, CH_3), 4.28 (1H), 4.70 (1H), 5.618 and 5.734 (Δδ = 0.116, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Ibuprofen + 6-CDA (entry 9). Method A (yield 90%). HRMS *m/z*: 432.2416 (Calcd. for $C_{27}H_{32}N_2O_3$: 432.2412). IR (KBr) cm^{-1}: 3330, 2854, 1721, 1630, 1421, 1232. ^{1}H NMR (δ): 0.85 and 0.87 (each 3H, isobutyl-CH_3), 1.515 and 1.524 (Δδ = 0.009, each 3H, 2”-CH_3), 4.20 (1H), 5.55 (1H), 5.645 and 5.664 (Δδ = 0.019, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Ketoprofen + 6-CDA (entry 10). Method A (yield 85%). HRMS *m/z*: 480.2049 (Calcd. for $C_{30}H_{28}N_2O_4$: 480.2048). IR (neat) cm^{-1}: 3294, 2910, 2842, 1671, 1594, 1555, 1249, 1191. ^{1}H NMR (δ): 1.544 and 1.553 (Δδ = 0.009, each 3H, 2”-CH_3), 4.20 (1H), 5.656 and 5.689 (Δδ = 0.033, each 1H, s, coumarin 3-H), 5.86 (1H, t).

(*R*)- and (*S*)-Flurbiprofen + 6-CDA (entry 11). Method A (yield 72%). HR-SIMS *m/z*: 471.2089 ($[M+H]^+$, Calcd. for $C_{29}H_{28}FN_2O_3$: 471.2083). IR (neat) cm^{-1}: 3330, 3020, 1686, 1609, 1549, 1419, 1218. ^{1}H NMR (δ): 1.56 (Δδ = 0, 3H, 2"-CH_3), 4.26 (1H), 5.685 and 5.703 (Δδ = 0.018, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Naproxen + 6-CDA (entry 12). Method A (yield 91%). HRMS *m/z*: 456.2070 (Calcd. for $C_{28}H_{28}N_2O_4$: 456.2048). IR (KBr) cm^{-1}: 3280, 3060, 1680, 1607, 1545, 1406, 1232, 1035. ^{1}H NMR (δ): 1.584 and 1.609 (Δδ = 0.025, each 3H, 2"-CH_3), 3.91 (3H, s, OCH_3), 4.25 (1H), 5.492 and 5.611 (Δδ = 0.119, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Fenoprofen + 6-CDA (entry 13). Method A (yield 81%). HRMS *m/z*: 468.2039 (Calcd. for $C_{29}H_{28}N_2O_4$: 468.2047). IR (neat) cm^{-1}: 3296, 3018, 1676, 1607, 1543, 1489, 1247, 1216, 1166. ^{1}H NMR (δ): 1.510 and 1.515 (Δδ = 0.005, each 3H, 2"-CH_3), 4.22 (1H), 5.61 (1H), 5.681 and 5.697 (Δδ = 0.016, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-proline + 6-CDA (entry 14).** Method A (crude). HRMS *m/z*: 437.1581 (Calcd. for $C_{21}H_{22}F_3N_3O_4$: 437.1561). IR (neat) cm^{-1}: 3310, 3018, 2952, 1684, 1609, 1553, 1454, 1234. ^{1}H NMR (δ): 4.21 (1H), 5.721 and 5.730 (Δδ = 0.009, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-alanine + 6-CDA (entry 15).** Method A (yield 84%). HR-SIMS *m/z*: 412.1466 ($[M+H]^+$, Calcd. for $C_{19}H_{21}F_3N_3O_4$: 412.1482). IR (neat) cm^{-1}: 3284, 3020, 2948, 1673, 1609, 1553, 1404, 1191. ^{1}H NMR (δ): 1.434 and 1.504 (Δδ = 0.070, each 3H, 2"-CH_3), 5.666 and 5.714 (Δδ = 0.048, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-valine + 6-CDA (entry 16).** Method A (yield 77%). HR-SIMS *m/z*: 440.1804 ($[M+H]^+$, Calcd. for $C_{21}H_{25}F_3N_3O_4$: 440.1796). IR (ATR) cm^{-1}: 3317, 2929, 1623, 1571, 1242, 1185. ^{1}H NMR (δ): 4.27 (1H), 5.738 (Δδ = 0, 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-leucine + 6-CDA (entry 17).** Method A (yield 82%). HR-SIMS *m/z*: 454.1960 ($[M+H]^+$, Calcd. for $C_{22}H_{27}F_3N_3O_4$: 454.1952). IR (ATR) cm^{-1}: 3317, 2928, 1624, 1573, 1242, 1186. ^{1}H NMR (δ): 4.24 (1H), 4.47 (1H), 5.695 and 5.729 (Δδ = 0.034, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenylpropanoic acid + 7-CDA (entry 1). Method C (yield 87%). HRMS *m/z*: 390.1919 (Calcd. for $C_{24}H_{26}N_2O_3$: 390.1942). IR (neat) cm^{-1}: 3304, 3014, 1680, 1607, 1543, 1452, 1218. ^{1}H NMR (δ): 1.448 and 1.465 (Δδ = 0.017, each 3H, CH_3), 4.30 (1H), 5.31 (1H), 5.617 and 5.645 (Δδ = 0.028, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-3-Phenylbutanoic acid + 7-CDA (entry 2). Method A (yield 90%). HRMS *m/z*: 404.2090 (Calcd. for $C_{25}H_{28}N_2O_3$: 404.2098). IR (neat) cm^{-1}: 3286, 2986, 1669, 1599, 1365, 1263. ^{1}H NMR (δ): 1.247 and 1.288 (Δδ = 0.041, each 3H, CH_3), 4.44 (1H), 5.31 (1H), 5.613 and 5.652 (Δδ = 0.039, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-4-Phenylpentanoic acid + 7-CDA (entry 3). Method A (yield 84%). HRMS *m/z*: 418.2234 (Calcd. for $C_{26}H_{30}N_2O_3$: 418.2254). IR (neat) cm^{-1}: 3306, 2936, 1680, 1607, 1545, 1452, 1287, 1199. ^{1}H NMR (δ): 1.225 and 1.251 (Δδ = 0.026, each 3H, CH_3), 4.30 (1H), 5.30 (1H), 5.691 and 5.705 (Δδ = 0.014, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-3-Methyl-2-phenylbutanoic acid + 7-CDA (entry 4). Method B (yield 85%). HRMS *m/z*: 418.2231 (Calcd. for $C_{26}H_{30}N_2O_3$: 418.2254). IR (ATR) cm^{-1}: 3315, 2930, 1664, 1626, 1540, 1448, 1245. ^{1}H NMR (δ): 0.67 (3H, d, CH_3), 0.954 and 1.026 (Δδ = 0.072, each 3H, CH_3), 4.34 (1H), 5.564 and 5.662 (Δδ = 0.098, each 1H, s, coumarin 3-H), 5.90 (1H).

(*R*)- and (*S*)-*O*-Acetylmandelic acid + 7-CDA (entry 5). Method B (yield 82%). HRMS *m/z*: 434.1848 (Calcd. for $C_{25}H_{26}N_2O_5$: 434.1842). IR (neat) cm^{-1}: 3300, 2938, 1742, 1680, 1607, 1543, 1373, 1230. ^{1}H NMR (δ): 2.044 and 2.091 (Δδ = 0.047, each 3H, s, OAc), 4.35 (1H), 5.688 and 5.694 (Δδ = 0.006, each 1H, s, coumarin 3-H), 5.890 and 6.000 (Δδ = 0.110, each 1H, s, mandelyl 2-H).

(*R*)- and (*S*)-*O*-Methylmandelic acid + 7-CDA (entry 6). Method A (yield 83%). HRMS *m/z*: 406.1902 (Calcd. for $C_{24}H_{26}N_2O_4$: 406.1891). IR (neat) cm^{-1}: 3328, 3012, 1773, 1676, 1618, 1560, 1452, 1218. ^{1}H NMR (δ): 3.462 and 3.520 (Δδ = 0.058, each 3H, s, OCH_3), 5.675 and 5.755 (Δδ = 0.080, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Phenylmalonic acid monobenzyl ester + 7-CDA (entry 7). Method B (yield 90%). HRMS *m/z*: 510.2133 (Calcd. for $C_{31}H_{30}N_2O_5$: 510.2155). IR (neat) cm^{-1}: 3401, 3072, 1690, 1601, 1512, 1226. ^{1}H NMR (δ): 4.34 (1H), 4.450 and 4.512 (Δδ = 0.062, each 1H, s, 2”-H), 5.13 and 5.18 (each 1H, Bzl-H), 5.630 and 5.694 (Δδ = 0.064, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-2-Phenoxypropanoic acid + 7-CDA (entry 8). Method B (yield 89%). HRMS *m/z*: 406.1861 (Calcd. for $C_{24}H_{26}N_2O_4$: 406.1891). IR (neat) cm^{-1}: 3326, 3062, 1684, 1607, 1545, 1230, 1197. ^{1}H NMR (δ): 1.446 and 1.554 (Δδ = 0.108, each 3H, CH_3), 4.36 (1H), 5.633 and 5.741 (Δδ = 0.108, each 1H, s, coumarin 3-H), 6.50 (1H).

(*R*)- and (*S*)-Ibuprofen + 7-CDA (entry 9). Method B (yield 87%). HRMS *m/z*: 446.2542 (Calcd. for $C_{28}H_{34}N_2O_3$: 446.2567). IR (ATR) cm^{-1}: 3315, 2927, 1669, 1606, 1540, 1254. ^{1}H NMR (δ): 0.86 and 0.88 (each 3H, isobutyl-CH_3), 1.430 and 1.456 (Δδ = 0.026, each 3H, 2”-CH_3), 4.28 (1H), 5.620 and 5.644 (Δδ = 0.024, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Ketoprofen + 7-CDA (entry 10). Method C (yield 94%). HRMS *m/z*: 494.2192 (Calcd. for $C_{31}H_{30}N_2O_4$: 484.2203). IR (neat) cm^{-1}: 3312, 3014, 1661, 1607, 1545, 1286. ^{1}H NMR (δ): 1.475 and 1.495 (Δδ = 0.020, each 3H, CH_3), 4.31 (1H), 5.58 (1H), 5.639 and 5.679 (Δδ = 0.040, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Flurbiprofen + 7-CDA (entry 11). Method B (yield 89%). HRMS *m/z*: 484.2150 (Calcd. for $C_{30}H_{29}FN_2O_3$: 484.2160). IR (ATR) cm^{-1}: 3299, 2932, 1668, 1608, 1556, 1254. ^{1}H NMR (δ): 1.466 and 1.485 (Δδ = 0.019, each 3H, d, CH_3), 4.30 (1H), 5.64 (1H), 5.669 and 5.695 (Δδ = 0.026, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Naproxen + 7-CDA (entry 12). Method A (yield 93%). HRMS *m/z*: 470.2193 (Calcd. for $C_{29}H_{30}N_2O_4$: 470.2203). IR (ATR) cm^{-1}: 3316, 2931, 1665, 1605, 1540, 1261. ^{1}H NMR (δ): 1.524 and 1.542 (Δδ = 0.018, each 3H, CH_3), 3.92 (3H, s, OCH_3), 4.30 (1H), 5.35 (1H), 5.601 and 5.635 (Δδ = 0.034, each 1H, s, coumarin 3-H).

(*R*)- and (*S*)-Fenoprofen + 7-CDA (entry 13). Method A (yield 68%). HRMS *m/z*: 482.2178 (Calcd. for $C_{30}H_{30}N_2O_4$: 482.2203). IR (neat) cm^{-1}: 3306, 2938, 1676, 1607, 1543, 1489, 1267. ^{1}H NMR (δ): 1.50 (Δδ = 0, 3H, CH_3), 4.30 (1H), 5.43 (1H), 5.661 and 5.683 (Δδ = 0.022, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-proline + 7-CDA (entry 14).** Method A (yield 78%). HR-SIMS *m/z*: 452.1792 ($[M+H]^+$, Calcd. for $C_{22}H_{25}F_3N_3O_4$: 452.1795). IR (KBr) cm^{-1}: 3302, 3017, 1680, 1599, 1474, 1160. ^{1}H NMR (δ): 4.29 (1H), 5.696 and 5.744 (Δδ = 0.048, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-alanine + 7-CDA (entry 15).** Method A (crude). HR-SIMS *m/z*: 426.1651 ($[M+H]^+$, Calcd. for $C_{20}H_{23}F_3N_3O_4$: 426.1640). IR (neat) cm^{-1}: 3286, 3022, 1719, 1673, 1609, 1545, 1419, 1216, 1168. ^{1}H NMR (δ): 1.296 and 1.369 (Δδ = 0.073, each 3H, d, CH_3), 5.747 and 5.783 (Δδ = 0.036, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-valine + 7-CDA (entry 16).** Method A (yield 82%). HR-SIMS *m/z*: 454.1976 ($[M+H]^+$, Calcd. for $C_{22}H_{27}F_3N_3O_4$: 454.1952). IR (ATR) cm^{-1}: 3315, 2931, 1625, 1576, 1243. ^{1}H NMR (δ): 1.329 and 1.336 (Δδ = 0.007, each 6H, CH_3), 5.764 and 5.789 (Δδ = 0.025, each 1H, s, coumarin 3-H).

***N*-Trifluoroacetyl-DL-leucine + 7-CDA (entry 17).** Method A (yield 85%). HR-SIMS *m/z*: 468.2138 ($[M+H]^+$, Calcd. for $C_{23}H_{29}F_3N_3O_4$: 468.2109). IR (ATR) cm^{-1}: 3266, 2931, 1709, 1656, 1606, 1540, 1249. ^{1}H NMR (δ): 4.32 (1H), 4.43 (1H), 5.756 and 5.797 (Δδ = 0.041, each 1H, s, coumarin 3-H).

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