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Candida antarctica lipase-B-catalyzed kinetic resolution of 1,3-dialkyl-3-hydroxymethyl oxindoles

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Abstract

Candida antarctica (CAL-B) lipase-catalyzed resolution of 1,3-dialkyl-3-hydroxymethyl oxindoles has been performed to obtain (*R*)-1,3-dialkyl-3-acetoxymethyl oxindoles with up to 99% *ee* and (*S*)-1,3-dialkyl-3-hydroxymethyl oxindoles with up to 78% *ee* using vinyl acetate as acylating agent and acetonitrile as solvent transforming (*S*)-3-allyl-3-hydroxymethyl oxindole to (3*S*)-1′-benzyl-5-(iodomethyl)-4,5-dihydro-2*H*-spiro[furan-3,3′-indolin]-2′-one. The optically active 3-substituted-3-hydroxymethyl oxindoles and spirooxindoles are among the key synthons in the synthesis of potentially biologically active molecules.

KEYWORDS

3,3-disubstituted oxindoles, *Candida antarctica* lipase, enantioselective, kinetic resolution, quaternary stereocenter

1 | INTRODUCTION

All-carbon quaternary stereocenter is present not only in wide range of pharmaceutically important molecules but also in a large variety of natural products.[1–6] Steric encumbrance as well as desired three-dimensional orientation of attached substituents offer a great deal of challenges in the synthesis of quaternary stereogenic center.[7–20] Although a number of catalytic methods have been developed in recent decades for the construction of tetra-substituted carbon centers,[21–29] only a few reliable options are available for the synthesis of all-carbon quaternary stereogenic center in enantioselective manner. Traditionally, these molecules are synthesized by (i) nucleophilic addition of trisubstituted carbons on electrophilic sp^2 carbon, (ii) desymmetrization of *meso* compounds,[30–33] and (iii) kinetic resolution of racemic compounds bearing quaternary carbon.[34,35] The desymmetrization technique provides higher yields, but strict availability of *meso* compounds offers a serious synthetic limitation. However, a biocatalytic kinetic resolution of racemic compounds offers its own advantages of easy availability, mild operating conditions, easy separation, being environmentally benign, and production of both enantiomers with high optical purity,[36–47] which is advantageous, especially in drug development where characterization of biological activity for all possible stereoisomers of the drug candidates is strictly required. On the other hand, 3,3-disubstituted oxindoles having all-carbon quaternary center are prominent scaffolds in natural products[48–50] as well as valuable pharmaceutical lead compounds such as NITD609,[51] Spirotryptostatin A and B,[52] and horsfiline,[53] Communesin F,[54] and perophoramidine[55] (Figure 1). The enantioselective discrimination of the primary alcohol at C-3 position of oxindole by lipase is feasible since the transformation takes place one bond away from the quaternary carbon, thus avoiding the unfavorable steric

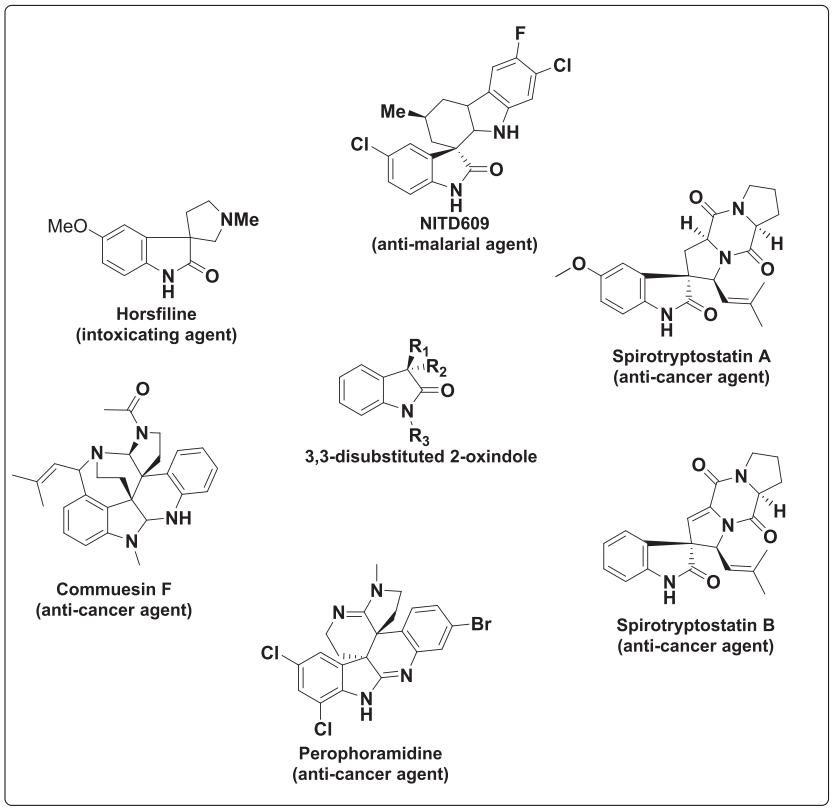


FIGURE 1 Some biologically important 3,3-disubstituted oxindole

hindrance at C-3 position of oxindole.[56,57] So, we planned to perform the enzyme catalyzed kinetic resolution of 1,3-dialkyl-3-(hydroxymethyl)indolin-2-one derivatives, with a primary alcohol unit present at the quaternary center of oxindole moiety using lipases as catalysts and vinyl acetate as acylating agent.

2 | MATERIALS AND METHODS

2.1 | Enzymes

Lipases from *Burkholderia cepacia* immobilized on ceramic particles (Lipase PS-C "Amano" I, Lot No. ILPSAA0550903R, *Pseudomonas fluorescens* (Lipase-AK "Amano" 20, Lot No. LAKY0950502, activity 20 000 U/g, at pH 7.0–9.0, optimum temperature 50°C), *B. cepacia* (Lipase PS-"Amano," Lot. No. LPSAZ0452412, activity 20 000 U/g, at pH 7.0, optimum temperature 35°C to 70°C) were obtained as gift from Amono Enzyme Inc., Nagoya, Japan.[58] The Porcine pancreatic lipase (PPL, Lot no. 09525AG, 30–90 units/mg protein) was commercially acquired from Sigma Aldrich®, *Candida antarctica* lipase B immobilized on macroporous acrylic resin (Novozym® 435, Batch No. LC200009, 10 000 PLU/g, optimum pH 5–9, optimum temperature 30°C to 60°C)[59] were obtained as a gift from Novo Nordisk, Denmark.

2.2 | Chemicals

All the chemical reagents were purchased from different commercial sources and used without further purification. The high-performance liquid chromatography (HPLC) grade solvents (hexane, methyl tertiary butyl ether [MTBE], and chloroform) were purchased from Merck, India. Tetrahydrofuran (THF), cyclohexane, 1,4-dioxane, toluene, and acetonitrile (MeCN) were purchased from Spectrochem, India. Anhydrous sodium sulfate (Na_2SO_4) were acquired from Merck, India. Thin layer chromatographic analyses were performed on glass plates (7.5 × 2.5 cm) coated with silica gel GF-254 (Spectrochem, India) containing 13% calcium sulfate as binder, and various combinations of ethyl acetate and hexane were used as eluents. Visualization of the spots was accomplished by exposing to UV light or iodine vapors. Column chromatography was performed on Spectrochem India silica gel (60–120 mesh) using mixture of ethyl acetate and hexane as eluent. All the *rac*-alcohol substrates (**1a–1t**) and *rac*-**3a–3t** were prepared as previously reported.[60–65]

For detailed synthetic procedures, see the Supporting Information.

2.3 | NMR and HRMS analysis

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at BRUKER AVANCE III operating at frequency 500 MHz and JEOL operating at frequency 400 MHz spectrometer for ^{1}H and at frequency 125 and 100 MHz for ^{13}C NMR in $CDCl_3$ as solvent with Me_4Si (TMS) as internal standard. The chemical shift (δ) values are relative to TMS, and coupling constants (J) are expressed in hertz. Optical rotation was determined with an AUTOPOL IV Polarimeter at 25°C using sodium D light. High-resolution mass spectra (HRMS) was recorded on BRUKER Micro TOF QII mass spectrometer.

2.4 | HPLC analysis

The HPLC analysis of crude reaction mixtures as well as pure samples was performed using Shimadzu Prominence LC-20AD equipped with automatic injector and D_2O/Tungsten detector for detection of all compounds. Racemic and chiral compounds have been resolved using hexane:isopropanol (90:10 or 80:20) as eluent at flow rate 1 mL/min, Daicel Chiralcel® OD-H, Daicel Chiralpak® AD-H, Daicel Chiralpak® IA, and Daicel Chiralpak® IE columns as stationary phase at 25°C temperature. For HPLC chromatograms see the Supporting Information.

2.5 | Calculation of enantiomeric excess, conversion, and enantioselectivity

The enantiomeric excess (*ee*), and enantioselectivity (E = enantiomeric ratio) of the enzyme-catalyzed kinetic resolution were calculated using the following equations.[66–68] Conversion (c) was obtained from HPLC chromatograms.

$$ee_s = \frac{A-B}{A+B} \times 100 \quad (1)$$

$$ee_p = \frac{C-D}{C+D} \times 100 \quad (2)$$

A, B and C, D represents the peak area of major and minor peaks of substrate and product, respectively, in HPLC chromatogram. The enantiomeric excess of the substrate and product is represented by *e.e.*$_s$ and *e.e.*$_p$, respectively.

$$E = \frac{\ln[1-c(1+ee_p)]}{\ln[1-c(1-ee_p)]}. \quad (3)$$

2.6 | General optimized procedure for kinetic resolution of *rac*-1a–1t

In a 10-mL round bottom flask, a suspension of 0.1-mmol **1a**–**1t**, 0.12-mmol **2a**, Novozym® 435 weight by weight (w:w) in mg (1:1 ratio to the substrate) in 0.5-mL acetonitrile has been stirred over magnetic stirrer at 25°C, 200 rpm for 4 h. After completion of reaction, the enzyme was separated from the reaction mixture by simple filtration over Hirsch funnel. The crude reaction mixture was purified over column chromatography using silica gel 60-120 as stationary phase and hexane/ethyl acetate 80:20 to 60:40 ratios as eluent to provide **1** in enantiomeric excess up to 78% with yield up to 85% and **3** in enantiomeric excess up to 99% with yield up to 54%.

2.6.1 | Characterization of compounds 1a–1t, 3a–3t, and 4

2.6.2 | (*S*)-1,3-Dibenzyl-3-(hydroxymethyl)indolin-2-one (1a)

White solid, mp = 123–125°C; $[\alpha]_D^{25}$ = +114.80 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.25–7.23 (m, 1H), 7.18–7.04 (m, 7H), 6.93–6.92 (m, 2H), 6.69 (d, J = 6.5 Hz, 2H), 6.46 (d, J = 7.5 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 4.07–4.03 (m, 1H), 3.90–3.87 (m, 1H), 3.39 (d, J = 13.0 Hz, 1H), 3.20 (d, J = 13.0 Hz, 1H), 2.60 (dd, J = 7.0 Hz, J = 2.5 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.6, 143.2, 135.5, 135.0, 130.1, 128.6, 128.4, 127.6, 126.6, 126.5, 123.5, 122.4, 109.4, 66.94, 55.83, 43.41, 38.76; Enantiomeric excess: 37%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1a**, 13.26 min (minor); for (*S*)-**1a**, 14.79 min (major); ESI-HRMS calcd for $C_{23}H_{21}NO_2$ $[M + Na]^+$ 366.1465, found 366.1462.

2.6.3 | (*S*)-1,3-Dibenzyl-5-chloro-3-(hydroxymethyl)indolin-2-one (1b)

White solid, mp = 136–138°C; $[\alpha]_D^{25}$ = +111.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16,

298 K, $CDCl_3$) δ 7.17–7.09 (m, 6H), 7.06 (dd, J = 8.5, J = 2 Hz, 2H), 6.93 (d, J = 7.2 Hz, 2H), 6.65 (d, J = 7.0 Hz, 2H), 6.35 (d, J = 8.5 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.50 (d, J = 16.0 Hz, 1H), 4.05 (t, J = 10.0 Hz, 2H), 3.90 (dd, J = 11.0, J = 2.5 Hz, 1H), 3.36 (d, J = 13.0 Hz, 1H), 3.17 (d, J = 13.5 Hz, 1H), 2.53 (s, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.0, 141.7, 135.0, 134.5, 131.0, 130.0, 128.6, 128.3, 128.1, 127.9, 127.3, 126.8, 126.5, 124.0, 110.3, 66.86, 56.38, 43.51, 38.77; Enantiomeric excess: 60%, determined by HPLC (Daicel chiralcel OD-H, hexane/i-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1b**, 17.04 min (minor); for (*S*)-**1b**, 20.40 min (major); ESI-HRMS calcd for $C_{23}H_{20}ClNO_2$ $[M + H]^+$ 378.1234, found 378.1255.

2.6.4 | (*S*)-1,3-Dibenzyl-5-bromo-3-(hydroxymethyl)indolin-2-one (1c)

White solid, mp = 120–122°C; $[\alpha]_D^{25}$ = +122.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.38 (s, 1H), 7.22–7.05 (m, 7H), 6.94 (d, J = 7.5 Hz, 2H), 6.65 (d, J = 7.0 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.50 (d, J = 16.0 Hz, 1H), 4.04 (t, J = 9.5 Hz, 1H), 3.90 (d, J = 10.0 Hz, 1H), 3.36 (d, J = 13.0 Hz, 1H), 3.17 (d, J = 13.5 Hz, 1H), 2.44 (d, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 177.9, 142.2, 135.0, 134.5, 131.4, 131.2, 130.1, 128.6, 128.1, 127.3, 126.8, 126.8, 126.5, 115.2, 110.8, 66.86, 56.28, 43.50, 38.78; Enantiomeric excess: 69.8%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1c**, 19.00 min (minor); for (*S*)-**1c**, 20.52 min (major); ESI-HRMS calcd for $C_{23}H_{20}BrNO_2$ $[M + Na]^+$ 444.0570, found 444.0454.

2.6.5 | (*S*)-1,3-Dibenzyl-3-(hydroxymethyl)-5-methoxyindolin-2-one (1d)

White solid; mp = 118–120°C; $[\alpha]_D^{25}$ = +74.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.18–7.09 (m, 6H), 6.97 (d, J = 7.0 Hz, 2H), 6.82 (d, J = 2.0 Hz, 1H), 6.69 (d, J = 6.7 Hz, 2H), 6.62 (dd, J = 8.5, J = 2.5 Hz, 1H), 6.35 (d, J = 8.0 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.50 (d, J = 16.0 Hz, 1H), 4.04–4.00 (m, 1H), 3.86 (d, J = 11.0 Hz, 1H), 3.75 (s, 3H), 3.36 (d, J = 13.0 Hz, 1H), 3.19 (d, J = 13.5 Hz, 1H), 2.68 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.3, 155.8, 136.6, 135.5, 135.1, 130.4, 130.2, 128.5, 128.0, 127.2, 126.6, 126.6112.5, 111.1, 109.8, 66.89, 56.09, 55.75, 43.49, 38.74; Enantiomeric excess: 17%, determined by HPLC (Daicel chiralpak AD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1d**, 24.42 min (minor); for (*S*)-**1d**, 30.70 min (major); ESI-HRMS calcd for $C_{24}H_{23}NO_3$ $[M + H]^+$ 375.1829, found 375.1857.

2.6.6 | (*S*)-1,3-Dibenzyl-3-(hydroxymethyl)-5-methylindolin-2-one (1e)

White solid; mp = 132–134°C; $[\alpha]_D^{25}$ = +54.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.17–7.06 (m, 7H), 6.93 (d, J = 7.5 Hz, 2H), 6.89 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 7 Hz, 2H), 6.33 (d, J = 8 Hz, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.48 (d, J = 16.0 Hz, 1H), 4.03 (t, J = 10.0 Hz, 1H), 3.86 (d, J = 11.0 Hz, 1H), 3.37 (d, J = 13.0 Hz, 1H), 3.18 (d, J = 13.0 Hz, 1H), 2.63 (d, J = 8.0 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.5, 140.8, 135.6, 135.1, 131.9, 130.1, 129.0, 128.7, 128.5, 127.9, 127.1, 126.6, 126.5, 124.3, 109.2, 66.99, 55.84, 43.40, 38.75, 21.18; Enantiomeric excess: 47%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1e**, 11.50 min (minor); for (*S*)-**1e**, 13.03 min (major); ESI-HRMS calcd for $C_{24}H_{23}NO_2$ $[M + H]^+$ 358.1802, found 358.9028.

2.6.7 | (*S*)-1,3-Dibenzyl-5-fluoro-3-(hydroxymethyl)indolin-2-one (1f)

White solid; mp = 72–74°C; $[\alpha]_D^{25}$ = +31.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.19–7.05 (m, 5H), 6.87–6.84. (m, 2H), 6.76–6.69 (m, 4H), 6.49 (d, J = 7.5 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.51 (d, J = 16.0 Hz, 1H), 4.04–4.00 (m, 1H), 3.88 (d, J = 11.0 Hz, 2H), 3.38 (d, J = 13.5 Hz, 1H), 3.16 (d, J = 13.5 Hz, 1H), 2.58 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.4, 161.8 (d, J = 242.5 Hz), 143.2, 134.9, 131.5 (d, J = 7.5 Hz), 131.2 (d, J = 3.75 Hz), 128.8, 128.6, 128.5, 127.3, 126.5, 123.4, 122.5, 114.7 (d, J = 21.2 Hz), 109.5, 66.86, 55.87, 43.43, 37.94; Enantiomeric excess: 69.2%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1f**, 14.01 min (minor); for (*S*)-**1f**, 15.74 min (major); ESI-HRMS calcd for $C_{23}H_{20}FNO_2$ $[M + H]^+$ 362.1551, found 362.1552.

2.6.8 | (*S*)-1-Benzyl-3-(hydroxymethyl)-3-(4-methoxybenzyl)indolin-2-one (1g)

White solid; mp = 122–124°C; $[\alpha]_D^{25}$ = +31.9 (*c* = 0.1 in $CHCl_3$); ^1H NMR (400 MHz, sw = 15 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.26–7.24 (m, 1H), 7.19–7.04 (m, 5H), 6.83–6.81 (m, 2H), 6.67–6.59 (m, 4H), 6.48–6.46 (m, 1H), 5.04 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.04 (d, *J* = 11.0 Hz, 1H), 3.88 (d, *J* = 11.0 Hz, 1H), 3.73 (s, 3H), 3.34 (d, *J* = 13.5 Hz, 1H), 3.15 (d, *J* = 13.5 Hz, 1H); ^{13}C NMR (100 MHz, sw = 15 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.8, 158.4, 143.3, 135.0, 131.2, 129.2, 128.5, 128.5, 127.6, 127.3, 126.6, 123.5, 122.5, 113.4, 109.5, 66.92, 56.07, 55.15, 43.44, 38.02. Enantiomeric excess: 49%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1g**, 18.26 min (minor); for (*S*)-**1g**, 20.55 min (major); ESI-HRMS calcd for $C_{24}H_{23}NO_3$ $[M + H]^+$ 374.1751, found 374.1766.

2.6.9 | (*S*)-3-Allyl-1-benzyl-3-(hydroxymethyl)indolin-2-one (1h)

White solid; $[\alpha]_D^{25}$ = +86.9 (*c* = 0.2 in $CHCl_3$); ^1H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.31–7.23 (m, 6H), 7.18–7.15 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 5.50–5.41 (m, 1H), 5.07(dd, *J* = 17.0, *J* = 1 Hz, 2H), 4.99–4.83 (m, 1H), 4.86 (d, *J* = 16.0 Hz, 1H), 3.98–3.94 (m, 1H) 3.82 (d, *J* = 11.0 Hz, 1H), 2.76–2.63 (m, 1H), 2.46 (d, *J* = 6 Hz, 1H) ppm. ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.9, 143.2, 135.6, 131.8, 129.4, 128.7, 128.3, 127.2, 123.3, 122.6, 119.2, 66.75, 54.32, 43.66, 37.40 ppm. Enantiomeric excess: 72%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 0.5 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1h**, 12.03 min (minor); for (*S*)-**1h**, 15.93 min (major); ESI-HRMS calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$ 294.1489, found 294.1528.

2.6.10 | (*S*)-1-Benzyl-3-(hydroxymethyl)-3-(naphthalen-2-ylmethyl)indolin-2-one (1i)

White solid; mp = 124–125°C; $[\alpha]_D^{25}$ = +114.90 (*c* = 0.2 in $CHCl_3$); ^1H NMR (400 MHz, sw = 15 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.74 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.53–7.30 (m, 5H), 7.09 (dd, *J* = 5.5, *J* = 3.2 Hz, 2H), 7.03–6.91 (m, 2H), 6.65 (t, *J* = 7.7 Hz, 2H), 6.47–6.35 (m, 3H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.40 (d, *J* = 16.0 Hz, 1H), 4.18–4.06 (m, 1H), 3.94 (d, *J* = 11.0 Hz, 1H), 3.59 (d, *J* = 13.2 Hz, 1H), 3.37 (d, *J* = 13.2 Hz, 1H), 2.62 (s, 1H) ppm; ^{13}C NMR (100 MHz, sw = 15 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.5, 143.2, 134.7, 133.2, 132.3, 128.9, 128.8, 128.5, 128.4, 128.2, 127.8, 127.4, 127.3, 127.0, 126.2, 125.8, 125.5, 123.5, 122.5, 109.5, 67.06, 56.0, 43.44, 38.93 ppm; Enantiomeric excess: 43%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 0.5 mL/min, λ = 254 nm): Retention times were: for (*R*)-**1i**, 32.02 min (minor); for (*S*)-**1i**, 35.86 min (major); ESI-HRMS calcd for $C_{27}H_{24}NO_2$ $[M + H]^+$ 394.1802, found 394.1972.

2.6.11 | (*S*)-1-Allyl-3-benzyl-3-(hydroxymethyl)indolin-2-one (1j)

White solid; mp = 106–108°C; $[\alpha]_D^{25}$ = +31.9 (*c* = 0.1 in $CHCl_3$); ^1H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.19 (d, *J* = 6.9 Hz, 2H), 7.09–7.03 (m, 5H), 6.89 (d, *J* = 6.6 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 5.45 (ddd, *J* = 22.0, *J* = 10.1, *J* = 4.9 Hz, 1H), 4.95 (d, *J* = 10.4 Hz, 1H), 4.62 (d, *J* = 17.2 Hz, 1H), 4.37–4.29 (m, 1H), 4.05–3.98 (m, 2H), 3.85 (dd, *J* = 11.0, *J* = 2.2 Hz, 1H), 3.31 (d, *J* = 13.2 Hz, 1H), 3.16 (d, *J* = 13.1 Hz, 1H), 2.65 (d, *J* = 7.0 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, 298 K, $CDCl_3$) δ 178.4, 143.2, 135.4, 130.6, 130.0, 130.0, 128.3, 127.7, 126.5, 123.7, 122.3, 116.9, 109.1, 66.53, 55.62, 41.89, 39.0; Enantiomeric excess: 32%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1j**, 17.94 min (major); for (*R*)-**1j**, 30.9 min (minor); ESI-HRMS calcd for $C_{19}H_{19}NO_2$ $[M + H]^+$ 316.1308, found 316.1344.

2.6.12 | (*S*)-1-Allyl-3-benzyl-5-chloro-3-(hydroxymethyl)indolin-2-one (1k)

White solid; mp = 109–110°C; $[\alpha]_D^{25}$ = +21.9 (*c* = 0.1 in $CHCl_3$); ^1H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.20 (d, *J* = 1.5, 1H) 7.17–7.15 (m, 1H), 7.11–7.08 (m, 3H), 6.90 (d, *J* = 5.5, 1H), 6.54 (d, *J* = 8.0 Hz, 1H), 5.45–5.37 (m, 1H), 4.95 (d, *J* = 10.5, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 4.33–4.29 (m, 1H), 4.03–3.93 (m, 2H), 3.87 (d, *J* = 11.0 Hz, 1H), 3.29 (d, *J* = 13.0 Hz, 1H), 3.12 (d, *J* = 13.0 Hz, 1H), 2.49 (d, *J* = 5.5, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 177.8, 141.8, 134.9, 130.9, 130.3, 129.9, 128.2, 127.9, 127.8, 126.8, 124.1, 117.2, 110.1, 66.42, 56.15, 41.99, 39.00; Enantiomeric excess: 34%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1k**, 19.20 min (major); for (*R*)-**1k**, 20.29 min (minor); ESI-HRMS calcd for $C_{19}H_{18}ClNO_2$ $[M + H]^+$ 350.0918, found 350.0982.

2.6.13 | (*S*)-1-Allyl-3-benzyl-5-bromo-3-(hydroxymethyl)indolin-2-one (1l)

White solid; mp = 92–94°C; $[\alpha]_D^{25}$ = +144.8 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) *δ* 7.33–7.28 (m, 1H), 7.12–7.05 (m, 3H), 6.90–6.88 (m, 2H), 6.50 (d, *J* = 8.0 Hz, 1H), 5.44–5.37 (m, 1H), 4.95 (d, *J* = 10.0 Hz, 1H), 4.59 (d, *J* = 17.5 Hz, 1H), 4.33–4.28 (m, 1H), 4.03–3.93 (m, 2H), 3.87 (dd, *J* = 11.0, *J* = 3.0, 1H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.12 (d, *J* = 13.5 Hz, 1H), 2.45–2.55 (m, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) *δ* 177.7, 142.3, 134.9, 131.3, 131.1, 130.2, 129.9, 127.9, 127.8, 126.8, 117.2, 115.0, 110.5, 66.42, 56.10, 41.96, 39.0; Enantiomeric excess: 67%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, *λ* = 254 nm): Retention times were: for (*S*)-**1l**, 18.73 min (major); for (*R*)-**1l**, 19.81 min (minor); ESI-HRMS calcd for $C_{19}H_{18}BrNO_3$ $[M + H]^+$ 372.0594, found 372.0626.

2.6.14 | (*S*)-1-Allyl-3-benzyl-3-(hydroxymethyl)-5-methoxyindolin-2-one (1m)

White solid; mp = 84–86°C; $[\alpha]_D^{25}$ = +41.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) *δ* 7.10–7.06 (m, 3H), 6.93–6.92 (m, 2H), 6.76 (d, *J* = 2.5 Hz, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.48–5.41 (m, 1H), 4.95 (d, *J* = 10.5, 1H), 4.63 (d, *J* = 17.0 Hz, 1H), 4.34–4.29 (m, 1H), 4.01–3.94 (m, 1H), 3.82 (d, *J* = 11.0 Hz, 1H), 3.78 (s, 3H), 3.29 (d, *J* = 13.0 Hz, 1H), 3.15 (d, *J* = 13.0 Hz, 1H), 2.66 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) *δ* 178.1, 155.7, 136.7, 135.4, 130.8, 130.3, 130.1, 127.8, 127.7, 126.6, 116.9, 112.5, 111.1, 109.5, 66.45, 55.80, 41.98, 38.93; Enantiomeric excess: 72%, determined by HPLC (Daicel chiralpak IC, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, *λ* = 254 nm): Retention times were: for (*R*)-**1m**, 21.28 min (minor); for (*S*)-**1m**, 24.56 min (major); ESI-HRMS calcd for $C_{20}H_{21}NO3$ $[M + H]^+$ 324.1516, found 324.1911.

2.6.15 | (*S*)-1-Allyl-3-benzyl-3-(hydroxymethyl)-5-methylindolin-2-one (1n)

White solid; mp = 80–82°C; $[\alpha]_D^{25}$ = +34.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) *δ* 7.10–7.04 (m, 3H), 7.00 (d, *J* = 5.0 Hz, 2H), 6.89 (d, *J* = 6.5 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 1H), 5.43 (m, 1H), 4.93 (d, *J* = 10.5 Hz, 1H), 4.60 (d, *J* = 17.0 Hz, 1H), 4.33–4.29 (m, 1H), 4.02–3.93 (m, 2H), 3.83 (d, *J* = 11.0 Hz, 1H), 3.30 (d, *J* = 13.0 Hz, 1H), 3.13 (d, *J* = 13.0 Hz, 1H), 2.65 (d, *J* = 6.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) *δ* 178.3, 140.8, 135.5, 131.8, 130.7, 130.0, 129.0, 128.6, 127.7, 126.5, 124.3, 116.8, 108.8, 66.55, 55.60, 41.89, 38.97, 21.18; Enantiomeric excess: 14.2%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, *λ* = 254 nm): Retention times were: for (*S*)-**1n**, 8.81 min (major); for (*R*)-**1n**, 9.36 min (minor); ESI-HRMS calcd for $C_{20}H_{21}NO_2$ $[M + H]^+$ 330.1464, found 330.1509.

2.6.16 | (*S*)-3-Benzyl-3-(hydroxymethyl)-1-methylindolin-2-one (1o)

White solid; mp = 144–146°C; $[\alpha]_D^{25}$ = +80.90 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) *δ* 7.24–7.21 (m, 1H), 7.09–7.02 (m, 5H), 6.91–6.90 (m, 2H), 6.67 (d, *J* = 8.0 Hz, 1H), 4.01–3.97 (m, 1H), 3.81 (dd, *J* = 11.0, *J* = 2.0 Hz, 1H), 3.23–3.16 (m, 2H), 3.03 (s, 3H), 2.68–2.66 (m, 1H);^{13}C NMR (125 MHz, $CDCl_3$) *δ* 178.9, 143.9, 135.4, 129.9, 128.9, 128.4, 127.6, 126.5, 123.7, 122.3, 108.1, 66.01, 55.28, 38.99, 25.93; Enantiomeric excess: 27%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, *λ* = 254 nm): Retention times were: for (*S*)-**1o**, 9.76 min (major); for (*R*)-**1o**, 18.78 min (minor); ESI-HRMS calcd for $C_{17}H_{17}NO_2$ $[M + H]^+$ 290.1151, found 290.1197.

2.6.17 | (*S*)-3-Benzyl-5-chloro-3-(hydroxymethyl)-1-methylindolin-2-one (1p)

White solid; mp = 130–132°C; $[\alpha]_D^{25}$ = +47.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) *δ* 7.20 (dd, *J* = 8.5, *J* = 2.0 Hz, 1H), 7.12–7.07 (m, 4H), 6.92–6.90 (m, 2H), 6.58 (d, *J* = 8.0 Hz, 1H), 4.01–3.97 (m, 1H), 3.83 (dd, *J* = 11.0, *J* = 3.5 Hz, 1H), 3.17 (dd, *J* = 37.0, *J* = 13.5 Hz, 2H), 3.00 (s, 3H), 2.50 (dd, *J* = 9.0, *J* = 3.5 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) *δ* 178.3, 142.5, 134.9, 130.9, 129.8, 128.3, 127.8, 127.7, 126.7, 124.2, 108.9, 65.93, 55.90, 39.01, 26.05; Enantiomeric excess: 60%, determined by HPLC (Daicel chiralcel OD-H, *hexane*/*i*-PrOH, 93:7, flow rate 1.0 mL/min, *λ* = 254 nm): Retention times were: for (*S*)-**1p**, 18.73 min (major); for (*R*)-**1p**, 24.83 min (minor); ESI-HRMS calcd for $C_{17}H_{16}ClNO_2$ $[M + H]^+$ 302.0942, found 302.0949.

2.6.18 | (*S*)-3-Benzyl-5-bromo-3-(hydroxymethyl)-1-methylindolin-2-one (1q)

White solid; $[\alpha]_D^{25}$ = +111.9 (*c* = 0.1 in $CHCl_3$); mp = 134–136°C; ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.35 (dd, *J* = 8.0, *J* = 1.5 Hz, 1H), 7.22 (d, *J* = 1.5 Hz, 1H), 7.14–7.10 (m, 3H), 6.91–6.90 (m, 2H), 6.53 (d, *J* = 8.2 Hz, 1H), 4.00–3.96 (m, 1H), 3.83 (dd, *J* = 11.0, *J* = 2.5 Hz, 1H), 3.16 (dd, *J* = 34.5, *J* = 13.5 Hz, 2H), 2.99 (s, 3H), 2.54 (m, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 178.2, 143.0, 134.9, 131.3, 131.2, 129.9, 127.8, 127.0, 126.8, 115.0, 109.4, 65.91, 55.81, 39.01, 26.02; Enantiomeric excess: 78%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1q**, 22.00 min (major); for (*R*)-**1q**, 24.95 min (minor); ESI-HRMS calcd for $C_{17}H_{16}BrNO_2$ $[M + H]^+$ 346.0437, found 346.0537.

2.6.19 | (*S*)-3-Benzyl-3-(hydroxymethyl)-5-methoxy-1-methylindolin-2-one (1r)

White solid; mp = 108–110°C; $[\alpha]_D^{25}$ = + 40.1 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.12–7.10 (m, 3H), 6.96–6.94 (m, 2H), 6.75 (dd, *J* = 8.5, *J* = 2.5 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 3.98–3.947 (m, 1H), 3.79–3.77 (m, 1H), 3.75 (s, 3H), 3.18 (s, 2H), 3.01 (s, 3H), 2.76–2.74 (m, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.4, 170.4, 155.7, 137.4, 134.6, 130.0, 129.9, 127.7, 126.6, 112.6, 111.3, 108.4, 66.0, 55.79, 55.46, 38.84, 26.02; Enantiomeric excess: 47%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1r**, 27.61 min (major); for (*R*)-**1r**, 33.18 min (minor); ESI-HRMS calcd for $C_{18}H_{19}NO_3$ $[M]^+$ 320.1257, found 320.1311.

2.6.20 | (*S*)-3-Benzyl-3-(hydroxymethyl)-1,5-dimethylindolin-2-one (1s)

White solid; mp = 114–116°C; $[\alpha]_D^{25}$ = +14.9 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.10–7.05 (m, 3H), 7.02 (d, *J* = 8.0 Hz, 1H), 6.91–6.88 (m, 3H), 6.55 (d, *J* = 8.0 Hz, 1H), 3.99–3.95 (m, 1H), 3.79 (d, *J* = 11.0 Hz, 1H), 3.20–3.13 (m, 2H), 2.98 (s, 3H), 2.83 (d, *J* = 6.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 178.8, 141.5, 135.5, 131.8, 129.9, 129.0, 128.6, 127.6, 126.5, 124.5, 107.8, 66.04, 55.35, 38.94, 25.92, 21.16; Enantiomeric excess: 43%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1s**, 9.57 min (major); for (*R*)-**1s**, 10.96 min (minor); ESI-HRMS calcd for $C_{18}H_{19}NO2$ $[M + H]^+$ 282.1489, found 282.1466.

2.6.21 | (*S*)-3-Benzyl-3-(hydroxymethyl)-1-phenylindolin-2-one (1t)

White solid; mp = 146–148°C; $[\alpha]_D^{25}$ = +25.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.42 (t, *J* = 7.5 Hz, 2H), 7.36–7.33 (m, 1H), 7.28 (d, *J* = 7.0 Hz, 1H), 7.16–7.07 (m, 5H), 6.9 (d, *J* = 7.5 Hz, 4H), 6.92 (d, *J* = 7.0 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 4.14–4.10 (m, 1H), 4.00 (m, 1H), 3.43 (d, *J* = 13.0 Hz, 1H), 3.18 (d, *J* = 13.0 Hz, 1H), 2.67–2.65 (m, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 178.2, 144.2, 135.3, 133.9, 130.0, 129.5, 128.9, 128.3, 128.1, 127.7, 126.6, 126.5, 123.7, 122.8, 109.3, 66.36, 55.77, 39.73; Enantiomeric excess: 15%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**1t**, 26.56 min (major); for (*R*)-**1t**, 32.55 min (minor); ESI-HRMS calcd for $C_{22}H_{20}NO_2$ $[M + H]^+$ 331.1489, found 331.1500.

2.6.22 | (*R*)-(1,3-Dibenzyl-2-oxoindolin-3-yl)methyl acetate (3a)

Colorless semi-solid; $[\alpha]_D^{25}$ = −146.50 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.28 (d, *J* = 7.5 Hz, 1H), 7.16–7.03 (m, 8H), 6.89 (d, *J* = 7.5 Hz, 2H), 6.78 (d, *J* = 6.0 Hz, 2H), 6.42(d, *J* = 7.5 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.73–4.68 (m, 2H), 4.39 (d, *J* = 10.5 Hz, 1H), 3.20 (dd, *J* = 13.0, *J* = 6.0 Hz, 2H), 1.87 (s, 3H) ppm; ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.7, 170.3, 143.1, 135.2, 134.7, 128.6, 128.5, 128.4, 128.0, 127.2, 126.8, 126.6, 123.9, 122.2, 109.2, 67.40, 54.17, 43.46, 39.49, 20.58 ppm; Enantiomeric excess: >98%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3a**, 11.79 min (minor); for (*R*)-**3a**, 18.26 min (major); ESI-HRMS calcd for $C_{25}H_{22}NO_3$ $[M + H]^+$ 386.1751, found 386.1759.

2.6.23 | (*R*)-(1,3-Dibenzyl-5-chloro-2-oxoindolin-3-yl)methyl acetate (3b)

Colorless semi-solid; $[\alpha]_D^{25}$ = −108.9 (*c* = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.27 (d, *J* = 2.0 Hz, 1H), 7.18–7.13 (m, 4H), 7.10

(t, J = 7.5 Hz, 2H), 7.05 (dd, J = 8.3, J = 2.0 Hz, 1H), 6.91 (d, J = 7.5 Hz, 2H), 6.75 (d, J = 6.5 Hz, 2H), 6.33 (d, J = 8.0 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 4.68 (d, J = 16.0, 1H), 4.65 (d, J = 11.0 Hz, 1H), 4.39 (d, J = 11.0 Hz, 1H), 3.19 (dd, J = 31.5, J = 13.0 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.2, 170.2, 141.6, 134.7, 134.2, 130.5, 130.0, 128.6, 128.4, 128.1, 127.7, 127.4, 127.0, 126.6, 124.3, 110.1, 67.29, 54.39, 43.57, 39.49, 20.61; Enantiomeric excess: 97.4%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm):): Retention times were: for (*S*)-**3b**, 10.67 min (minor); for (*R*)-**3b**, 13.54 min (major); ESI-HRMS calcd for $C_{25}H_{22}ClNO_3$ $[M + H]^+$ 420.1361, found 420.1369.

2.6.24 | (*R*)-(1,3-Dibenzyl-5-bromo-2-oxoindolin-3-yl)methyl acetate (3c)

Colorless semi-solid; $[\alpha]_D^{25}$ = −106.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.39 (d, J = 1.9 Hz, 1H), 7.22 (dd, J = 6.5, J = 2.0, 1H) 7.18–7.07 (m, 7H), 6.91 (d, J = 7.0 Hz, 2H), 6.75 (d, J = 6.5 Hz, 2H), 6.29 (d, J = 8.5 Hz, 1H), 4.77 (d, J = 16.0 Hz, 1H), 4.70 (d, J = 11.0 Hz, 1H), 4.64 (d, J = 11.0 Hz, 1H), 4.40 (d, J = 11.0 Hz, 1H), 3.18 (dd, J = 17.0, J = 13.0 Hz, 2H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 130.1, 128.6, 128.1, 127.4, 127.1, 127.0, 126.6, 114.9, 67.30, 54.32, 43.54, 39.51, 20.61; Enantiomeric excess: 73%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3c**, 18.33 min (major); for (*S*)-**3c**, 30.81 min (minor); ESI-HRMS calcd for $C_{25}H_{22}BrNO_3$ $[M + H]^+$ 464.0856, found 464.0867.

2.6.25 | (*R*)-(1,3-Dibenzyl-5-methoxy-2-oxoindolin-3-yl)methyl acetate (3d)

Colorless semi-solid; $[\alpha]_D^{25}$ = −96.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.17–7.13 (m, 4H), 7.10 (t, J = 7.5 Hz, 2H), 6.93 (d, J = 7.5 Hz, 2H), 6.87 (d, J = 2.5 Hz, 1H), 6.78–6.77 (m, 2H), 6.61 (dd, J = 8.5, J = 2.5 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 4.78 (d, J = 16.0 Hz, 1H), 4.68 (dd, J = 13.5, J = 2.5 Hz, 2H), 4.38 (d, J = 10.7 Hz, 1H), 3.76 (s, 3H), 3.25–3.12 (m, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.3, 170.3, 155.6, 136.6, 135.3, 134.7, 130.1, 130.0, 128.5, 127.9, 127.2, 126.8, 126.6, 112.7, 111.3, 109.5, 67.46, 55.76, 54.43, 43.54, 39.56, 20.65; Enantiomeric excess: 99%, determined by HPLC (Daicel chiralpak AD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3d**, 21.51 min (major); for (*S*)-**3d**, 31.52 min (minor); ESI-HRMS calcd for $C_{24}H_{24}NO_3$ $[M + H]^+$ 416.1856, found 416.1890.

2.6.26 | (*R*)-(1,3-Dibenzyl-5-methyl-2-oxoindolin-3-yl)methyl acetate (3e)

Colorless semi-solid; $[\alpha]_D^{25}$ = −98.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.15–7.06 (m, 7H), 6.90–6.87 (m, 3H), 6.77 (d, J = 6.5 Hz, 2H), 6.31 (d, J = 7.5 Hz, 1H), 4.77 (d, J = 15.5 Hz, 1H), 4.68–4.65 (m, 2H), 4.38 (d, J = 10.5 Hz, 1H), 3.17 (dd, J = 21.0, J = 13.0 Hz, 2H), 2.32 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.6, 170.4, 140.7, 135.3, 134.8, 131.7, 130.1, 128.7, 128.6, 128.5, 127.9, 127.1, 126.7, 126.6, 124.6, 108.8, 67.53, 54.11, 43.46, 39.52, 21.19, 20.64; Enantiomeric excess: 99%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3e**, 9.13 min (major); for (*S*)-**3e**, 17.62 min (minor); ESI-HRMS calcd for $C_{26}H_{25}NO_3$ $[M + H]^+$ 400.1907, found 400.1910.

2.6.27 | (*R*)-(1-Benzyl-3-(4-fluorobenzyl)-2-oxoindolin-3-yl)methyl acetate (3f)

Colorless semi-solid; $[\alpha]_D^{25}$ = −88.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.32–7.30 (m, 1H), 7.22–7.15 (m, 3H), 7.13–7.09 (m, 1H), 7.07–7.03 (m, 1H), 6.85–6.71 (m, 6H), 6.47–6.45 (m, 1H), 4.82(d, J = 19.5 Hz, 1H), 4.73–4.64 (m, 2H), 4.36 (d, J = 13.5 Hz, 1H), 3.17 (dd, J = 35.0, J = 16.5 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.5, 170.3, 143.1, 135.1, 131.6, 131.5, 130.4 (d, J = 4.1 Hz), 128.6, 128.5, 128.3, 127.3, 126.6, 126.6, 123.7, 122.3, 114.7 (d, J = 26.2 Hz), 109.2, 67.30, 54.24, 54.23, 43.44, 38.59, 20.60; Enantiomeric excess: 89%, determined by HPLC (Daicel chiralpak IA, hexane/i-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3f**, 12.98 min (major); for (*S*)-**3f**, 21.70 min (minor); ESI-HRMS calcd for $C_{25}H_{22}FNO_3$ $[M + H]^+$ 404.1656, found 404.1648.

2.6.28 | (*R*)-(1-Benzyl-3-(4-methoxybenzyl)-2-oxoindolin-3-yl) methyl acetate (3g)

Colorless semi-solid; $[\alpha]_D^{25}$ = −120.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, sw = 15 ppm, scans = 16,

298 K, $CDCl_3$) δ 7.30–7.28 (m, 1H), 7.16–7.15 (m, 4H), 7.08 (dd, J = 9.5, J = 1.4 Hz, 1H), 7.06–7.02 (m, 1H), 6.80–6.78 (m, 2H), 6.76–6.74 (m, 2H), 6.61–6.59 (m, 2H), 6.44–6.42 (m, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.71 (d, J = 10.8 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 4.37 (d, J = 10.8 Hz, 1H), 3.72 (s, 3H), 3.15 (d, J = 2.0 Hz, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, sw = 15 ppm, scans = 1024, 298 K, $CDCl_3$) δ 176.8, 170.4, 158.4, 143.1, 135.1, 131.1, 131.1, 128.7, 128.4, 128.4, 127.2, 126.6, 126.6, 123.8, 122.2, 113.3, 109.2, 67.37, 55.03, 54.32, 43.43, 38.69, 20.6; Enantiomeric excess: 99%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3g**, 15.1 min (major); for (*S*)-**3g**, 17.7 min (minor); ESI-HRMS calcd for $C_{26}H_{25}NO_4$ $[M + H]^+$ 416.1856, found 416.1890.

2.6.29 | (*R*)-(3-Allyl-1-benzyl-2-oxoindolin-3-yl)methyl acetate (3h)

Colorless semi-solid; $[\alpha]_D^{25}$ = −39.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.29–7.23 (m, 6H), 7.17 (t, J = 7.5 Hz, 1H), 7.03 (t, J = 7.5 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.49–5.41 (m, 1H), 5.09–5.05 (m, 1H), 4.97 (d, J = 16.0 Hz, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.63 (d, J = 10.5 Hz, 1H), 4.18 (d, J = 10.5 Hz, 1H), 2.63 (d, J = 7.0 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 177.1, 170.3, 143.1, 135.7, 131.0, 129.0, 128.6, 128.4, 127.5, 127.2, 123.5, 122.5, 119.7, 109.1, 67.09, 52.34, 43.69, 38.05, 20.53; Enantiomeric excess: 93%, determined by HPLC (Daicel chiralpak AD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3h**, 12.17 min (minor); for (*R*)-**3h**, 19.52 min (major); ESI-HRMS calcd for $C_{21}H_{21}NO_3$ $[M + H]^+$ 336.1594, found 336.1609.

2.6.30 | (*R*)-(1-Benzyl-3-(naphthalen-2-ylmethyl)-2-oxoindolin-3-yl)methyl acetate (3i)

Colorless semi-solid; $[\alpha]_D^{25}$ = −146.8 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 7.43–7.37 (m, 4H), 7.08–7.05 (m, 2H), 6.98 (t, J = 7.5 Hz, 1H), 6.94 (dd, J = 8.5, J = 2.0 Hz, 1 Hz), 6.72 (t, J = 8.0 Hz, 1H), 6.54 (d, J = 7.5 Hz, 1H), 6.37–6.33 (m, 1H), 4.85 (d, J = 16.0 Hz, 1H), 4.78 (d, J = 10.5 Hz, 1H), 4.55 (d, J = 16.0 Hz, 1H), 4.43 (d, J = 11.0 Hz, 1H), 3.38 (dd, J = 23.5, J = 13.0 Hz, 2H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 170.3, 143.2, 133.2, 132.4, 132.3, 128.9, 128.6, 128.5, 128.2, 128.2, 127.8, 127.3, 127.0, 126.4, 125.8, 125.6, 124.0, 122.3, 109.2, 67.5, 54.36, 43.15, 39.62, 20.60; Enantiomeric excess: 98%, determined by HPLC (Daicel chiralpak IA, hexane/i-PrOH, 90:10, flow rate 0.5 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3i**, 28.16 min (major); for (*S*)-**3i**, 43.99 min (minor); ESI-HRMS calcd for $C_{24}H_{21}NO_3$ $[M + H]^+$ 436.1907, found 436.1943.

2.6.31 | (*R*)-(1-Allyl-3-benzyl-2-oxoindolin-3-yl)methyl acetate (3j)

Colorless semi-solid; $[\alpha]_D^{25}$ = −60.9 (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.26 (d, J = 2.1 Hz, 1H), 7.21–7.16 (m, 1H), 7.11–7.01 (m, 4H), 6.89–6.82 (m, 2H), 6.59 (d, J = 7.8 Hz, 1H), 5.44 (ddt, J = 17.1, J = 10.1, J = 4.9 Hz, 1H), 4.96 (dd, J = 10.4, J = 1.0 Hz, 1H), 4.69 (d, J = 10.8 Hz, 2H), 4.35 (d, J = 10.8 Hz, 1H), 4.26–4.19 (m, 1H), 4.10–4.03 (m, 1H), 3.17 (d, J = 13.0 Hz, 1H), 3.13 (d, J = 5.9 Hz, 1H), 1.88 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.3, 170.3, 143.2, 134.6, 130.7, 130.0, 129.9, 128.5, 128.3, 127.7, 127.6, 126.7, 124.0, 123.9, 122.1, 108.9, 108.1, 67.06, 54.08, 41.90, 39.75, 20.60, 11.19; Enantiomeric excess: 56%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3j**, 10.49 min (minor); for (*R*)-**3j**, 11.68 min (major); ESI-HRMS calcd for $C_{21}H_{21}NO_3$ $[M + H]^+$ 336.1594, found 336.1603.

2.6.32 | (*R*)-(1-Allyl-3-benzyl-5-chloro-2-oxoindolin-3-yl)methyl acetate (3k)

Colorless semi-solid; $[\alpha]_D^{25}$ = −83.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.24 (d, J = 2.0 Hz, 1H), 7.16 (dd, J = 8.0, 2.0 Hz, 1H), 7.11–7.08 (m, 3H), 6.85 (d, J = 7.0 Hz, 2H), 6.51 (d, J = 8.5 Hz, 1H), 5.44–5.37 (m, 1H), 4.96 (d, J = 10.5 Hz, 1H), 4.66 (d, J = 17.0 Hz, 1H), 4.61 (d, J = 10.5 Hz, 1H), 4.36 (d, J = 11.0 Hz, 1H), 4.22–4.17 (m, 1H), 4.04 (dd, J = 16.5, J = 5.0 Hz, 1H), 3.17 (dd, J = 33.5, J = 13.0 Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 175.8, 170.2, 141.7, 134.1, 130.5, 130.3, 129.9, 128.3, 127.9, 127.6, 126.9, 124.3, 117.0, 109.9, 66.93, 54.30, 42.05, 39.75, 20.51; Enantiomeric excess: 91%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 93:7, flow rate

1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3k**, 11.21 min (minor); for (*R*)-**3k**, 12.63 min (major); ESI-HRMS calcd for $C_{21}H_{20}NO_3$ $[M + H]^+$ 370.1204, found 370.1308.

2.6.33 | (*R*)-(1-Allyl-3-benzyl-5-bromo-2-oxoindolin-3-yl)methyl acetate (3l)

Colorless semi-solid; $[\alpha]_D^{25}$ = −126.8 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.38 (d, *J* = 1.5 Hz, 1H), 7.32–7.30 (m, 1H), 7.10–7.06 (m, 3H), 6.86 (d, *J* = 6.5 Hz, 2H), 6.46 (d, *J* = 8.0 Hz, 1H), 5.44–5.37 (m, 1H), 4.96 (d, *J* = 10.5 Hz, 1H), 4.65 (d, *J* = 17.0 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 11.0 Hz, 1H), 4.21–4.17 (m, 1H), 4.05–4.01 (m, 1H), 3.17–3.09 (m, 2H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 175.7, 170.2, 142.2, 134.1, 131.2, 130.9, 130.3, 129.9, 127.9, 127.0, 117.0, 114.8, 110.4, 66.93, 54.23, 42.0, 39.76, 20.62; Enantiomeric excess: 75%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3l**, 10.97 min (minor); for (*R*)-**3l**, 12.40 min (major); ESI-HRMS calcd for $C_{21}H_{20}BrNO_3$ $[M + H]^+$ 414.0699, found 414.0711.f

2.6.34 | (*R*)-(1-Allyl-3-benzyl-5-methoxy-2-oxoindolin-3-yl)methyl acetate (3m)

Colorless semi-solid; $[\alpha]_D^{25}$ = −123.9 (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.09–7.05 (m, 3H), 6.88–6.83 (m, 3H), 6.74–6.70 (m, 1H), 6.55–6.49 (m, 1H), 5.46–5.41 (m, 1H), 4.95 (dd, *J* = 10.5, *J* = 1 Hz, 1H), 4.69–4.60 (m, 2H), 4.35 (d, *J* = 10.5 Hz, 1H), 4.22–4.18 (m, 1H), 4.06–4.02 (m, 1H), 3.79 (s, 3H), 3.16–3.09 (m, 2H), 1.90 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.0, 170.3, 155.5, 136.7, 134.4, 130.9, 130.0, 127.8, 126.7, 116.7, 112.7, 111.3, 109.2, 108.5, 67.10, 56.82, 54.34, 42.04, 39.80, 20.65; Enantiomeric excess: 74%, determined by HPLC (Daicel chiralpak IC, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3m**, 16.76 min (minor); for (*R*)-**3m**, 17.55 min (major); ESI-HRMS calcd for $C_{22}H_{23}NO_4$ $[M + H]^+$ 366.1700, found 366.1709.

2.6.35 | (*R*)-(1-Allyl-3-benzyl-5-methyl-2-oxoindolin-3-yl)methyl acetate (3n)

Colorless semi-solid; $[\alpha]_D^{25}$ = −98.9 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.09–7.03 (m, 4H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.0 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.46–5.39 (m, 1H), 4.93 (d, *J* = 10.0 Hz, 1H), 4.67–4.62 (m, 2H), 4.35 (d, *J* = 11.0 Hz, 1H), 4.22–4.17 (m, 1H), 4.03 (dd, *J* = 16.5, *J* = 5.1 Hz, 1H), 3.12 (dd, *J* = 21.0, *J* = 13.0 Hz, 2H), 2.35 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.3, 170.4, 140.8, 134.7, 131.6, 130.8, 130.0, 128.6, 128.6, 127.7, 126.7, 124.6, 116.6, 108.6, 67.17, 54.01, 41.94, 39.76, 21.20, 20.66; Enantiomeric excess: 99%, determined by HPLC (Daicel chiralpak IA, hexane/i-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3n**, 7.58 min (major); for (*S*)-**3n**, 8.66 min (minor); ESI-HRMS calcd for $C_{22}H_{23}NO_3$ $[M + H]^+$ 350.1751, found 350.1768.

2.6.36 | (*R*)-(3-Benzyl-1-methyl-2-oxoindolin-3-yl)methyl acetate (3o)

Colorless semi-solid; $[\alpha]_D^{25}$ = −83.9 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, sw = 15 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.23–7.19 (m, 2H), 7.09–7.02 (m, 4H), 6.85–6.82 (m, 2H), 6.62–6.60 (m, 1H), 4.66 (d, *J* = 10.8 Hz, 1H), 4.33 (d, *J* = 10.8 Hz, 1H), 3.11 (d, *J* = 2.8 Hz, 2H), 2.98 (s, 3H), 1.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 170.5, 143.8, 134.6, 129.8, 128.5, 128.4, 127.6, 126.7, 123.9, 122.2, 107.8, 66.63, 53.97, 39.94, 25.98, 20.67; Enantiomeric excess: >93%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3o**, 8.14 min (major); for (*S*)-**3o**, 9.40 min (minor); ESI-HRMS calcd for $C_{19}H_{19}NO_3$ $[M + H]^+$ 310.1438, found 310.1440.

2.6.37 | (*R*)-(3-Benzyl-5-chloro-1-methyl-2-oxoindolin-3-yl)methyl acetate (3p)

Colorless semi-solid; $[\alpha]_D^{25}$ = −82.9 (*c* = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.20–7.17 (m, 2H), 7.11–7.05 (m, 3H), 6.84 (dd, *J* = 5.5, *J* = 1.5 Hz, 2H), 6.53 (d, *J* = 8.5 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 11.0 Hz, 1H), 3.11 (dd, *J* = 17.0, *J* = 13.0 Hz, 2H), 2.96 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.2, 170.3, 142.4, 134.1, 130.5, 129.8, 128.4, 127.8, 127.6, 126.9, 124.4, 108.7, 66.48, 54.22, 39.97, 26.09, 20.6; Enantiomeric excess: 69%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3p**, 11.07 min (major); for (*S*)-**3p**, 13.16 min (minor); ESI-HRMS calcd for $C_{19}H_{18}ClNO_3$ $[M + H]^+$ 344.1048, found 344.1059.

2.6.38 | (*R*)-(3-Benzyl-5-bromo-1-methyl-2-oxoindolin-3-yl)methyl acetate (3q)

Colorless semi-solid; $[\alpha]_D^{25} = -95.9$ (c = 0.2 in $CHCl_3$); ^{1}H NMR (400 MHz, sw = 15 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.35–7.32 (m, 2H), 7.09–7.05 (m, 3H), 6.85–6.83 (m, 2H), 6.49 (d, J = 8.4 Hz, 1H), 4.58 (d, J = 11.2 Hz, 1H), 4.34 (d, J = 11.0 Hz, 1H), 3.15–3.05 (m, 2H), 2.95 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 170.3, 142.9, 134.1, 131.3, 130.8, 129.8, 127.8, 127.1, 126.9, 114.8, 109.3, 66.48, 54.14, 39.97, 26.07, 20.68; Enantiomeric excess: 71%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3q**, 14.72 min (major); for (*S*)-**3q**, 16.89 min (minor); ESI-HRMS calcd for $C_{19}H_{18}BrNO_3$ $[M + H]^+$ 388.0543, found 388.0553.

2.6.39 | (*R*)-(3-Benzyl-5-methoxy-1-methyl-2-oxoindolin-3-yl)methyl acetate (3r)

Colorless semi-solid; $[\alpha]_D^{25} = -98.9$ (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.08–7.06 (m, 3H), 6.87–6.86 (m, 2H), 6.79 (d, J = 2.5 Hz, 1H), 6.74 (dd, J = 8.5, 2.0 Hz, 1H), 6.52 (d, J = 8.5 Hz, 1H), 4.61 (d, J = 11.0 Hz, 1H), 4.33 (d, J = 11.0 Hz, 1H), 3.78 (s, 3H), 3.12–3.07 (m, 2H), 2.96 (s, 3H), 1.91 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.4, 170.4, 155.6, 137.4, 134.6, 129.9, 129.9, 127.6, 126.7, 112.6, 111.5, 108.1, 66.67, 55.82, 54.24, 39.98, 26.07, 20.69; Enantiomeric excess: 82%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 95:5, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3r**, 18.72 min (major); for (*S*)-**3r**, 23.59 min (minor); ESI-HRMS calcd for $C_{20}H_{21}NO_4$ $[M + H]^+$ 340.1543, found 340.1549.

2.6.40 | (*R*)-(3-Benzyl-1,5-dimethyl-2-oxoindolin-3-yl)methyl acetate (3s)

Colorless semi-solid; $[\alpha]_D^{25} = -98.9$ (c = 0.1 in $CHCl_3$); ^{1}H NMR (400 MHz, sw = 15 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.08–6.99 (m, 5H), 6.85–6.82 (m, 2H), 6.50 (d, J = 8.4 Hz, 1H), 4.61 (d, J = 10.8 Hz, 1H), 4.33 (d, J = 10.8 Hz, 1H), 3.07 (dd, J = 13.2, J = 2.8 Hz, 2H) 2.96 (s, 3H), 2.34 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, sw = 15 ppm, scans = 1024, 298 K, $CDCl_3$) δ 176.6, 170.5, 141.5, 134.7, 131.6, 129.9, 128.8, 128.6, 127.6, 126.6, 124.7, 107.5, 66.75, 53.93, 39.98, 25.99, 21.20, 20.70; Enantiomeric excess: 83%, determined by HPLC (Daicel chiralcel OD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*R*)-**3s**, 7.65 min (major); for (*S*)-**3s**, 8.25 min (minor); ESI-HRMS calcd for $C_{20}H_{21}NO_3$ $[M + H]^+$ 324.1594, found 324.1603.

2.6.41 | (*R*)-(3-Benzyl-2-oxo-1-phenylindolin-3-yl)methyl acetate (3t)

Colorless semi-solid; $[\alpha]_D^{25} = -60.9$ (c = 0.2 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.43–7.40 (m, 2H), 7.36–7.32 (m, 2H), 7.49–7.05 (m, 5H), 6.95–6.93 (m, 2H), 6.88–6.85 (m, 2H), 6.88–6.85 (m, 2H), 6.50–6.48 (m, 1H), 4.77 (d, J = 11.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 3.26 (d, J = 13.0 Hz, 1H), 3.17 (d, J = 13.0 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 176.0, 170.4, 144.1, 134.5, 134.1, 130.0, 129.5, 128.5, 128.3, 128.1, 127.7, 126.8, 126.6, 124.0, 122.6, 109.1, 66.99, 54.33, 40.32, 20.67; Enantiomeric excess: 92%, determined by HPLC (Daicel chiralpak IA, hexane/*i*-PrOH, 93:7, flow rate 1.0 mL/min, λ = 254 nm): Retention times were: for (*S*)-**3t**, 21.12 min (minor); for (*R*)-**3t**, 22.70 min (major); ESI-HRMS calcd for $C_{24}H_{21}NO_3$ $[M + H]^+$ 372.1594, found 372.1603.

2.6.42 | (3*R*)-1′-Benzyl-5-(iodomethyl)-4,5-dihydro-2*H*-spiro[furan-3,3′-indolin]-2′-one (4)

Colorless semisolid; $[\alpha]_D^{25} = -39.9$ (c = 0.1 in $CHCl_3$); ^{1}H NMR (500 MHz, sw = 20 ppm, scans = 16, 298 K, $CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 1H), 7.33–7.30 (m, 2H), 7.28–7.25 (m, 3H), 7.19–7.16 (m, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 4.94–4.87 (m, 2H), 4.41–4.36 (m, 1H), 4.20–4.16 (m, 2H), 3.52–3.43 (m, 2H), 2.64 (dd, J = 12.5, J = 6.5 Hz, 1H), 2.06 (dd, J = 13.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, sw = 236 ppm, scans = 1024, $CDCl_3$) δ 178.7, 142.2, 135.6, 132.7, 128.8, 128.2, 127.7, 127.2, 123.2, 122.8, 109.1, 79.20, 77.33, 54.80, 44.86, 43.89, 29.69, 8.33; Diastereomeric ratio (dr) 56:44, Enantiomeric excess: 99% major diastereomer and 69% minor diastereomer, determined by HPLC (Daicel chiralpak AD-H, hexane/*i*-PrOH, 90:10, flow rate 1.0 mL/min, λ = 254 nm): t_R = 12.1 min (major), t_R = 19.5 min (minor); ESI-HRMS calcd for $C_{19}H_{18}INO_2$ $[M + H]^+$ 420.0455, found 420.0472.

2.7 | Crystallization procedure of 1a

The crystallization of the optically active compound **1a** has been achieved by partial evaporation technique in

absolute ethanol at room temperature. The absolute configurations of compound **1a** were attributed by crystallographic analysis using molybdenum radiation source at 25°C.

3 | RESULTS AND DISCUSSION

3.1 | Optimization of the catalyst

Initially, kinetic resolution of racemic 1,3-dibenzyl-3-(hydroxymethyl)indolin-2-one (**1a**, 0.1 mmol, 34.3 mg), catalyzed by *B. cepacia*[69] (Lipase PS-C, 50 mg) was investigated using vinyl acetate (0.5 mL) both as acyl donor and solvent at room temperature. The reaction was stopped after 21 h, the evaluation of the crude reaction mixture on chiral HPLC showed the conversion to be 9%, and the acylated product **3a** was found to have 89% enantiomeric excess (*ee*), whereas the unreacted substrate **1a** was found to have 11% *ee*. The model reaction was performed using lipases from different sources like *Pseudomonas cepacia*[70] (Lipase-PS powder), *P. fluorescens*[70] (Lipase-AK), *B. cepacia*[71] (Lipase PS-Amano) and Porcine pancreatic lipase[72] (PPL), but no transformation was observed even after 48 h with these lipases. On performing the reaction using *C. antarctica* lipase B (Novozym® 435) as catalyst,[73] 50% conversion of **1a** was observed in 36 h (see Table S1). The chiral HPLC analysis of the crude showed the formation of (1,3-dibenzyl-2-oxoindolin-3-yl)methyl acetate **3a** in 72% *ee* and unreacted substrate 1,3-dibenzyl-3-(hydroxymethyl) indolin-2-one (+)-**1a** with 87% *ee*. So, *C. antarctica* lipase B (CAL-B) was chosen as the best catalyst for the model reaction, and further optimizations were carried out using this enzyme.

3.2 | Solvent screening and effect of temperature

Because it has been reported in the literature that the organic solvent can alter the enzyme activity,[74–77] the model reaction was studied utilizing different organic solvents as reaction medium. Initially, the effect of solvents like DIPE, MTBE, 1,4-dioxane, tetrahydrofuran, hexane, cyclohexane, toluene, acetone and chloroform were investigated on the model reaction. Among these organic solvents, the reaction performed in acetonitrile gave 50% conversion in 24 h at 25°C providing **3a** in 89% *ee* and unreacted **1a** in 95% *ee* with enantiomeric ratio (*E*) 63, so acetonitrile was selected to perform further optimization of the reaction (see Table S1).

The effect of temperature on enzyme-catalyzed kinetic resolution of **1a** was studied by performing the reaction (0.1 mmol **1a** in 0.5 mL acetonitrile) at different reaction temperatures ranging from 10°C to 40°C. Performing the reaction at 10°C for 24 and 48 h gave conversion of 16%, 51% with **3a** in 85% *ee*, 78% *ee* and **1a** in 15% *ee*, 80% *ee*, respectively (Table 1, entries 1 and 2). The reaction stirred at 25°C furnished 50% conversion with 89% *ee* of **3a** and 95% *ee* of **1a** in 24 h (Table 1, entry 3). The reactions performed at 30°C, 35°C, and 40°C gave the product **3a** in 90%, 90%, and 82% *ee* in 24 h, whereas unreacted **1a** was obtained in 88%, 86%, and 91% *ee*, respectively (Table 1, entries 4–6). Because the best results were obtained at 25°C, it was selected as the optimum temperature for further optimizations.

3.3 | Selection of acetylating agent

After this, amount of acetylating agent was optimized in the model reaction. Using 1 equivalent of vinyl acetate, the observed conversion was only 32% with 95% *ee* of **3a** and 45% *ee* of unreacted **1a** in 48 h (Table 1, entry 7). While using 5 equivalents of vinyl acetate, the conversion 50% with 95% enantiomeric excess of **3a** and 83% *ee* of unused **1a** in 24 h was obtained (Table 1, entry 8). With 10 equivalents of vinyl acetate the conversion was 50% at 24 h with 89% *ee* of **3a** and 95% *ee* of unreacted **1a** (Table 1, entry 9). So, we decided to proceed further with 5 equivalents of vinyl acetate as an acetylating agent. The effect of different acyl donor on CAL-B-catalyzed transesterification of **1a** was studied by using ethyl acetate and isopropenyl acetate as acylating agents. Use of ethyl acetate afforded 47% conversion with 74% *ee* of **3a** and 67% *ee* of unreacted **1a** after 60 h, whereas reaction performed with isopropenyl acetate provided 43% conversion with 94% *ee* of **3a** and 83% *ee* of **1a** in 24 h (Table 1, entries 10 and 11). However, vinyl acetate showed better $E = 101$ (conversion 50%) than isopropenyl acetate $E = 84$ (conversion 43%) so vinyl acetate was used for further studies.

Thus, the optimized conditions consist of stirring **1a** with CAL-B in 0.5 mL of acetonitrile at 200 rpm with 5 equivalents vinyl acetate as acetylating agent at 25°C, which were used for further optimizations.

3.4 | Study on enzyme:substrate ratio and reaction time

The kinetic resolution of rac-**1a** using lipase from CAL-B was also investigated by varying the enzyme:substrate ratio (1:1, 3:1, 5:1 ratio w/w) in the model reaction. The initial reactions were performed with 50 mg (1.5:1

TABLE 1 Effect of temperature, acyl donor, and acetylating agent on CAL-B-catalyzed kinetic resolution of **1a**

Entry	Temperature (°C)	Time (h)	Conversion (%)[a]	*ee* 3a (%)[b]	*ee* 1a (%)[b]	*E*
1	10	24	16	85	15	14
2	10	48	51	78	80	19
3	25	24	50	89	95	64
4	30	24	50	90	88	55
5	35	24	51	90	86	52
6	40	24	50	82	91	32
7[c]	25	48	32	95	45	57
8[d]	25	24	50	95	83	101
9[e]	25	24	50	89	95	63
10[f]	25	60	47	74	67	13
11[g]	25	24	43	94	83	84

Note: Reaction conditions: 0.1 mmol of oxindole derivative **1a**, 10 equiv. of vinyl acetate **2a**, CAL-B (50 mg), acetonitrile (0.5 mL).
[a]Conversion determined by chiral HPLC.
[b]Enantiomeric excess (*ee*) determined by chiral HPLC.
[c]1 Equiv. vinyl acetate.
[d]5 equiv. vinyl acetate.
[e]10 equiv. vinyl acetate.
[f]Ethyl acetate (5 equiv.).
[g]Isopropenyl acetate (5 equiv.).

enzyme:substrate ratio) of immobilized enzyme and 0.1 mmol of the substrate **1a** in 0.5 mL of solvent at 25°C for 24 h. The reaction with higher amount of catalyst, that is, 3:1 and 5:1 ratio, showed higher conversion (>50%) of **1a** but resulted in low *ee* 75% and 68% of the acetylated product **3a**, respectively (Figure 2). Moreover, when enzyme:substrate ratio 1:1 was used, good conversion (45%) and high *ee* (95%) of the product **3a** was achieved. So, enzyme:substrate ratio 1:1 was selected for performing further optimizations.

Further, under optimized conditions, the course of reaction was examined by taking aliquots from reaction mixture after every hour. It was observed that when reaction was stirred up to 4 h, high *E* (>200) as well as excellent enantiomeric excess of the acetylated product **3a** up to >99% *ee* can be obtained. With increase in reaction time, the *ee* of the acylated product **3a** decreases from 99% to 93% after 13 h. So, we chose to stop the reaction after 4 h to achieve high *ee* of **3a** as well as high selectivity *E* value (Figure 3).

Thus, the final optimized conditions consists of stirring **1a** with CAL-B in a ratio of 1:1 (w/w), 0.5 mL of acetonitrile at 200 rpm with vinyl acetate (5 equivalents) as acetylating agent at 25°C for 4 h. These optimized conditions were used for the study of substrate scope.

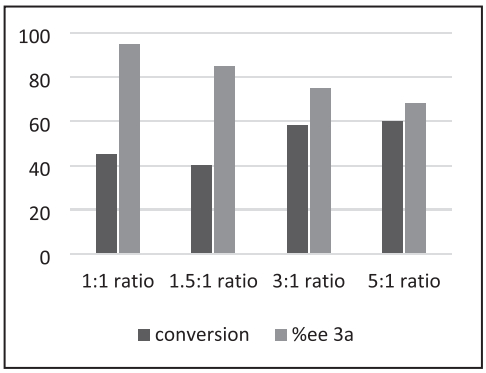


FIGURE 2 Catalyst amount screening

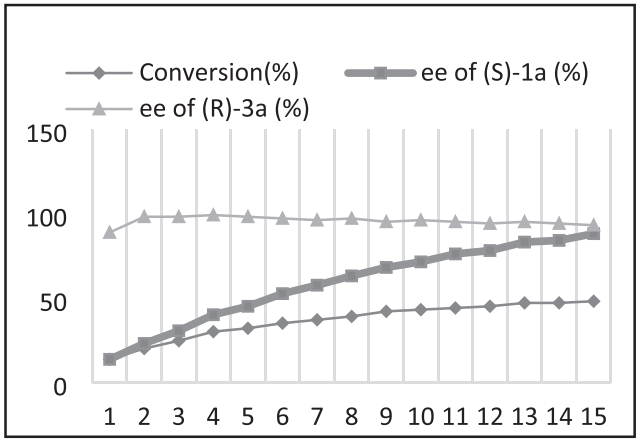
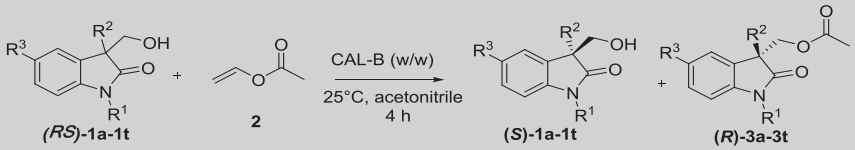


FIGURE 3 Time course of the enzymatic kinetic resolution of substrate **1a** throughout 15 h reaction time

3.5 | Substrate scope

With the optimized conditions in hand, substrate scope was investigated with different derivatives of 5-substituted-1,3-dialkyl-3-(hydroxymethyl)indolin-2-one. A broad range of substrates having 5-substituent with diverse electronic and steric properties readily participated in the enzyme catalyzed kinetic resolution, giving the desired products in reasonable yields and excellent enantioselectivity (*ee* >99%) (Table 2). The substrate **1b** provided the acetylated product **3b** with 41% conversion and 97.4% enantiomeric excess, and substrate **1c** gave **3c** with 35% conversion and 73% *ee* (Table 2, entries 2 and 3). The derivatives **1d** and **1e** showed a conversion of 17% and 25% with >99% *ee* of product **3d** and **3e**, respectively (Table 2, entries 4 and 5). Further, the oxindole derivatives **1f** and **1g** provided product **3f** and **3g** in 89% and 99% *ee*, respectively (Table 2, entries 6 and 7). The derivative **1h** having an allyl group at 3-position, reacted slowly to provide **3h** in 42% conversion and 93% *ee* after 13 h (Table 2, entry 8). On the other hand, increasing the bulkiness on C-3 of oxindole **1i** by introducing naphthalen-2-ylmethyl group provided **3i** in 98% *ee* and 32% conversion (Table 2, entry 9). The *N*-allyl oxindole derivative **1j** gave **3j** in 56% *ee* and 32% conversion (Table 2, entry 10), whereas the derivatives **1k** and **1l**

TABLE 2 Substrate scope of CAL-B-catalyzed kinetic resolution of 3,1-disubstituted-3-hydroxymethyl oxindole



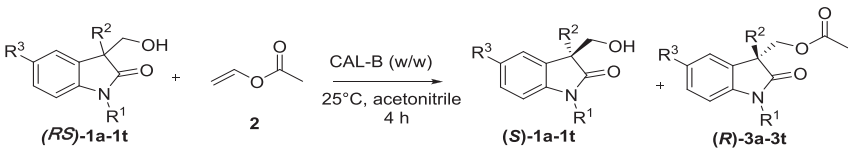
Entry	1 (R^1, R^2, R^3)	Time (h)	Conversion[a] (%)	(3a–3t) *ee*[a] (%) Yield[b] (%)		(unreacted 1a–1t) *ee*[a] (%) Yield[b] (%)		*E*
1	**1a** (R^1 = R^2 = -CH_2Ph, R^3 = H)	4	28	>98 (**3a**)	28	37 (**1a**)	66	142
2	**1b** (R^1 = R^2 = -CH_2Ph, R^3 = Cl)	4	41	>97 (**3b**)	35	60 (**1b**)	58	121
3	**1c** (R^1 = R^2 = -CH_2Ph, R^3 = Br)	4	35	73 (**3c**)	34	70 (**1c**)	61	13
4	**1d** (R^1 = R^2 = -CH_2Ph, R^3 = OMe)	4	17	>99 (**3d**)	16	17 (**1d**)	79	235
5	**1e** (R^1 = R^2 = -CH_2Ph, R^3 = Me)	4	25	>99 (**3e**)	25	47 (**1e**)	71	317
6	**1f** (R^1 = -CH_2Ph, R^2 = -4F-PhCH_2, R^3 = H)	4	49	89 (**3f**)	45	69 (**1f**)	49	35
7	**1g** (R^1 = -CH_2Ph, R^2 = -4MeO-PhCH_2, R^3 = H)	4	32	99 (**3g**)	30	49 (**1g**)	64	324
8	**1h** (R^1 = -CH_2Ph, R^2 = -CH_2CHCH_2, R^3 = H)	13	42	93 (**3h**)	39	72 (**1h**)	54	59
9	**1i** (R^1 = -CH_2Ph, R^2 = -Napthyl, R^3 = H)	4	32	98 (**3i**)	30	43 (**1i**)	65	151
10	**1j** (R^1 = -CH_2CHCH_2, R^2 = -CH_2Ph, R^3 = H)	4	32	56 (**3j**)	28	32 (**1j**)	65	5
11	**1k** (R^1 = -CH_2CHCH_2, R^2 = -CH_2Ph, R^3 = Cl)	4	30	91 (**3k**)	27	34 (**1k**)	67	29
12	**1l** (R^1 = -CH_2CHCH_2, R^2 = -CH_2Ph, R^3 = Br)	4	44	75 (**3l**)	42	67 (**1l**)	46	14
13	**1m** (R^1 = -CH_2CHCH_2,R^2 = -CH_2Ph, R^3 = OMe)	4	30	73 (**3m**)	28	72 (**1m**)	65	14
14	**1n**(R^1 = -CH_2CHCH_2, R^2 = -CH_2Ph, R^3 = Me)	4	12	99 (**3n**)	11	14 (**1n**)	85	228
15	**1o** (R^1 = Me, R^2 = -CH_2Ph, R^3 = H)	4	23	93 (**3o**)	23	27 (**1o**)	67	36
16	**1p** (R^1 = Me, R^2 = -CH_2Ph, R^3 = cl)	4	48	69 (**3p**)	46	60 (**1p**)	49	10
17	**1q** (R^1 = Me, R^2 = -CH_2Ph, R^3 = Br)	4	54	71 (**3q**)	49	78 (**1q**)	43	14
18	**1r** (R^1 = Me, R^2 = -CH_2Ph, R^3 = OMe)	4	38	82(**3r**)	36	47 (**1r**)	60	16
19	**1s** (R^1 = R^3 = Me, R^2 = -CH_2Ph)	4	35	83 (**3s**)	32	43 (**1s**)	57	16
20	**1t** (R^1 = Ph, R^2 = -CH_2Ph, R^3 = H)	4	21	92 (**3t**)	19	15 (**1t**)	76	27

Note: Reaction conditions: 0.1 mmol of substrate **1a–1t**, 5 equiv. of vinyl acetate **2a**, CAL-B (w/w, 1:1 to **1a–1t**), acetonitrile (0.5 mL).

[a]Conversion and Enantiomeric excess (*ee*) determined by chiral HPLC.

[b]isolated yields after column chromatography.

SCHEME 1 Synthetic transformation of chiral product **1h**



furnished **3k** and **3l** in 91% *ee*, 75% *ee* and 30%, 44% conversion, respectively (Table 2, entries 11 and 12). Furthermore, kinetic resolution of **1m** and **1n** showed 30% and 12% conversion with 73% *ee* of **3m** and 99% *ee* of **3n** (Table 2, entries 13 and 14).

The *N*-methyl oxindole derivative **1o** was kinetically resolved to give **3o** in 93% *ee* and 23% conversion (Table 2, entry 15), whereas **1p** and **1q** were kinetically resolved to give **3p** in 69% *ee* and 48% conversion and **3q** in 71% *ee* and conversion 54%, respectively (Table 2, entries 16 and 17). Similarly, **1r** and **1s** gave product **3r** and **3s** with 38%, 35% conversion and 82% *ee* and 83% *ee*, respectively (Table 2, entries 18 and 19). Further, the *N*-phenyl derivative **1t** furnished the acylated product **3t** in 92% *ee* and 21% conversion (Table 2, entry 20). In addition, to achieve high *ee* of the unreacted substrates **1a**–**1t**, the enzyme-catalyzed kinetic resolution of derivatives was also performed for 13 h, which resulted in the enantiomeric excess of unreacted alcohols up to 99% *ee* (see Table S2).

3.6 | Reusability of CAL-B

The reusability of the enzyme,[78] Novozym® 435 (CAL-B immobilized on macro-porous acrylic resin), was evaluated by recycling the enzyme for six consecutive reactions under the optimized conditions using substrate 1,3-dibenzyl-3-(hydroxymethyl)indolin-2-one **1a** (0.1 mmol), vinyl acetate (0.5 mmol) as acyl donor, immobilized CAL-B enzyme w/w 1:1 ratio in mg to alcohol substrate **1a** at 25°C for 4 h. The enzyme was recovered by simple filtration from crude reaction mixture, washed with acetonitrile (3 × 1 mL), dried under vacuum, and used for subsequent batches to provide the product **3a** in 98–99% enantiomeric excess for 5 cycles but conversion reduces gradually from 28% to 13% after the fifth cycle.

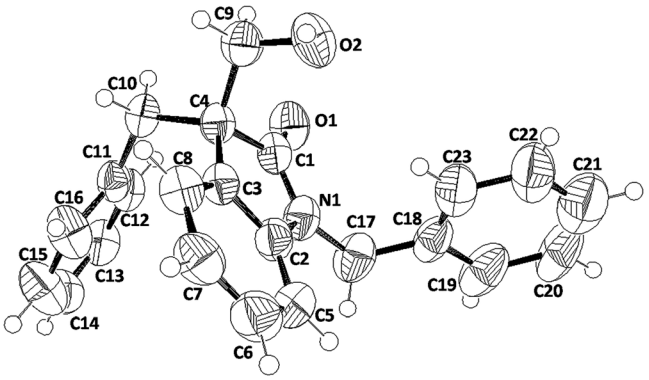


FIGURE 4 ORTEP diagram of the optically active molecule **1a** showing 50% ellipsoid probability

3.7 | Synthetic transformation

In synthetic utilization of the reaction, iodolactonization or intramolecular cyclization of (*S*)-3-allyl-3-hydroxymethyl oxindole **1h** was performed to synthesize (3*S*)-1′-benzyl-5-(iodomethyl)-4,5-dihydro-2*H*-spiro[furan-3,3′-indolin]-2′-one **4** with 56:44 diastereomeric ratio and 99% *ee* of major diastereomer and 69% *ee* of minor diastereomer (Scheme 1).[79]

The optically pure **1a** was assigned (*S*)-absolute configuration[80] on the basis of single-crystal X-ray diffraction analysis (Figure 4), which suggest that CAL-B selectively acetylated the (*R*)-enantiomer of **1a**. So, the acetylated product **3a** was assigned (*R*)-absolute configuration. Moreover, for all the substrates resolved here, the unreactive **1a**–**1t** were found to be dextrorotatory and the corresponding acetates **3a**–**3t** were found to be levorotatory in polarimetric determination of optical rotation. Because the sign of optical rotation remains the same for enantiomers in a homologous series,[81] the optically active unreactive alcohols were assigned (*S*)-configuration whereas acetates were assigned (*R*)-configuration.

4 | CONCLUSION

The 3,3-disubstituted oxindoles with a primary alcohol at the chiral quaternary center were successfully kinetically resolved by the *C. antarctica* lipase B (Novozym® 435) to get high to excellent enantiomeric excess (*ee*) of the acylated product and unreacted alcohol substrates in

acetonitrile as reaction medium. The enzyme-catalyzed kinetic resolution furnished biologically relevant (*S*)-(+)-1,3-dialkyl-3-(hydroxymethyl)indolin-2-ones and (*R*)-(−)-(1,3-dialkyl-2-oxoindolin-3-yl)methyl acetates with all carbon chiral quaternary center. The immobilized enzyme can be reused several times and are found to give reproducible results up to five repeated cycles.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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