Supporting Information

Asymmetric synthesis of warfarin and its analogs catalyzed by C$_2$-symmetric squaramide-based primary diamines

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1. General Remarks

The NMR $^1$H and $^{13}$C spectra were recorded by Bruker AM 300 in CDCl$_3$ and DMSO–$d_6$. The chemical shifts of $^1$H and $^{13}$C were measured relative to Me$_4$Si or CDCl$_3$, respectively. The high resolution mass spectra (HRMS) were measured by Bruker microTOF II with electrospray ionization (ESI). The optical rotations were measured on a polarimeter and calibrated with a pure solvent as a blank. The HPLC analyses were performed on an HPLC system equipped with chiral stationary phase columns, detection at 220 or 254 nm. Silica gel 0.060 – 0.200 was used for column chromatography. Linalool-derived isoprenoid acids 12b and 12c were used as mixtures of isomers with regard to the double bond at C$^5$ (E/Z ~4:1).

2. General procedure for selective mono-Boc protection of diamines 1

\[
\begin{align*}
R & \quad R \\
\text{H}_2\text{N} & \quad \text{NH}_2 \\
1 & \quad 1)	ext{TMSCl (1 equiv.)} \\
 & \quad 2) \text{Boc}_2\text{O (1 equiv.)} \\
 & \quad 3) \text{NaOH} \\
 & \quad \text{H}_2\text{N} \\
 & \quad \text{NHBOc} \\
R & \quad R
\end{align*}
\]

TMSCl (0.01 mol, 1.26 mL) was added to MeOH and the resulting solution was stirred for 10 min at 0°C. Next, diamines 1 (0.01 mol) were added at 0°C. The mixture was stirred for 15 min at room temperature and the solution of (Boc)$_2$O (0.01 mol, 2.16 g) in MeOH (15 mL) was added dropwise for 10 min. The resulting solution was stirred for 1.5 h. The mixture was concentrated in vacuo. The residue was transferred to a filter and washed by diethyl ether (3 × 30 mL). The resulting pale-yellow solid was successively treated with the 3 N NaOH solution (25 mL) and water (3 × 10 mL). The product was dried in vacuo to afford mono-Boc amines 2 as colorless solids.

**Tert-butyl ((1R,2R)-2-amino-1,2-diphenylethyl)carbamate (R,R-2a)** [1].

Yield 2.65 g (85%) as colorless solid. Mp: 100-101°C. $[\alpha]_D^{22} = +29.15$ (c 0.5, CHCl$_3$). $^1$H NMR (300 MHz, DMSO–$d_6$) δ 7.33 (d, $J = 8.2$ Hz, 1H), 7.27 – 6.90 (m, 10H), 4.63 (t, $J = 7.2$ Hz, 1H), 4.02 (d, $J = 6.6$ Hz, 1H), 1.85 (br s, 2H), 1.44 – 0.95 (m, 9H) ppm.

**Tert-butyl ((1S,2S)-2-amino-1,2-diphenylethyl)carbamate (S,S-2a).**

Yield 2.69 g (86%) as colorless solid. Mp: 100-101°C. $[\alpha]_D^{22} = -28.90$ (c 0.5, CHCl$_3$). The $^1$H NMR spectra was identically (R,R-2a).
**Tert**-butyl ((1R,2R)-2-aminocyclohexyl)carbamate (R,R-2b) [2].

Yield 1.8 g (85%) as colorless solid. Mp: 113-115°C. \([\alpha]_{D}^{22} = -32.16 \) (c 0.5, CH₃OH). \(^1\)H NMR (300 MHz, DMSO- \(d_6\)) \(\delta\) 6.62 (d, \(J = 8.3\) Hz, 1H), 2.96 – 2.78 (m, 1H), 2.31 (td, \(J = 10.3, 4.0\) Hz, 1H), 1.82 – 1.68 (m, 2H), 1.65 – 1.52 (m, 2H), 1.38 (br s, 9H), 1.23 – 0.89 (m, 4H) ppm.

**Tert**-butyl ((1S,2S)-2-amino-1,2-di(pyridin-2-yl)ethyl)carbamate (R,R-2c).

Yield 2.45 g (78%) as colorless solid. Mp: 123-125 °C, \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 8.56 (d, \(J = 4.4\) Hz, 2H), 7.57 (t, \(J = 7.6\) Hz, 2H), 7.26 – 6.99 (m, 4H), 6.15 (d, \(J = 6.2\) Hz, 1H), 5.22 – 5.03 (m, 1H), 4.58 (d, \(J = 4.4\) Hz, 1H), 2.62 (s, 2H), 1.36 (s, 9H) ppm. \(^{13}\)C NMR (75 MHz, CDCl₃): \(\delta\) 160.4, 159.3, 155.7, 148.9, 148.8, 136.2, 136.1, 122.1, 122.1, 121.9, 79.2, 60.2, 28.2 ppm. HRMS (ESI): \(m/z\) [M]\(^+\) calcd for C₁₇H₂₂N₄O₂: 315.1816; found 315.1809; [M + Na]\(^+\) calcd 337.1635; found 337.1631; [M + K]\(^+\) calcd 353.1374 found 353.1369.

### 3. Preparation of the catalysts 6 and 7

![Diagram](https://via.placeholder.com/150)

4,4’-((1S,2S)-1,2-Di(pyridin-2-yl)ethane-1,2-diyl)bis(azonediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (S,S-5).

(1S,2S)-1,2-Di(pyridin-2-yl)ethane-1,2-diamine S,S-1c (627 mg, 2.93 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione 3 (975 mg, 6.15 mmol) were dissolved in methanol (5 mL) and stirred for 12 hours. The precipitate was filtered off, washed with MeOH (2 × 5 mL) and Et₂O (3 × 10 mL) and dried under reduced pressure (0.5 Torr) at 50 °C for 1 h to afford the amide compound S,S-5 as colorless solid. Yield 826 mg (65%) as colorless solid. Mp: 213-215°C. \(^1\)H NMR (300 MHz, DMSO- \(d_6\)) \(\delta\) 9.64 – 9.14 (m, 2H), 8.53 (br s, 2H), 7.66 (br s, 2H), 7.57 (t, \(J = 7.6\) Hz, 2H), 7.26 – 6.99 (m, 4H), 6.15 (d, \(J = 6.2\) Hz, 1H), 5.22 – 5.03 (m, 1H), 4.58 (d, \(J = 4.4\) Hz, 1H), 2.62 (s, 2H), 1.36 (s, 9H) ppm.
7.21 (br s, 4H), 5.98 (br s, 1H), 5.52 (br s, 1H), 4.25 (s, 6H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 189.0, 183.0, 177.7, 172.6, 172.3, 157.7, 157.1, 149.6, 137.3, 123.4, 62.2, 61.9, 61.1, 60.7, 60.5, 60.3 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{22}$H$_{18}$N$_4$O$_6$: 435.1299; found 435.1295; [M + Na]$^+$ calcd 457.1119; found 457.1115; [M + K]$^+$ calcd 473.0858 found 473.0848.

4,4'-'-((1$R$,2$R$)-1,2-Di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (R,R-5).

Compound R,R-5 was prepared similarly to S,S-5 from R,R-1c. Yield 877 mg (69%) as colorless solid. Spectral data for R,R-5 were identical to those for enantiomer S,S-5.

4,4'-(((1$S$,2$S$)-1,2-Diphenylethane-1,2-diyl)bis(azanediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (S,S-4).

Compound S,S-4 was prepared similarly to S,S-5 from S,S-1a. Yield 785 mg (62%) as colorless solid. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.92 – 9.31 (m, 2H, NH), 7.53 – 6.97 (m, 10H), 5.76 – 5.37 (m, 1H), 5.23 – 4.90 (m, 1H), 4.28 (d, $J$ = 7.4 Hz, 6H) ppm.

4,4'-'-((1$R$,2$R$)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (R,R-4).

Compound R,R-4 was prepared similarly to S,S-5 from R,R-1a. Yield 835 mg (66%) as colorless solid. Spectral data for R,R-4 were identical to those for enantiomer S,S-4.

Di-tert-butyl ((1$S$,1'S,2$S$,2'')-(((1$S$,2$S$)-1,2-di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl)) dicarbamate (Boc-7a).

The suspension of the compounds S,S-5 (204 mg, 0.47 mmol) and S,S-2a (320 mg, 1.03 mmol) in methanol (5 mL) was stirred for 12 hours. The precipitate was filtered off, washed with MeOH (3 x 10 mL) and Et$_2$O (3 x 10 mL) and dried under reduced pressure (0.5 Torr) at 50 °C for 1 h to afford the compound Boc-7a as colorless solid. Yield 350 mg (75%) as colorless solid. Mp: 241-245°C. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 8.56 (s, 1H), 8.23 – 8.03 (m, 2H, NH), 7.60 (t, $J$ = 7.2 Hz, 1H), 7.32 – 6.92 (m, 12H), 5.86 (d, $J$ = 7.0 Hz, 1H), 5.20 (t, $J$ = 9.2 Hz, 1H), 4.85 (t, $J$ = 9.0 Hz, 1H), 1.10 (s, 9H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 183.1, 182.9, 168.7, 168.1, 167.7, 157.9, 157.7, 155.5, 149.7, 140.8, 140.4, 137.3, 128.6, 128.5, 128.3, 127.9, 127.6, 127.5, 124.0, 123.5, 78.6, 62.2, 60.9, 60.7, 59.2, 28.6 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{58}$H$_{58}$N$_8$O$_8$: 995.4450; found 995.4431; [M + Na]$^+$ calcd 1017.4270; found 1017.4258.
Di-tert-butyl ((1R,1'R,2R,2'R)-((((1R,2R)-1,2-di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl)) bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl)) dicarbamate (Boc-ent-7a).

Compound Boc-ent-7a was prepared similarly to Boc-7a from R,R-5 and R,R-2a. Yield 355 mg (76%) as colorless solid. Spectral data for Boc-ent-7a were identical to those for enantiomer Boc-7a.

Di-tert-butyl ((1S,1'S,2S,2'S)-((((1R,2R)-1,2-di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl)) bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl)) dicarbamate (Boc-7b).

Compound Boc-7b was prepared similarly to Boc-7a from R,R-5 and S,S-2a. Yield 348 mg (75%) as colorless solid. Mp: 261-263°C. $^1$H NMR (300 MHz, DMSO- $d_6$) δ 8.56 (s, 1H), 8.25 – 8.00 (m, 2H), 7.68 – 7.50 (m, 1H), 7.35 – 6.87 (m, 26H), 5.85 (d, $J = 6.2$ Hz, 1H), 5.20 (t, $J = 9.4$ Hz, 1H), 4.94 – 4.74 (m, 1H), 1.09 (s, 9H) ppm. $^{13}$C NMR (75 MHz, DMSO- $d_6$) δ 183.1, 182.9, 168.6, 168.1, 167.6, 157.8, 157.6, 155.4, 149.6, 140.7, 137.3, 128.6, 128.5, 128.2, 127.9, 127.5, 127.4, 123.9, 123.4, 78.5, 62.1, 60.8, 60.6, 59.1, 28.5 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{58}$H$_{58}$N$_8$O$_8$: 995.4450; found 995.4429; [M + Na]$^+$ calcd 1017.4270; found 1017.4248; [M + K]$^+$ calcd 1033.4009 found 1033.3987.

Di-tert-butyl ((1S,1'S,2S,2'S)-((((1S,2S)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl)) dicarbamate (Boc-6a).

Compound Boc-6a was prepared similarly to Boc-7a from S,S-4 and S,S-2a. Yield 340 mg (72%) as colorless solid. Mp: 261-263°C. $^1$H NMR (300 MHz, DMSO- $d_6$) δ 8.15 – 7.55 (m, 4H, NH), 7.49 – 6.78 (m, 32H), 5.71 – 5.45 (m, 2H), 5.03 – 4.85 (m, 2H), 4.17 (br s, 2H), 1.43 – 0.95 (m, 18H) ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{60}$H$_{60}$N$_6$O$_8$: 993.4545; found 993.4540.

Di-tert-butyl ((1S,1'S,2S,2'S)-((((1S,2S)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl)) dicarbamate (Boc-6b).

Compound Boc-6b was prepared similarly to Boc-7a from R,R-4 and S,S-2a. Yield 331 mg (70%) as colorless solid. Mp: 228-231°C. $^1$H NMR (300 MHz, DMSO- $d_6$) δ 8.15 – 7.55 (m, 4H, NH), 7.49 – 6.78 (m, 32H), 5.71 – 5.45 (m, 2H), 5.03 – 4.85 (m, 2H), 4.17 (br s, 2H), 1.43 – 0.95 (m, 18H) ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{60}$H$_{60}$N$_6$O$_8$: 993.4545; found 993.4549.
Trifluoroacetic acid (0.5 mL) was added to compound Boc-7a (250 mg, 0.25 mmol). The resulting solution was stirred for 1 hour. Then the excess of trifluoroacetic acid was evaporated under reduced pressure (15 Torr). The residue was washed with 4 N NaOH (5mL), then with Et₂O (3 × 10 mL) and dried under reduced pressure (0.5 Torr) for 1 h to afford the compound 7a as colorless solid, yield 227 mg (89%). Mp: 222-227°C. 

\[
\delta 8.89 – 8.39 \text{ (m, 7H)}, 8.29 \text{ (d, } J = 5.8 \text{ Hz, 2H)}, 8.10 \text{ (d, } J = 7.9 \text{ Hz, 2H)}, 7.57 \text{ (t, } J = 7.4 \text{ Hz, 2H)}, 7.39 – 6.90 \text{ (m, 26H)}, 5.87 \text{ (d, } J = 6.2 \text{ Hz, 2H)}, 5.49 \text{ (t, } J = 10.3 \text{ Hz, 2H)}, 4.74 \text{ (d, } J = 9.8 \text{ Hz, 2H)} \text{ ppm. HRMS (ESI): m/z [M]⁺ calcld for } C_{48}H_{42}N_8O_4: 795.3402; \text{ found } 795.3395; [M + Na]⁺ calcld 817.3221; \text{ found } 817.3214; [M + K]⁺ calcld 833.2961 \text{ found } 833.2950.
\]

Compound ent-7a was prepared similarly to 7a from Boc-ent-7a. Yield 225 mg (88%) as colorless solid. Spectral data for ent-7a were identical to those for enantiomer 7a.

Compound 7b was prepared similarly to 7a from Boc-7b. Yield 230 mg (90%) as colorless solid. Mp: 227-230°C. ¹H NMR (300 MHz, DMSO-\text{d}_6 + TFA) δ 9.07 – 8.59 (m, 9H), 8.57 – 8.04 (m, 4H), 7.56 (br s, 2H), 7.45 – 6.64 (m, 26H), 5.93 (br s, 2H), 5.56 (br s, 2H), 4.96 (br s, 2H) ppm. HRMS (ESI): m/z [M]⁺ calcld for C_{48}H_{42}N_8O_4: 795.3402; found 795.3393; [M + Na]⁺ calcld 817.3221; found 817.3218; [M + K]⁺ calcld 833.2961 found 833.2955.

Compound 6a was prepared similarly to 7a from Boc-6a. Yield 230 mg (90%) as light yellow solid. Mp: 280-283°C. ¹H NMR (300 MHz, DMSO-\text{d}_6 + TFA) δ 8.74 – 8.38 (m, 8H), 8.08 (br s, 2H), 7.41 – 6.83 (m, 40H), 5.62 (br s, 2H), 5.48 (t, J = 9.8 Hz, 2H), 4.70 (d, J = 8.7 Hz, 2H) ppm. HRMS (ESI): m/z [M]⁺ calcld for C_{50}H_{44}N_8O_4: 793.3497; found 793.3495.
(S,S)-4,4′-(((1R,2R)-1,2-Diphenylethane-1,2-diyl)bis(azanediyl))bis(3-(((1S,2S)-2-amino-1,2-diphenylethyl)amino)cyclobut-3-ene-1,2-dione) (6b).

Compound 6b was prepared similarly to 7a from Boc-6b. Yield 222 mg (89%) as light yellow solid. Mp: 267-270°C. 1H NMR (300 MHz, DMSO-d6 + TFA) δ 8.87 – 8.42 (m, 8H), 8.16 (br s, 2H), 7.54 – 6.70 (m, 40H), 5.60 (br s, 3H), 5.47 (br s, 2H), 4.73 (br s, 2H) ppm. HRMS (ESI): m/z [M]+ calcd for C50H44N8O4: 793.3497; found 793.3493.

4. General procedure for asymmetric Michael addition

The mixture of 4-hydroxy coumarin 8a or 4-hydroxy-6-methyl-2H-pyran-2-one 8b (0.126 mmol), α,β-unsaturated ketone 9 (0.151 mmol), catalyst 7a or ent-7a (10 mg, 12.6 µmol), AcOH (70 µL), and CH2Cl2 (300 µL) was stirred at ambient temperature for 24 h. The solvent and AcOH were removed under reduced pressure (15 Torr) and the residue was extracted with Et2O (5 x 3 mL). The combined organic extracts were evaporated under reduced pressure (15 Torr). Corresponding products 10 or 11 were purified via flash-chromatography on silica gel (n-hexane/EtOAc 2:1).

4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin) (10a). [3]

Yield 37 mg 10a (96%) as colorless solid. Mp: 155-158°C. [α]D20 = -10.2 (c 1, MeCN, 96% ee). 1H NMR (300 MHz, CDCl3) δ 9.67 (s, 0.16H), 7.96 – 7.74 (m, 1.42H), 7.59-7.39 (m, 1.67H), 7.39-7.13 (m, 8.47H), 4.77 (d, J = 10.1 Hz, 0.16H), 4.30-4.13 (m, 1.23H), 3.90-3.78 (m, 0.36H), 3.37-3.30 (d, 0.19H), 2.53-2.35 (m, 1.50H), 2.29 (s, 0.32H) 2.07-1.95 (m, 0.74), 1.69-1.67 (m, 3H) ppm.

4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one (10b). [3]

Yield 39 mg 10b (93%) as colorless solid. Mp: 165-678°C. [α]D20 = +14.64 (c 1, MeCN, 84 % ee). 1H NMR (300 MHz, CDCl3) δ 9.45 (s, 0.15H), 7.94-7.81 (m, 1.04H), 7.58-7.50 (m, 1.45H), 7.35- 7.14 (m, 4.59H), 6.89-6.83 (m, 2.15H), 4.66 (m, 0.17H), 4.26 (m, 0.50H), 4.13 (m, 0.53H), 3.79-3.78 (m, 3H), 2.57-2.38 (m, 1.83H), 2.29 (s, 0.53H), 1.72 - 1.69 (m, 2.70H) ppm.

3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-2H-chromen-2-one (10c). [3]

Yield 39 mg 10c (91%) as colorless solid. Mp: 175-176°C. [α]D20 = +22.44 (c 1, MeCN, 88 % ee). 1H NMR (300 MHz, CDCl3) δ 9.72 (0.18H), 7.90-7.81 (m, 1H), 7.59-7.44 (m, 1.29H), 7.37 – 7.14 (m, 6.64), 4.68 (d, J = 8.4 Hz, 0.16H), 4.38 (br s, 0.41H), 4.22-4.05 (m, 1.10H), 3.91-
3.70 (m, 0.55H), 3.32-3.26 (m, 0.20H) 2.48-2.35 (m, 1.28H), 2.28 (s, 0.31H), 2.05 – 1.89 (m, 1.25H), 1.72 (s, 1.43H), 1.69 (s, 0.98H) ppm.

4-Hydroxy-3-(3-oxocyclohexyl)-2H-chromen-2-one (10d). [4]

Yield 29 mg 10c (89%) as colorless solid. \([\alpha]_D^{20} = +15.52\) (c 1, MeCN, 50 % ee). \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 12.32 (br s, 0.47H) 7.83-7.74 (d, \(J = 7.6\) Hz, 1.00H), 7.61-7.56 (t, \(J = 7.8\) Hz, 1.00H), 7.36-7.30 (m, 2.00H), 3.19 (s, 0.66H), 2.30-2.19 (m, 1.00H), 2.12-1.99 (m, 2.00H), 1.87-1.79 (m, 2.00H), 1.64-1.57 (m, 2.00H), 1.41-1.35 (m, 1.00H) ppm.

4-Hydroxy-6-methyl-3-(3-oxo-1-phenylbutyl)-2H-pyran-2-one (11a). [3]

Yield 33 mg 11a (97%) as light yellow oil. \([\alpha]_D^{20} = -30.25\) (c 1, CHCl\(_3\), 94 % ee). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.68 – 6.83 (m, 5H), 5.88 (s, 0.4H), 5.79 (s, 0.6H), 4.80 – 4.47 (m, 0.4 H), 4.30 – 4.07 (m, 0.6H), 3.82 – 3.58 (m, 0.4H), 3.33 – 3.08 (m, 0.4H), 2.45 – 2.31 (m, 0.6H), 2.27 (s, 1.2H), 2.21 (s, 1.8H), 2.08 (s, 1H), 1.98 – 1.81 (m, 0.6H), 1.58 (s, 1.2H), 1.56 (s, 1.8H) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 171.5, 164.8, 164.3, 161.4, 161.0, 143.2, 141.7, 128.9, 128.47, 128.1, 127.8, 127.0, 126.3, 101.1, 100.8, 100.2, 98.7, 60.4, 45.7, 42.6, 40.3, 34.9, 34.5, 33.9, 27.8, 27.2, 21.0, 19.7, 14.2 ppm. NMR HRMS (ESI): \(m/z\) [M]\(^+\) calcd for C\(_{16}\)H\(_{16}\)O\(_4\): 273.1121; found 273.1124.

4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-6-methyl-2H-pyran-2-one (11b). [5]

Yield 36 mg 11b (95%) as light yellow oil. \([\alpha]_D^{20} = -21.10\) (c 0.66, CHCl\(_3\), 86 % ee). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.43 – 7.19 (m, 2H), 7.19 – 6.98 (m, 2H), 5.87 (s, 0.5H), 5.77 (s, 0.5H), 4.83 – 4.53 (m, 0.5H), 4.09 – 3.91 (m, 0.5H), 3.79 (s, 3H), 3.67 – 3.44 (m, 0.5H), 3.33 – 3.06 (m, 0.5H), 2.48 – 2.09 (m, 3.5H), 2.06 (s, 1H), 1.97 – 1.76 (m, 0.5H), 1.54 (s, 3H) ppm. \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 210.20, 171.28, 164.58, 164.24, 164.10, 163.62, 161.40, 160.99, 158.51, 158.00, 135.12, 133.25, 128.89, 128.64, 128.01, 114.50, 113.93, 113.51, 101.19, 101.02, 100.78, 100.71, 100.20, 98.78, 98.66, 60.44, 55.18, 45.92, 42.70, 40.11, 34.18, 33.74, 32.87, 30.14, 29.67, 27.92, 27.45, 21.03, 19.81, 19.71, 19.49, 14.17 ppm. HRMS (ESI): \(m/z\) [M]\(^+\) calcd for C\(_{17}\)H\(_{18}\)O\(_5\): 303.1227; found 303.1231.

3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-6-methyl-2H-pyran-2-one (11c). [5]

Yield 37 mg 11c (95%) as light yellow oil. \([\alpha]_D^{20} = -34.86\) (c 1, CHCl\(_3\), 89 % ee). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.09 (m, 4H), 5.88 (s, 0.45H), 5.80 (s, 0.55H), 4.74 – 4.56 (m, 0.45H), 4.21 – 4.06 (m, 0.55H), 3.81 – 3.55 (m, 0.45H), 3.33 – 3.07 (m, 0.45H), 2.48 – 2.29 (m,
0.55H), 2.28 (s, 1.35H), 2.22 (s, 1.65H), 2.09 (s, 1H), 1.97 – 1.80 (m, 0.55H), 1.57 (d, J = 4.0 Hz, 3H) ppm. 13C NMR (75 MHz, CDCl3) δ 209.60, 166.39, 165.57, 164.96, 164.60, 164.43, 163.97, 161.47, 161.05, 160.49, 143.20, 142.60, 141.75, 128.92, 128.46, 128.10, 127.88, 127.02, 126.89, 126.28, 104.11, 101.04, 100.31, 98.86, 98.57, 60.49, 45.83, 42.70, 40.39, 35.06, 34.58, 34.06, 30.14, 27.80, 27.18, 19.80, 19.70, 19.55, 14.18 ppm.


4-Hydroxy-6-methyl-3-(3-oxocyclohexyl)-2H-pyran-2-one (11d). [6]

Yield 25 mg 11d (91%) as light yellow oil. [α]D22 = +88.72 (c 0.66, CHCl3, 63 % ee). 1H NMR (300 MHz, CDCl3) δ 5.77 (s, 1H), 4.32 (br s, 1H), 3.22 (s, 1H), 2.18 (s, 3H), 2.14 – 1.30 (m, 8H) ppm. 13C NMR (75 MHz, CDCl3) δ 166.5, 164.4, 160.8, 101.8, 100.2, 99.9, 77.5, 77.1, 76.6, 38.4, 35.7, 28.5, 28.2, 19.8, 18.9 ppm. HRMS (ESI): m/z [M]+ calcd for C12H14O4: 223.0965; found 223.0961.

5. Scaling catalytic reaction and catalyst recovery

The mixture of 4-hydroxycoumarin 8a (1.62 g, 10.0 mmol), α,β-unsaturated ketone 9a (1.75 g, 12.0 mmol), catalyst 7a (0.79 g, 1.0 mmol), AcOH (0.57 mL), and CH2Cl2 (5 mL) was stirred at ambient temperature for 24 h. The solvent and AcOH were removed under reduced pressure (15 Torr) and the residue was extracted with Et2O (5 x 30 mL). The combined organic extracts were evaporated under reduced pressure (15 Torr) to afford the product 10a. After extraction of product 10a with Et2O, remained catalyst 7a was dried under reduced pressure (1.0 Torr, 30 min). Fresh portions of 8a, 9a, AcOH and CH2Cl2 were added to the recovered catalyst and the reaction was re-performed.

6. General procedure for warfarin esterification

Warfarin 10a (0.154 g, 0.5 mmol), acid 12 (0.5 mmol), DCC (0.11 g, 0.5 mmol), DMAP (cat.) and DCM (0.5 mL) were stirred for 24 h. The precipitate was filtered off and washed with DCM (3×5 mL). The combined organic washings were evaporated and the residue was purified by column chromatography on silica gel (eluent: n-hexane/EtOAc, 4:1-2:1) to afford ester 13.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-acetoxybenzoate (13a).

Yield 0.2 g (85%) as colorless oil. [α]D22 = +4.67 (c, 0.2, CHCl3, 96 % ee). 1H NMR (300 MHz, DMSO-d6) δ 7.85 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.54 – 7.05 (m, 11H), 4.06
- 3.82 (m, 1H), 3.00 – 2.69 (m, 1H), 2.16-2.06 (m, 1H), 2.05 (s, 3H), 1.94 (s, 3H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 168.9, 160.1, 157.7, 152.8, 143.3, 132.8, 128.8, 127.6, 126.7, 124.7, 123.1, 116.7, 115.1, 104.8, 103.0, 41.0, 34.9, 24.3, 22.1 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{28}$H$_{22}$O$_7$: 471.1438; found 471.1435; [M + NH$_4$]$^+$ calcd 488.1704, found 488.1703.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 5,9-dimethyldeca-4,8-dienoate (13b).

Yield 0.21 g (86%) as colorless oil. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.84 (d, $J = 7.5$ Hz, 1H), 7.66 (t, $J = 7.8$ Hz, 1H), 7.49 – 7.07 (m, 7H), 5.05 – 4.84 (m, 2H), 3.98 – 3.80 (m, 1H), 2.83 (m, 1H), 2.33 (m, 2H), 2.13 (m, 2H), 2.05 – 1.83 (m, 6H), 1.78 (m, 2H), 1.66 – 1.39 (m, 9H) ppm. $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 170.9, 160.0, 157.7, 152.7, 143.2, 136.5, 136.4, 132.8, 131.3, 131.1, 128.8, 127.5, 126.7, 124.6, 124.4, 123.2, 123.0, 122.4, 116.7, 115.1, 104.8, 102.9, 102.9, 41.2, 35.2, 35.1, 31.8, 26.5, 26.3, 25.9, 25.8, 24.2, 23.5, 23.4, 17.9, 17.8, 16.2 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{31}$H$_{34}$O$_5$: 487.2479; found 487.2469; [M + NH$_4$]$^+$ calcd 504.2744, found 504.2734; [M + Na]$^+$ calcd 509.2298, found 509.2288.

2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoate (13c).

Yield 0.21 g (75%) as colorless oil. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.69 – 7.07 (m, 9H), 5.43 – 5.24 (m, 1H), 5.21 – 5.02 (m, 1H), 4.90 – 4.76 (m, 1H), 3.93 – 3.51 (m, 1H), 3.50 – 3.11 (m, 1H), 2.90 – 2.70 (m, 1H), 2.69 – 2.54 (m, 1H), 2.53 – 2.30 (m, 1H), 2.28 – 1.43 (m, 21H), 1.26 (m, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 206.1, 171.8, 171.8, 160.9, 152.5, 140.0, 138.2, 131.7, 131.6, 128.3, 127.8, 127.7, 126.7, 124.1, 124.0, 123.7, 121.2, 121.1, 116.6, 116.1, 109.9, 77.5, 77.1, 76.7, 52.0, 45.2, 40.0, 39.9, 39.8, 37.5, 36.5, 36.5, 31.4, 31.2, 30.3, 29.9, 27.0, 26.6, 26.4, 26.3, 26.2, 25.7, 23.5, 22.4, 17.8, 17.7, 16.3 ppm. HRMS (ESI): $m/z$ [M]$^+$ calcd for C$_{37}$H$_{44}$O$_5$: 569.3262, found 569.3257; [M + NH$_4$]$^+$ calcd 586.3527, found 586.3524; [M + Na]$^+$ calcd 591.3081, found 591.3076; [M + K]$^+$ calcd 607.2820, found 607.2821.
7. Pictures of $^1$H and $^{13}$C NMR spectra for novel compounds

_Tert-buty (1S,2S)-2-amino-1,2-di(pyridin-2-yl)ethyl)carbamate (2c)._
4,4'-(((1S,2S)-1,2-Di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (S,S-5).
Di-tert-butyl ((1S,1'S,2S,2'S)-((((1S,2S)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl))dicarbamate (Boc-6a).

Di-tert-butyl ((1S,1'S,2S,2'S)-((((1R,2R)-1,2-diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl))dicarbamate (Boc-6b).
(1S,1'S,2S,2'S)-2,2'-(((1S,2S)-1,2-Diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethanaminium) trifluoroacetate (6a).

(1S,1'S,2S,2'S)-2,2'-(((1R,2R)-1,2-Diphenylethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethanaminium) trifluoroacetate (6b).
Di-tert-Butyl (((1S,1'S,2S,2'S))-(((1S,2S)-1,2-di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl))dicarbamate (Boc-7a).
Di-tert-Butyl ((1S,1'S,2S,2'S)-((((1R,2R)-1,2-di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethane-2,1-diyl))dicarbamate (Boc-7b).
(1S,1’S,2S,2’S)-2,2’-((((1S,2S)-1,2-Di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethanaminium) trifluoroacetate (7a).

(1S,1’S,2S,2’S)-2,2’-((((1R,2R)-1,2-Di(pyridin-2-yl)ethane-1,2-diyl)bis(azanediyl))bis(3,4-dioxocyclobut-1-ene-2,1-diyl))bis(azanediyl))bis(1,2-diphenylethanaminium) trifluoroacetate (7b).
4-Hydroxy-6-methyl-3-(3-oxo-1-phenylbutyl)-2H-pyran-2-one (11a).
4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-6-methyl-2H-pyran-2-one (11b).
3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-6-methyl-2H-pyran-2-one (11c).
4-Hydroxy-6-methyl-3-(3-oxocyclohexyl)-2H-pyran-2-one (11d).
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-acetoxybenzoate (13a).
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 5,9-dimethyldeca-4,8-dienoate (13b).
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl 2-cyclohexyl-5,9-dimethyldeca-4,8-dienoate (13c).
8. Pictures of $^1$H NMR spectra for known compounds

(1S,2S)-$N$-($tert$-Butoxycarbonyl)-1,2-diphenylethylenediamine ($S,S$-2a).

(1S,2S)-$N$-($tert$-Butoxycarbonyl)-1,2-cyclohexanediamine (2b).
4,4’-(((1S,2S)-1,2-Diphenylethane-1,2-diyl)bis(azanediyl))bis(3-methoxycyclobut-3-ene-1,2-dione) (S,S-4).

4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin) (10a).
4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one (10b).

3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-2H-chromen-2-one (Coumachlor) (10c).
4-Hydroxy-3-(3-oxocyclohexyl)-2H-chromen-2-one (10d).
9. HPLC data

4-Hydroxy-3-(3-oxo-1-phenylbutyl)-2H-chromen-2-one (Warfarin) (10a).

HPLC (Daicel Chiralcel AD-H; n-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; λ = 254 nm): $t_1 = 5.2$ min., $t_2 = 10.3$ min.
4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-2H-chromen-2-one (10b).

HPLC (Daicel Chiralcel AD-H; n-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; \( \lambda = 254 \text{ nm} \)): \( t_1 = 7.07 \text{ min.}, t_2 = 18.84 \text{ min.} \)
3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-2H-chromen-2-one (Coumachlor) (10c).

HPLC (Daicel Chiralcel OD-H; $n$-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; $\lambda$ = 254 nm): $t_1 = 6.14$ min., $t_2 = 14.74$ min.
4-Hydroxy-3-(3-oxocyclohexyl)-2H-chromen-2-one (10d).

HPLC (Daicel Chiralcel OJ-H; n-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; $\lambda = 220$ nm): $t_1 = 5.55$ min., $t_2 = 6.48$ min.
4-Hydroxy-6-methyl-3-(3-oxo-1-phenylbutyl)-2H-pyran-2-one (11a).

HPLC (Daicel Chiralcel AD-H; n-hexane/2-propanol, 90:10; flow rate = 0.8 mL/min; λ = 220 nm): $t_1 = 14.8$ min., $t_2 = 25.9$ min.
4-Hydroxy-3-(1-(4-methoxyphenyl)-3-oxobutyl)-6-methyl-2H-pyran-2-one (11b).

HPLC (Daicel Chiralpak AS-H; n-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; \( \lambda = 254 \) nm): \( t_1 = 9.63 \) min., \( t_2 = 11.78 \) min.

![Graph of HPLC analysis](image1.png)

**RESULTS**

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![Graph of HPLC analysis](image2.png)

**RESULTS**

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3-(1-(4-Chlorophenyl)-3-oxobutyl)-4-hydroxy-6-methyl-2H-pyran-2-one (11c).

HPLC (Daicel Chiralpak AS-H; $n$-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; $\lambda = 254$ nm): $t_1 = 7.22$ min., $t_2 = 10.29$ min.
4-Hydroxy-6-methyl-3-(3-oxocyclohexyl)-2H-pyran-2-one (11d).

HPLC (Daicel Chiralpak AS-H; n-hexane/2-propanol, 70:30; flow rate = 0.8 mL/min; λ = 254 nm): t₁ = 10.03 min., t₂ = 16.14 min.
2-Oxo-3-(3-oxo-1-phenylbutyl)-2H-chromen-4-yl -2-acetoxybenzoate (13a).

HPLC (Daicel Chiralpak AS-H; n-hexane/2-propanol, 99:1; flow rate = 0.8 mL/min; \( \lambda = 254 \) nm): \( t_1 = 22.22 \) min., \( t_2 = 24.19 \) min.
10. References


