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# Supporting Information

# Absolute Asymmetric Synthesis of a Sanguinarine Derivative through Crystal-Solution Interactions

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## 1. Materials

Sanguinarium chloride (SGNCl) salt was obtained from Shanghai Boyle Chemical CO.LTD, with greater than 98% purity. All analytical grade solvents were purchased from the Sinopharm Chemical Reagent Company and were used without further purification. The glass beads for Viedma ripening were purchased from Sigma-Aldrich and washed extensively with methanol before use. $^1$H-NMR experiments were recorded on a Bruker 400 MHz spectrometer.

## 2. Synthesis and characterization of compound 1

Sanguinarium chloride (14.68 mg, 0.04 mmol) was dissolved in MeOH (3 mL) to give a yellow solution; into the solution, MeONa (30wt%, 9 μL, 0.05mmol) was introduced by a needle syringe in one portion. The mixture was then heated to 50 °C and stirred at 700 r.p.m. using a PTFE magnetic stirring bar for 1 hour, the yellow solution turned to a clear solution as the reaction progress.

**Table S1**. Crystallographic data for *R*- and *S*-**1** and its racemate crystal.

| | ***R***-1 | ***S*-1** | **racemate** |
|---|---|---|---|
| Formula | $C_{21}H_{17}NO_5$ | $C_{21}H_{17}NO_5$ | $C_{21}H_{17}NO_5$ |
| Crystal system | Orthorhombic | Orthorhombic | Monoclinic |
| Space group | $P\,2_12_12_1$ | $P\,2_12_12_1$ | $P\,2_1/c$ |
| Temperature(K) | 170(2) | 170(2) | 170(2) |
| a(Å) | 7.7154(2) | 7.7230(2) | 12.3648(3) |
| b(Å) | 9.5901(3) | 9.6004(3) | 7.7330(2) |
| c(Å) | 22.5595(6) | 22.5562(7) | 19.4502(4) |
| α(°) | 90 | 90 | 90 |
| β(°) | 90 | 90 | 114.440(1) |
| γ(°) | 90 | 90 | 90 |
| Cell volume(Å$^3$) | 1669.21(8) | 1672.40(9) | 1693.13(7) |
| Calc.density(g/cm$^3$) | 1.446 | 1.443 | 1.426 |
| Z | 4 | 4 | 4 |
| $R_{int}$ | 0.0960 | 0.0313 | 0.0774 |
| $R_1$(I>2sigma(I)) | 0.0370 | 0.0346 | 0.0409 |
| $wR_2$ | 0.0999 | 0.1053 | 0.1069 |

| | | | |
|---|---|---|---|
| GOF | 1.035 | 0.980 | 1.046 |
| Flack parameter | 0.0(2) | 0.02(15) | -- |
| CCDC | 1454991 | 1454992 | 1454990 |

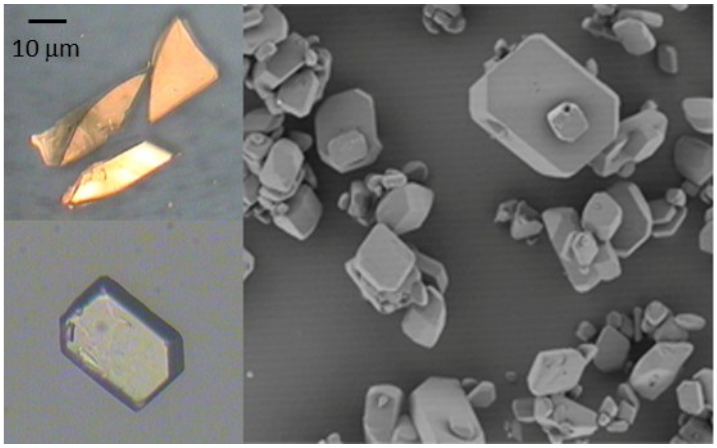


**Figure S1.** Polarized light microscope (PLM) pictures of racemate (left up), conglomerate crystal (left bottom) and scanning electron microscope (SEM) picture of conglomerate crystals (right).

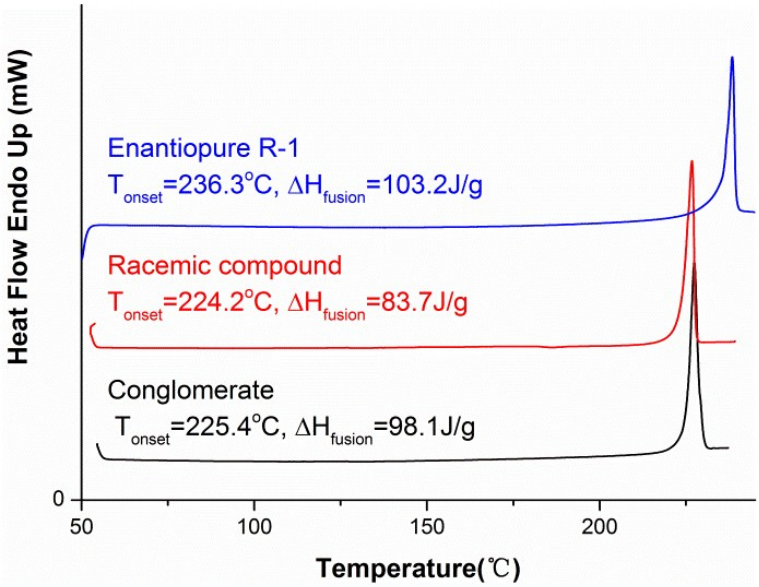


**Figure S2.** DSC curves for different crystals of compound 1.

**Table S2.** Absolute asymmetric synthesis of sanguinarine derivatives under cooling crystallization conditions[a].

| Run | Cooling rates (°C/min) | Yield[b](%) | ee[c](%) |
|---|---|---|---|
| 1 | 0.05 | 28.7 | 86.9 (S) |
| 2 | 0.05 | 28.0 | 12.4 (R) |

| | | | |
|---|---|---|---|
| 3 | 0.05 | 26.3 | 39.1 (S) |
| 4 | 0.05 | 31.7 | 9.7 (R) |
| 5 | 0.1 | 28.1 | 18.2 (S) |
| 6 | 0.1 | 28.1 | 15.4 (S) |
| 7 | 0.1 | 30.7 | 66.6 (S) |
| 8 | 0.1 | 30.6 | 40.4 (S) |
| 9 | 0.2 | 29.4 | 85.1 (R) |
| 10 | 0.2 | 28.7 | 100 (S) |
| 11 | 0.2 | n.d.[d] | 100 (R) |
| 12 | 0.2 | n.d. | 61.0 (R) |
| 13 | 0.5 | n.d. | 89.3 (R) |
| 14 | 0.5 | n.d. | 67.0 (S) |
| 15 | 0.5 | 26.9 | 100(R) |
| 16 | 0.5 | 27.1 | 90.9 (R) |
| 17 | 1.0 | n.d. | 89.8 (R) |
| 18 | 1.0 | n.d. | 77.9 (R) |
| 19 | 1.0 | n.d. | 25.1 (S) |
| 20 | 1.0 | n.d. | 99.9 (R) |
| 21 | 1.5 | n.d. | 95.3(S) |
| 22 | 1.5 | n.d. | 39.6 (R) |
| 23 | 1.5 | n.d. | 7.3 (S) |
| 24 | 1.5 | n.d. | 51.2 (S) |
| 25 | 2.0 | n.d. | 100 (S) |
| 26 | 2.0 | n.d. | 70.3 (S) |
| 27 | 2.0 | 29.4 | 100 (R) |
| 28 | 2.0 | 32.6 | 45.3 (R) |
| 29 | 2.5 | n.d. | 16.0 (R) |
| 30 | 2.5 | n.d. | 41.7 (R) |
| 31 | 2.5 | n.d. | 47.4 (R) |
| 32 | 2.5 | n.d. | 12.8 (S) |
| 33 | 3.0 | n.d. | 23.8 (R) |
| 34 | 3.0 | n.d. | 64.8 (R) |
| 35 | 3.0 | n.d. | 92.4 (S) |
| 36 | 3.0 | n.d. | 28.0 (R) |
| 37 | 3.5 | n.d. | 32.4 (R) |
| 38 | 3.5 | n.d. | 20.7 (R) |
| 39 | 3.5 | n.d. | 3.2 (R) |

| | | | |
|---|---|---|---|
| 40 | 3.5 | n.d. | 99.8 (S) |
| 41 | 4.0 | n.d. | 89.2 (R) |
| 42 | 4.0 | n.d. | 33.6 (R) |
| 43 | 4.0 | n.d. | 18.2 (S) |
| 44 | 4.5 | n.d. | 28.2 (R) |
| 45 | 4.5 | n.d. | 20.5 (S) |
| 46 | 4.5 | n.d. | 42.3 (S) |
| 47 | 5.0 | n.d. | 99.0 (S) |
| 48 | 5.0 | n.d. | 98.0 (S) |
| 49 | 5.0 | 29.2 | 100 (S) |
| 50 | 5.0 | 26.8 | 99.9 (R) |

[a]Powder product was allowed to equilibrate under controlled conditions for at least 24 h before isolation of the precipitants by centrifuge. [b]The isolated yield of crystal powder of 1. The product left in the solution phase was not included. [c]The ee values were determined by CD methods, detailed calibration curve and calculations were given in the supporting information. [d]Not determined.

**3. Cooling crystallization**

Cooling crystallization experiments were carried out on Crystalline system from Advantium Pharma B.V.. To an 8 mL thermostated flask, equipped with PTFE magnetic stirring bar, Sanguinarium chloride (7.34 mg, 0.02 mmol) and MeONa (0.45μL, 0.025 mmol) were added with 5 mL MeOH as solvent. The solution were continuously stirred at 300 r.p.m., then was kept at 40 °C over a period of 30 min. The homogeneous solution was cooled to 36.4 °C at a preset cooling rate and the temperature was maintained at 36.4 °C for 1 h to ensure no more precipitation occurred. If needed, R/S seeds can be added before the cooling program. The solids were isolated by centrifugation and dried over vacuum oven to determine the *ee* and yield. NMR analysis (Figure S3) revealed the product is conformed to the previous reported data. $^1$H-NMR (400MHz, $CDCl_3$): δ = 7.77-7.73 (d, 1H, $C_{15}$-H), 7.69 (s, 1H, $C_4$-H), 7.50-7.47 (d, 1H, $C_{16}$-H), 7.43-7.40 (d, 1H, $C_{12}$-H), 7.13 (s, 1H, $C_1$-H), 6.95-6.93 (d, 1H, $C_{11}$-H), 6.13-6.06 (d, 2H, $C_{19}$-H), 6.07 (d, 2H, $C_{18}$-H), 5.38 (s, 1H, $C_7$-H), 3.46 (s, 3H, $OCH_3$), 2.79 (s, 3H, $NCH_3$).

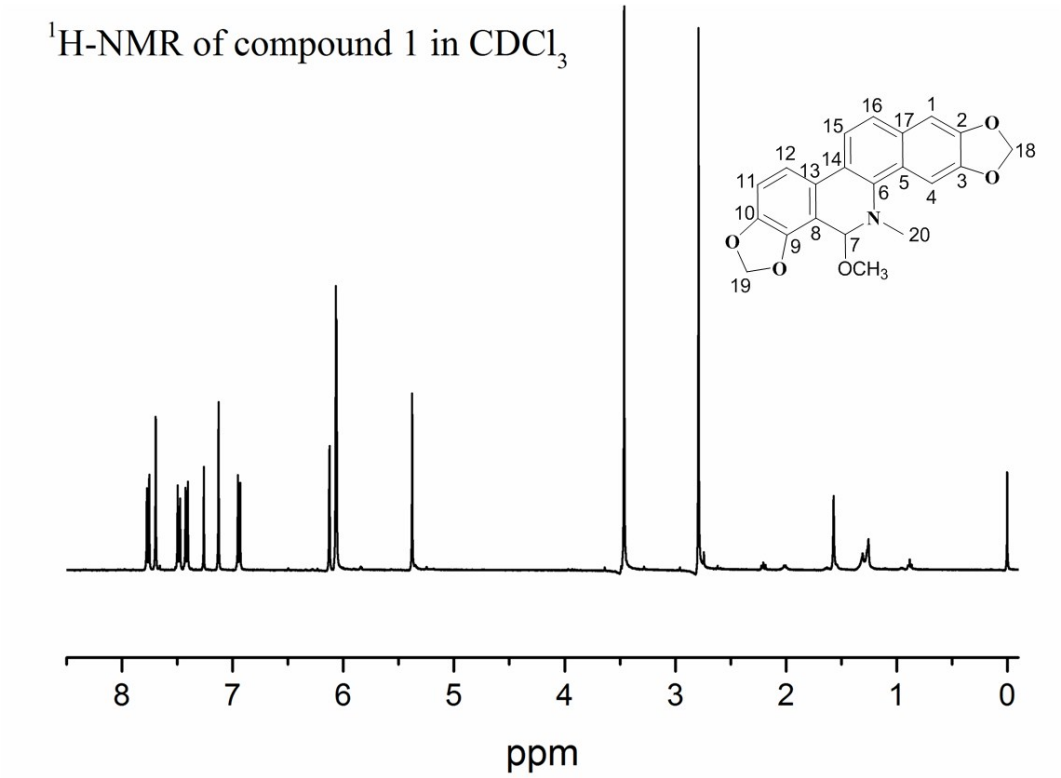


**Figure S3.** $^1$H-NMR of compound 1.

**4. Viedma ripening experiment**

A typical experiment consists of combining sanguinarium chloride with MeONa in MeOH solution in the presence of glass beads and a PTFE magnetic stirring bar. The solution is subsequently kept at strong stirring conditions until the enantiopure product emerged. Specifically, in a round-bottom flask, a solution was prepared by dissolving SGNCl (29.36 mg, 0.080 mmol) and MeONa (30wt%, 18 μL, 0.097 mmol) in MeOH (6 mL). The yellow colored solution was stirred at 700 r.p.m. using a PTFE magnetic stirring bar in the presence of glass beads (Ø= 1 mm). After prolonged grinding under preset temperature, the solid phase of compound 1 evolved to enantiopure solids, which were isolated by centrifugation and dried over vacuum oven to give enantiopure crystalline solids (50°C, 84.5% yield; 25 °C, 86.7% yield).

**5. Single crystal X-ray diffraction**

Single crystal X-ray diffraction measurements were conducted on a Bruker Smart Apex II diffractometer using Cu-Kα radiation ($\lambda$=1.54178 Å) with a graphite monochromator. Integration and scaling of the intensity data were accomplished using the SAINT program. The structures were solved by Direct Methods using SHELXS-97, and refinement was conducted by the full-matrix least-squares technique using SHELXL-97. The hydrogen atoms were refined isotropically, and the heavy atoms were refined anisotropically. C−H hydrogens were placed in calculated positions and refined with a riding model. Data were corrected for the effects of absorption using SADABS.

**6. Scanning Electron Microscopy (SEM)**

The surface morphology of all of the samples was viewed using scanning electron microscopy (Agilent 8500) operated at a beam voltage of 1 kV. The samples were mounted onto a steel stage using double-sided adhesive tape before the analysis.

**7. Polarized light microscopy (PLM)**

All PLM examinations were performed on an XPV-400E polar-izingmicroscope and an XPH-300 hot stage coupled with aJVC TK-C9201 EC digital video recorder (Shanghai Changfang Optical Instrument Company, Limited).

**8. Differential scanning calorimetry (DSC)**

Differential scanning calorimetry was performed with a PerkinElmer DSC 8500 instrument. Two-point calibration using indium and tin was carried out to check the temperature axis and heat flow of the equipment. Samples weighting 3–5 mg were heated in standard aluminum pans at a scan rate of 10°C/min under nitrogen gas flow of 20 mL/min.

**9. Determination of the solid state *ee* by CD analysis**

**Sample and method** Circular dichroism (CD) spectra was collected by Applied Photophysics BRIGHTTIME Chirascan. In order to select a suitable solvent, the stability experiments of enantiopure compound 1 in different solvents were performed. The results showed that enantiopure compound 1 could keep unchanged for 6h in acetonitrile (ACN). Hence, ACN was chosen as the test solvent. To determine the solid *ee* using CD, quantitative concentration of ACN solution (~ 0.2 mg/mL) was prepared. Samples were measured in wavelength range of 190-400 nm with a scan speed of 2 nm/s (1 nm/step, 1 step/0.5 s). Bandwidth was 1 nm and cell path was 0.5 mm. All data were acquired at 20 °C.

**CD~ee curve** The ACN solution of specific concentration (0.20 mg/mL) with varying *ee* composition (+100, +80,+60,+40, +20, 0, -20, -40, -60, -80, -100) were prepared. The CD analysis was carried out as described above (Figure S4). Different solid *ee* mixture had different CD responses at this concentration. The Cotton effect amplitudes measured at 214, 247, 327 nm were plotted against % *ee* (Figure S5). The best linear relationship between CD amplitude at 327 nm and ee was obtained, y = 0.098x (1), $R^2$=0.999.

**CD~ Concentration curve** Different concentrations has different CD responses. The ACN solution of enantiopure (R) with varying concentration (0.50 mg/mL, then stepwise dilution) was prepared. The Cotton effect amplitudes measured at 327 nm were plotted against concentration (Figure S6). The linear relationship between CD amplitude at 327 nm and the concentration was obtained (Figure S7), y = 47.99x (2), $R^2$=0.997.

**Computational formula** With the known concentration, the theoretical CD amplitude of 100% *ee* at 327 nm can be calculated from formula (2) above, i.e. (100%, 47.99 *c*). When R:S ratio was 1:1, the CD amplitude would be zero, i.e. (0, 0). On account of the linear relationship between CD amplitude and ee, then the computational formula can be deduced as $ee(\%) = \frac{CD_{exptl}}{17.40 \times c(mM)}$ (Figure S8).

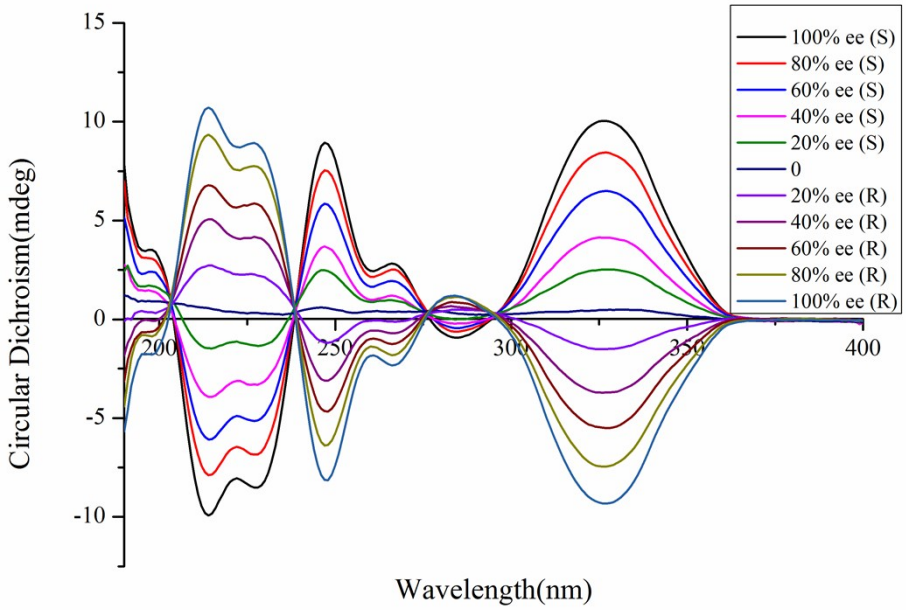


**Figure S4.** CD spectra of compound **1** in different ee% and chirality.

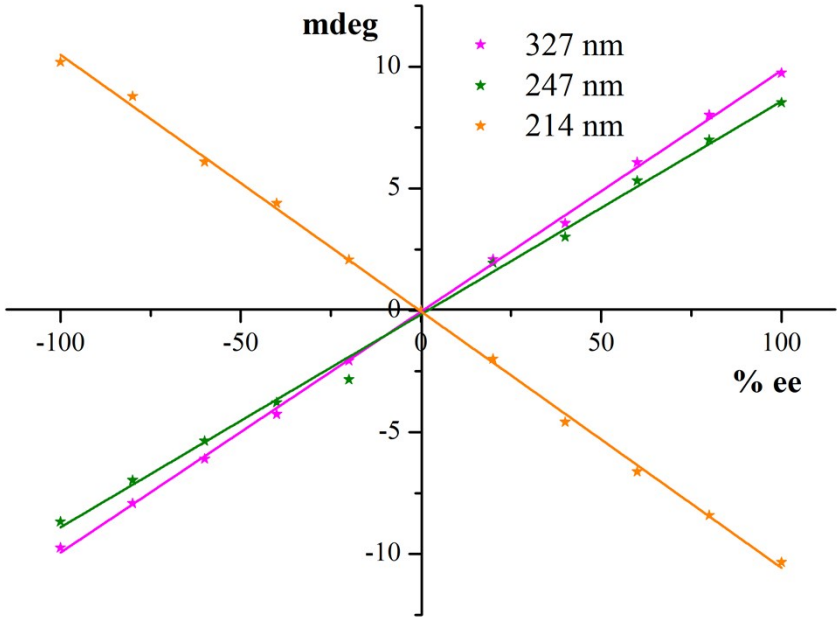


**Figure S5.** Linear relationship between ee% and CD signal under various local maximum wavelength.

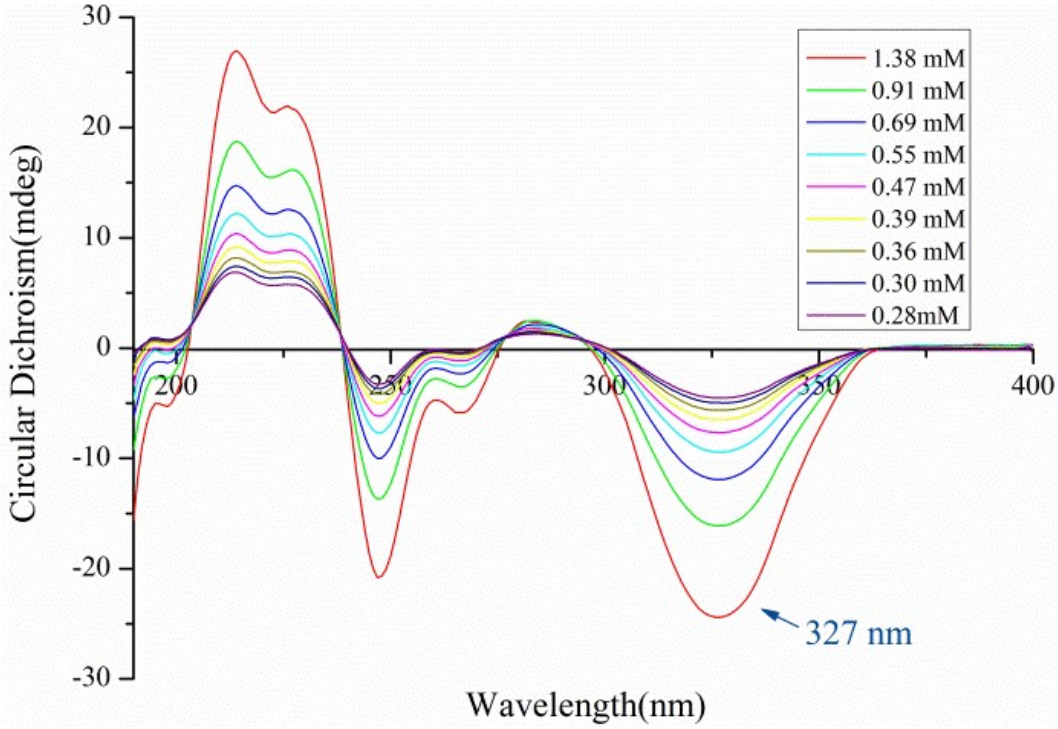


**Figure S6.** CD spectra of 100% ee *S*-**1** under a series of different concentrations.

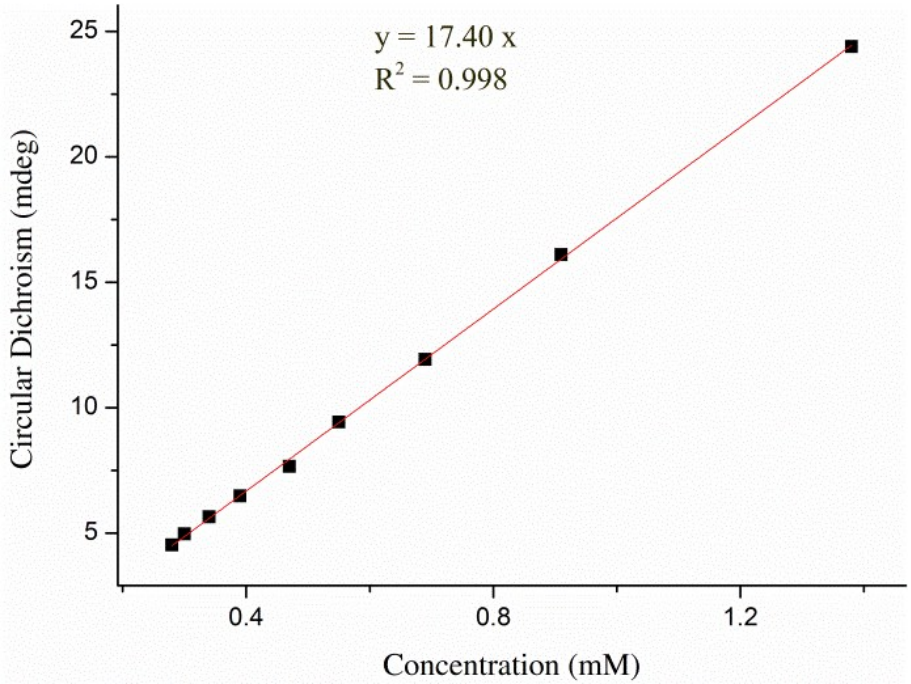


**Figure S7.** Linear relationship between concentration of *S*-**1** and CD signal (327 nm).

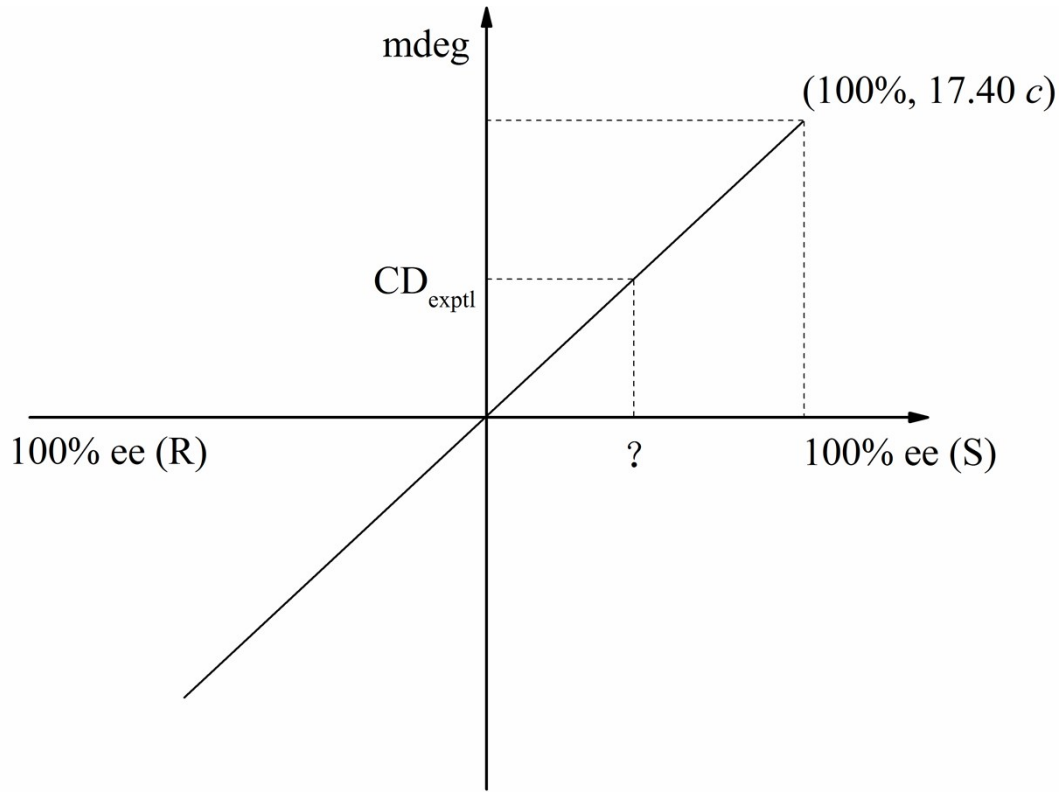


**Figure S8.** Linear relationship between ee% and CD signal under certain concentration.

**Table S3.** Enantioselective spontaneous formation of sanguinarium derivatives under cooling crystallization conditions with seeding.

| Run | Cooling rate (°C /min) | Seeding (%) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | 0.05 | 5.2 (S) | 30.3 | 90.8 (S) |
| 2 | 0.05 | 5.1 (R) | 32.1 | 98.9 (R) |
| 3 | 0.1 | 5.1 (S) | 32.9 | 92.9 (S) |
| 4 | 0.1 | 5.1 (R) | 31.5 | 100.0 (R) |
| 5 | 0.2 | 5.1 (S) | 33.4 | 100.4 (S) |
| 6 | 0.2 | 5.2 (R) | 31.8 | 95.6 (R) |
| 7 | 0.5 | 5.0 (S) | 29.4 | 100.1 (R) |
| 8 | 0.5 | 5.2 (R) | 28.3 | 94.7 (R) |
| 9 | 2 | 5.0 (S) | 29.1 | 83.8 (S) |
| 10 | 2 | 5.0 (R) | 32.9 | 100.0 (R) |
| 11 | 5 | 4.9 (S) | 31.8 | 86.9 (S) |
| 12 | 5 | 5.1 (R) | 28.4 | 100.3 (R) |

| | | | | |
|---|---|---|---|---|
| 13 | 0.1 | 0.5 (R) | 27.2 | 88.5 (R) |
| 14 | 0.1 | 0.5 (S) | 24.5 | 86.2 (S) |
| 15 | 1.0 | 0.6 (R) | 25.4 | 97.5 (R) |
| 16 | 1.0 | 0.5 (S) | 24.8 | 94.7 (S) |
| 17 | 3.0 | 0.6 (R) | 25.3 | 90.1 (R) |
| 18 | 3.0 | 0.5 (S) | 31.6 | 100.9 (S) |
| 19 | 5.0 | 0.5 (R) | 23.9 | 91.7 (R) |
| 20 | 5.0 | 0.5 (R) | 22.6 | 86.1 (R) |
| 21 | 0.1* | 0.6 (R) | 15.2 | 100.3 (R) |
| 22 | 0.1* | 0.5 (S) | 20.3 | 100.4 (S) |
| 23 | 1.0* | 0.5 (R) | 20.9 | 96.4 (R) |

* The reaction and crystallization were performed under unstirred condition.