NOVEL CHIRAL DERIVATIZING AGENTS FOR $^1$H NMR DETERMINATION OF ENANTIOMIC 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. During our studies on coumarin chemistry, 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. This signal is more distinct than the methoxy protons in Mosher’s acid, 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 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**

(S)-pyrrolidin-3-amine

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, \text{Et}_3\text{N, rt} & \rightarrow \\
\end{align*}
\]


**Scheme 2**

L-ornithine HCl

\[
\text{SOCl}_2, \text{MeOH, reflux} \rightarrow 1) \text{NaOMe} \rightarrow 2) \text{HCl} \rightarrow 1) \text{LiAlH}_4
\]

**Scheme 3**

L-lysine HCl

\[
\text{SOCl}_2, \text{MeOH, reflux} \rightarrow 1) \text{NaOMe} \rightarrow 2) \text{HCl} \rightarrow 1) \text{LiAlH}_4
\]
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-dimethylanilinopyridine (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 \(^1\text{H}\) 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 (\( \Delta \delta \) 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, baseline resolution was observed with most of the racemic acid substrates in Table 1. For example, the \(^1\text{H}\) 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 \( \Delta \delta \) ppm values (ca. 0.015) with all three CDAs. Also, no chemical shift differences were found for the coumarin H-3 of

**Figure 1.** \(^1\text{H}\) 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, $\Delta \delta$ ppm of Diastereomeric Amides with CDAs$^a$)

<table>
<thead>
<tr>
<th>entry</th>
<th>$dl$-R-CO$_2$H</th>
<th>5-CDA</th>
<th>6-CDA</th>
<th>7-CDA</th>
<th>entry</th>
<th>$dl$-R-CO$_2$H</th>
<th>5-CDA</th>
<th>6-CDA</th>
<th>7-CDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>0</td>
<td>0.032</td>
<td>0.028</td>
<td>10</td>
<td>PhCOPh</td>
<td>0.016</td>
<td>0.033</td>
<td>0.040</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>0.017</td>
<td>0.040</td>
<td>0.039</td>
<td>11</td>
<td>PhPh(F)</td>
<td>0.020</td>
<td>0.018</td>
<td>0.026</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>0.015</td>
<td>0.015</td>
<td>0.014</td>
<td>12</td>
<td>MeONaph</td>
<td>0.018</td>
<td>0.119</td>
<td>0.034</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>0.008</td>
<td>0.061</td>
<td>0.098</td>
<td>13</td>
<td>PhOPh</td>
<td>0</td>
<td>0.016</td>
<td>0.022</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>0.023</td>
<td>0.012</td>
<td>0.006</td>
<td>14</td>
<td>$N$-COCF$_3$</td>
<td>0.056</td>
<td>0.009</td>
<td>0.048</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>0.011</td>
<td>0.029</td>
<td>0.080</td>
<td>15</td>
<td>NHCOCF$_3$</td>
<td>0.010</td>
<td>0.048</td>
<td>0.036</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>0</td>
<td>0.026</td>
<td>0.064</td>
<td>16</td>
<td>NHCOCF$_3$</td>
<td>0.011</td>
<td>0</td>
<td>0.025</td>
</tr>
<tr>
<td>8</td>
<td>PhO</td>
<td>0.078</td>
<td>0.116</td>
<td>0.108</td>
<td>17</td>
<td>NHCOCF$_3$</td>
<td>0</td>
<td>0.034</td>
<td>0.041</td>
</tr>
<tr>
<td>9</td>
<td>iPrCH$_2$Ph</td>
<td>0.009</td>
<td>0.019</td>
<td>0.024</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 ($\Delta \delta$ 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 $\Delta \delta$ 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 $\Delta \delta$ 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 $\Delta \delta$ 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 Δδ 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 Δδ 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 Δδ 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 1H 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 1H NMR Integration**

<table>
<thead>
<tr>
<th>CDA</th>
<th>%e.e.</th>
<th>Diastereomeric ratio of CDAs amide by 1H NMR</th>
<th>%d.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-CDA</td>
<td>60.0</td>
<td>79.4 : 20.6</td>
<td>58.8</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>59.5 : 40.5</td>
<td>19.0</td>
</tr>
<tr>
<td></td>
<td>50.0</td>
<td>50.3 : 49.7</td>
<td>0.6</td>
</tr>
<tr>
<td>6-CDA</td>
<td>60.0</td>
<td>80.6 : 19.4</td>
<td>61.2</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>61.0 : 39.0</td>
<td>22.0</td>
</tr>
<tr>
<td></td>
<td>50.0</td>
<td>48.8 : 51.2</td>
<td>2.4</td>
</tr>
<tr>
<td>7-CDA</td>
<td>60.0</td>
<td>78.7 : 21.3</td>
<td>57.4</td>
</tr>
<tr>
<td></td>
<td>20.0</td>
<td>60.6 : 39.4</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>50.0</td>
<td>51.0 : 49.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

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 CDCl₃ 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 °C under Ar and triethylamine (4.4 mL, 31.7 mmol) was added dropwise at 0 °C. (S)-Pyrrolidin-3-amine (5.0 g, 58.0 mmol) dissolved in DCM (50 mL) was added dropwise over 30 min at 0 °C, 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, [α]D20 –5.5 (c 1, CH2Cl2). Anal. Calcd for C13H14N2O2: 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. 1H 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). 13C 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 °C under Ar. Thionyl chloride (160 mL, 2.19 mol) was added dropwise over 40 min at 0 °C. The solution was stirred for 30 min at 0 °C 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 °C 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 Et2O (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, [α]D25 +17.3 (c 0.6, MeOH). HRMS m/z: 114.0789 (Calcd. for C₅H₁₀N₂O: 114.0792). IR (ATR) cm⁻¹: 2867, 1646, 1586, 1262. 1H NMR (δ, CD₃OD): 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 °C under Ar. Compound 2 (28.0 g, 186 mmol) was added and the solution was stirred for 15 min at 0 °C, 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 °C in vacuo (20 Torr) to give (S)-piperidin-3-amine (3: 11.8 g, yield 63%).

3: [α]D20 -1.8 (c 10, CHCl₃). HRMS m/z: 100.1017 (Calcd. for C₅H₁₂N₂: 100.1000). IR (ATR) cm⁻¹: 3273, 2936, 1646, 1262. 1H 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). 13C 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 CHCl3-MeOH (4:1) to give (S)-4-(3-aminopiperidin-1-yl)coumarin (4: 3.71 g, yield 61%).

4: mp 163.5-165 ºC, [α]D 20 –25.4 (c 1, MeOH). HRMS m/z: 244.1196 (Calcd. for C14H16N2O2: 244.1210).

IR (KBr) cm⁻¹: 3422, 2942, 2870, 1669, 1630, 1605, 1549, 1419. 1H 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). 13C 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 ºC (dec.), [α]D 25 -26.4 (c 1.03, 1N HCl). Anal. Calcd for C6H12N2•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: [α]D 20 -9.1 (c 5.0, CHCl3). HRMS m/z: 114.1160 (Calcd. for C6H14N2: 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 ºC, $[\alpha]_D^{20}$ –9.1 (c 1, MeOH). Anal. Calcd for C$_{15}$H$_{18}$N$_2$O$_2$•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$_2$O$_2$: 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$_2$CO$_3$, 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%). $[\alpha]_D^{20}$ +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%). $[\alpha]_D^{20}$ +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%). $[\alpha]_D^{20}$ -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_{2}O_{3}: 362.1629). IR (ATR) cm\(^{-1}\): 3317, 2930, 1652, 1626, 1536, 1259, 1244. \(^1\)H NMR (\(\delta\)): 1.478 and 1.502 (\(\Delta\delta = 0.024\), each 3H, CH\(_3\)), 4.69 (1H), 5.116 (\(\Delta\delta = 0\), 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_{2}O_{3}: 376.1785). IR (neat) cm\(^{-1}\): 3296, 2932, 1663, 1541, 1446, 1365, 1261, 1199. \(^1\)H NMR (\(\delta\)): 1.297 and 1.308 (\(\Delta\delta = 0.011\), each 3H, CH\(_3\)), 4.63 (1H), 5.118 and 5.135 (\(\Delta\delta = 0.015\), 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_{2}O_{3}: 390.1942). IR (ATR) cm\(^{-1}\): 3280, 2933, 1659, 1594, 1536, 1259. \(^1\)H NMR (\(\delta\)): 1.208 and 1.213 (\(\Delta\delta = 0.005\), each 3H, CH\(_3\)), 4.72 (1H), 5.127 and 5.142 (\(\Delta\delta = 0.015\), 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_{2}O_{3}: 390.1942). IR (ATR) cm\(^{-1}\): 3274, 2932, 1649, 1595, 1537, 1258. \(^1\)H NMR (\(\delta\)): 1.013 and 1.095 (\(\Delta\delta = 0.082\), each 6H, CH\(_3\)), 4.75 (1H), 5.147 and 5.155 (\(\Delta\delta = 0.008\), 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_{2}O_{5}: 406.1527). IR (neat) cm\(^{-1}\): 3272, 3016, 1742, 1667, 1541, 1423, 1236, 1048. \(^1\)H NMR (\(\delta\)): 2.146 and 2.152 (\(\Delta\delta = 0.006\), each 3H, s, OAc), 5.160 and 5.183 (\(\Delta\delta = 0.023\), each 1H, s, coumarin 3-H), 5.993 and 6.015 (\(\Delta\delta = 0.022\), 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_{2}O_{4}: 378.1579). IR (KBr) cm\(^{-1}\): 3246, 2932, 1709, 1665, 1539, 1444, 1259, 1197. \(^1\)H NMR (\(\delta\)): 3.343 and 3.348 (\(\Delta\delta = 0.005\), each 3H, s, OCH\(_3\)), 5.292 and 5.303 (\(\Delta\delta = 0.011\), 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_{2}O_{5}: 482.1842). IR (neat) cm\(^{-1}\): 3317, 2986, 1670, 1601, 1415, 1160. \(^1\)H NMR (\(\delta\)): 4.654 and 4.670 (\(\Delta\delta = 0.016\), each 1H, s, 2"-H), 5.11 and 5.16 (each 1H, s, Bzl-H), 5.181 (\(\Delta\delta = 0\), 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_{2}O_{4}: 378.1579). IR (neat) cm\(^{-1}\): 3371, 3096, 2874, 1701, 1609, 1554, 1223. \(^1\)H NMR (\(\delta\)): 1.583 and 1.586 (\(\Delta\delta = 0.003\), each 3H, d, CH\(_3\)), 4.62 (1H), 5.145 and 5.223 (\(\Delta\delta = 0.078\), 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_{2}O_{3}: 418.2254). IR (KBr) cm\(^{-1}\): 3326, 3264, 2930, 1692, 1665, 1539, 1359, 1197. \(^1\)H NMR (\(\delta\)): 0.83 and 0.89 (each 3H, d, isobutyl-CH\(_3\)), 1.463 and 1.490 (\(\Delta\delta = 0.027\), each 3H, d, 2"-CH\(_3\)), 5.125 and
5.134 (Δδ = 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_{2}O_{4}: 466.1891). IR (ATR) cm⁻¹: 3270, 1650, 1594, 1535, 1258. ¹H NMR (δ): 1.508 and 1.536 (Δδ = 0.028, each 3H, d, 2"-CH₃), 5.094 and 5.110 (Δδ = 0.016, each 1H, s, coumarin 3-H).

(R)- and (S)-Ketoprofen + 5-CDA (entry 11). Method B (yield 83%). HRMS m/z: 456.1829 (Calcd. for C_{28}H_{25}FN_{2}O_{3}: 456.1849). IR (KBr) cm⁻¹: 3274, 3062, 2932, 1669, 1611, 1541, 1261, 1197. ¹H NMR (δ): 1.492 and 1.525 (Δδ = 0.033, each 3H, d, 2"-CH₃), 5.118 and 5.138 (Δδ = 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_{2}O_{4}: 442.1891). IR (ATR) cm⁻¹: 3317, 2930, 1624, 1606, 1575, 1537, 1263, 1243, 1195. ¹H NMR (δ): 1.525 and 1.563 (Δδ = 0.038, each 3H, d, 2"-CH₃), 3.92 (3H, s, OCH₃), 4.999 and 5.017 (Δδ = 0.018, each 1H, s, coumarin 3-H).

(R)- and (S)-Fenoprofen + 5-CDA (entry 13). Method A (yield 85%). HR-MS m/z: 451.1682 (Calcd. for C_{28}H_{23}N_{2}O_{4}: 451.1667). IR (ATR) cm⁻¹: 3274, 2932, 1659, 1593, 1537, 1263, 1243, 1199. ¹H NMR (δ): 1.466 and 1.493 (Δδ = 0.027, each 3H, d, 2"-CH₃), 5.141 (Δδ = 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_{3}N_{3}O_{4}: 424.1483). IR (neat) cm⁻¹: 3278, 3018, 1671, 1613, 1541, 1446, 1216, 1152. ¹H NMR (δ): 5.177 and 5.233 (Δδ = 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_{3}N_{3}O_{4}: 398.1327). IR (ATR) cm⁻¹: 3278, 3018, 1671, 1613, 1541, 1446, 1216, 1152. ¹H NMR (δ): 1.457 and 1.509 (Δδ = 0.052, each 3H, d, 2"-CH₃), 4.82 (1H), 5.161 and 5.171 (Δδ = 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_{3}N_{3}O_{4}: 425.1561). IR (ATR) cm⁻¹: 3278, 3018, 1671, 1613, 1541, 1446, 1216, 1152. ¹H NMR (δ): 5.191 and 5.202 (Δδ = 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_{3}N_{3}O_{4}: 440.1795). IR (ATR) cm⁻¹: 3316, 2932, 1662, 1624, 1539, 1243, 1199. ¹H NMR (δ): 1.01 and 1.02 (each 3H, d, CH₃), 4.54 (1H), 5.290 (Δδ = 0, 1H, s, coumarin 3-H).

(R)- and (S)-2-Phenylpropanoic acid + 6-CDA (entry 1). Method A (yield 80%). HR-MS m/z: 376.1811 (Calcd. for C_{23}H_{24}N_{2}O_{4}: 376.1786). IR (ATR) cm⁻¹: 3316, 2932, 1623, 1570, 1537, 1242, 1185. ¹H NMR (δ): 1.448 and 1.463 (Δδ = 0.015, each 3H, CH₃), 4.29 (1H), 5.31 (1H), 5.609 and 5.641 (Δδ = 0.032, each 1H, s, coumarin 3-H).

(R)- and (S)-3-Phenylbutanoic acid + 6-CDA (entry 2). Method A (yield 80%). HR-MS m/z: 390.1951
(Calcd. for C_{24}H_{26}N_{2}O_{3}: 390.1942). IR (neat) cm\(^{-1}\): 3308, 2936, 1669, 1607, 1543, 1373. \(^1\)H NMR (\(\delta\)): 5.31 (1H), 5.608 and 5.648 (\(\Delta \delta = 0.040\), 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_{2}O_{3}: 404.2099). IR (neat) cm\(^{-1}\): 3310, 3030, 1711, 1607, 1553, 1493, 1274, 1193. \(^1\)H NMR (\(\delta\)): 5.31 (1H), 5.608 and 5.648 (\(\Delta \delta = 0.040\), each 1H, s, coumarin 3-H).

\((R)-\) 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_{2}O_{3}: 404.2099). IR (ATR) cm\(^{-1}\): 3317, 2930, 1605, 1550, 1230. \(^1\)H NMR (\(\delta\)): 0.71 (3H, CH\(_3\)), 1.000 and 1.064 (\(\Delta \delta = 0.064\), each 3H, CH\(_3\)), 4.25 (1H), 5.648 and 5.709 (\(\Delta \delta = 0.061\), each 1H, s, coumarin 3-H).

\((R)-\) and \((S)-O\)-Acetylmandelic acid + 6-CDA (entry 5). Method A (crude). HRMS \(m/z\): 420.1663 (Calcd. for C_{24}H_{24}N_{2}O_{5}: 420.1683). IR (ATR) cm\(^{-1}\): 3294, 2938, 1667, 1609, 1555, 1470, 1232, 1195. \(^1\)H NMR (\(\delta\)): 2.143 and 2.182 (\(\Delta \delta = 0.039\), each 3H, s, OAc), 4.28 (1H), 5.722 and 5.734 (\(\Delta \delta = 0.012\), 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_{2}O_{4}: 392.1735). IR (neat) cm\(^{-1}\): 3410, 3058, 1711, 1609, 1555, 1518, 1470, 1232, 1195. \(^1\)H NMR (\(\delta\)): 3.337 and 3.367 (\(\Delta \delta = 0.030\), each 3H, s, OCH\(_3\)), 4.23 (1H), 4.613 and 4.633 (\(\Delta \delta = 0.020\), each 1H, s, 2\(^\prime\)-H), 5.722 and 5.751 (\(\Delta \delta = 0.029\), 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_{2}O_{4}: 392.1734). IR (KBr) cm\(^{-1}\): 3330, 2932, 2854, 1692, 1659, 1524, 1493, 1234, 1199. \(^1\)H NMR (\(\delta\)): 1.575 and 1.600 (\(\Delta \delta = 0.025\), each 3H, CH\(_3\)), 4.28 (1H), 4.70 (1H), 5.618 and 5.734 (\(\Delta \delta = 0.116\), 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_{2}O_{3}: 432.2412). IR (KBr) cm\(^{-1}\): 3330, 2932, 1721, 1630, 1421, 1232. \(^1\)H NMR (\(\delta\)): 0.85 and 0.87 (each 3H, isobutyl-CH\(_3\)), 1.515 and 1.524 (\(\Delta \delta = 0.009\), each 3H, 2\(^\prime\)-CH\(_3\)), 4.20 (1H), 5.55 (1H), 5.645 and 5.664 (\(\Delta \delta = 0.019\), 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_{2}O_{4}: 480.2048). IR (neat) cm\(^{-1}\): 3294, 2910, 2842, 1671, 1594, 1555, 1249, 1191. \(^1\)H NMR (\(\delta\)): 1.544 and 1.553 (\(\Delta \delta = 0.009\), each 3H, 2\(^\prime\)-CH\(_3\)), 4.20 (1H), 5.656 and 5.689 (\(\Delta \delta = 0.033\), 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, 1543, 1489, 1247, 1216, 1166. $^1$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, 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 $C_{23}H_{25}N_2O_3$: 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 $C_{23}H_{25}N_2O_3$: 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_{2}O_{3}: 418.2254). IR (neat) cm⁻¹: 3306, 2936, 1680, 1607, 1545, 1452, 1287, 1199. ¹H NMR (δ): 1.225 and 1.251 (Δδ = 0.026, each 3H, CH₃), 4.30 (1H), 5.30 (1H), 5.691 and 5.705 (Δδ = 0.014, each 1H, s, coumarin 3-H).

(R)- and (S)-4-Phenylpentanoic acid + 7-CDA (entry 4). Method B (yield 85%). HRMS m/z: 418.2231 (Calcd. for C_{26}H_{30}N_{2}O_{3}: 418.2254). IR (ATR) cm⁻¹: 3315, 2930, 1664, 1626, 1540, 1448, 1245. ¹H NMR (δ): 0.67 (3H, d, CH₃), 0.954 and 1.026 (Δδ = 0.072, each 3H, CH₃), 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_{2}O_{5}: 434.1842). IR (neat) cm⁻¹: 3300, 2938, 1742, 1680, 1607, 1543, 1373, 1230. ¹H 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_{2}O_{4}: 406.1891). IR (neat) cm⁻¹: 3328, 3012, 1773, 1676, 1618, 1560, 1452, 1218. ¹H NMR (δ): 3.462 and 3.520 (Δδ = 0.058, each 3H, s, OCH₃), 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_{2}O_{5}: 510.2155). IR (neat) cm⁻¹: 3401, 3072, 1690, 1601, 1512, 1226. ¹H 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_{2}O_{4}: 406.1891). IR (neat) cm⁻¹: 3326, 3062, 1684, 1607, 1545, 1230, 1197. ¹H NMR (δ): 1.446 and 1.554 (Δδ = 0.108, each 3H, CH₃), 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_{2}O_{3}: 446.2567). IR (ATR) cm⁻¹: 3315, 2927, 1669, 1606, 1540, 1254. ¹H NMR (δ): 0.86 and 0.88 (each 3H, isobutyl-CH₃), 1.430 and 1.456 (Δδ = 0.026, each 3H, 2”-CH₃), 4.28 (1H), 5.620 and 5.644 (Δδ = 0.024, each 1H, s, coumarin 3-H).

(R)- and (S)-Ibuprofen + 7-CDA (entry 10). Method C (yield 94%). HRMS m/z: 494.2192 (Calcd. for C_{31}H_{30}N_{2}O_{4}: 484.2203). IR (neat) cm⁻¹: 3312, 3014, 1661, 1607, 1545, 1286. ¹H NMR (δ): 1.475 and 1.495 (Δδ = 0.020, each 3H, CH₃), 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_{2}O_{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, CH₃), 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_{2}O_{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, CH₃), 3.92 (3H, s, OCH₃), 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_{2}O_{4}: 482.2203). IR (neat) cm⁻¹: 3306, 2938, 1676, 1607, 1543, 1489, 1267. \(^1\)H NMR (δ): 1.50 (Δδ = 0, 3H, CH₃), 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}F₃N₃O₄: 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}F₃N₃O₄: 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, CH₃), 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}F₃N₃O₄: 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, CH₃), 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}F₃N₃O₄: 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).

REFERENCES


2. (a) K. Nagasawa, H. Kanbara, K. Matsushita, and K. Ito, Tetrahedron Lett., 1985, 26, 6477; (b) K.


