Supporting Information

Establishment of atropisomerism in 3-indolyl furanoids: A synthetic, experimental and theoretical perspective

Sourav Chatterjee, [a], ‡ Pinaki Bhattacharjee, [a], ‡ Glenn L. Butterfoss, [b] Anushree Achari, [a] and Parasuraman Jaisankar*[a]

[a] Laboratory of Catalysis and Chemical Biology, Department of Organic and Medicinal Chemistry, CSIR-Indian Institute of Chemical Biology, 4 Raja S. C. Mullick Road, Kolkata - 700 032, India.
[b] Center for Genomics and Systems Biology, New York University, Abu Dhabi, Abu Dhabi-129188, United Arab Emirates.

‡ These authors contributed equally.

* Corresponding authors: Parasuraman Jaisankar; E-mail: jaisankar@iicb.res.in

Table of contents

Section A: General Information S02
Section B: Synthetic procedures and spectroscopic data S02-S08
Section C: 1H NMR, 13C NMR Spectra, and HPLC profiles S08-S34
Section D: HPLC chromatograms of 3db, 3dg, 3dh and 3di S35-S63
Section E: Determination of kinetic and thermodynamical parameters S64-S65
Section F: Temperature dependent ECD analysis S65-S67
Section G: Verification of kinetic and thermodynamical parameters S67-S68
Section H: Determination of Enthalpy and Entropy S69
Section I: X-ray crystal structure determination for 3db, 3dg, 3dh, and 3di S70-S78
Section J: Computational results S78-S89
Section K: References S90
Section A: General Information

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Melting points were determined in open glass capillaries and are uncorrected. All reactions were carried out with Stanrad Schlenk techniques under predried nitrogen. $^1$H NMR spectra were recorded on a Bruker DPX 300 MHz, JEOL JNM-ECZ 400 MHz, and Bruker DRX 600 MHz NMR instrument at ambient temperature either in CDCl$_3$, CD$_3$OD or DMSO-d$_6$. $^{13}$C NMR spectra were recorded at 75 MHz, 100 MHz, and 150 MHz at ambient temperature. The chemical shifts were recorded in parts per million (ppm) with TMS as internal reference. $^1$H NMR is reported as follows: Chemical shift, multiplicity (s=singlet, d=doublet, dd=doublet of doublet, brs=broad singlet, t=triplet, q=quartet, m=multiplet), coupling constant and integration. Coupling constants values are given in Hz. All $^{13}$C NMR spectra were recorded with complete proton decoupling. Analytical thin-layer chromatography (TLC) was carried out on Merck 20 × 20 cm silica gel 60-F$_{254}$ plates. Column chromatography was done with Biotage flash, silica gel 100-200 mesh. Mass spectral data are corresponds to EIMS or ESIMS and are given in m/z unit. HRMS (m/z) were recorded on a Q-TOF MicroTM mass spectrometer (ESI mode), Waters Xevo G2-XS QTof (ESI mode) and JEOL-JMS 700 (EI mode). Optical rotations were measured on a Perkin Elmer Model-341 polarimeter. Circular Dichroism spectra were recorded on a JASCO J815 unit (Jasco International Co.) equipped with a temperature controller and thermal programmer model PFD 425L/15 in strain free quartz cuvette (55.0 × 10.0 × 2.0 mm internal dimension) having PTFE stopper in "ground type" joint. HPLC analyses were performed on a Shimadzu SPD-M10AVP using Daicel Chiral column. Yield reported was the isolated yield by flash chromatography.

Section B : Synthetic procedures and spectroscopic data

Synthesis of enediones (2b-2i)

(E)-1,2,4-triphenylbut-2-ene-1,4-dione (2b). To a stirred solution of benzil (1.0g, 4.75 mmol) and acetophenone (0.55 mL, 4.75 mmol) in methanol (50 mL), was added aq NaOH (209 mg, 5.225 mmol in 10 mL water) dropwise under cold condition. The solution was allowed to stir for 36 h at room temperature. After completion of reaction, methanol was evaporated from the reaction mass, added crushed ice and neutralized with drop wise addition of conc. HCl. A yellowish white precipitate appeared which was filtered through sintered funnel, washed with cold water, and dried. The solid mass was further crystallized in hot methanol to afford 785 mg (53 %) of (E)-1,2,4-triphenylbut-2-ene-1,4-dione (2b) as pale yellow solid. Analytical data was matched with the literature report.$^1$

Pale yellow solid; Yield: 53% 785 mg. m.p. 143-148°C; $^1$H NMR (600 MHz, CDCl$_3$) δ 8.01-7.99 (m, 4H), 7.65 (s, 1H), 7.63 (d, J= 6Hz, 2H), 7.58 (t, J = 12 Hz, 1H), 7.53 (t, J = 12 Hz, 1H), 7.49-7.40 (m, 7H).

2d-i were also synthesized following this protocol.
(E)-2-benzoyl-1-oxoethyl-4-phenylbut-2-enoate (2c). A mixture of acetophenone (600 mg, 5.0 mmol), ethyl benzoyl acetate (990 mg, 5.0 mmol), iodine (1.40 g, 5.5 mmol), and CuO (440 mg, 5.5 mmol) in 20 mL DMSO was stirred at 70 °C for 15 h. The reaction mixture was cooled to room temperature, filtered through a pad of celite and eluted with ethyl acetate. To the filtrate, water was added and this aqueous phase was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium thiosulphate, water and brine successively. After drying over Na₂SO₄ and evaporation, the crude product (1.3 gm, Yield: ~84%) was used for further reaction with 2-phenyl indole.

(E)-1,2-diphenyl-4-(pyridin-2-yl)but-2-ene-1,4-dione (2d). Brownish yellow solid; Yield: 50% 745 mg. m.p. 142-147 °C; 1H NMR (400 MHz, CDCl₃) δ 8.73 – 8.66 (m, 1H), 8.44 (s, 1H), 8.03-7.95 (m, 3H), 7.74 (t, J = 8 Hz, 1H), 7.66 (d, J = 8 Hz, 2H), 7.52-7.46 (m, 1H), 7.44-7.32 (m, 6H); 13C NMR (400 MHz, CDCl₃): δ 198.38, 188.27, 156.41, 153.58, 148.96, 137.17, 136.18, 134.89, 133.44, 130.88, 129.19, 128.87, 128.77, 127.59, 127.31, 123.11, 120.16; HRMS (ESI) m/z: Calcd. for C₂₁H₁₆NO₂ [M + H]+ 314.1181; found 314.1186.

(E)-4-(4-bromophenyl)-1,2-diphenylbut-2-ene-1,4-dione (2e). Yellowish white solid; Yield: 63% 1.17 g. m.p. 143-148 °C; 1H NMR (300 MHz, CDCl₃) δ 7.97 (d, J = 6 Hz, 2H), 7.85 (d, J = 9 Hz, 2H), 7.65-7.58 (m, 4H), 7.56 (s, 1H), 7.52 (d, J = 9 Hz, 1H), 7.43 (t, J = 9 Hz, 5H).

(E)-4-(4-(tert-butyl)phenyl)-1,2-diphenylbut-2-ene-1,4-dione (2f). Yellow solid; Yield: 59% 1.03 g. m.p. 158-163 °C; 1H NMR (600 MHz, CDCl₃) δ 8.03 (d, J = 12 Hz, 2H), 7.99 (d, J = 6Hz, 2H), 7.70 (s, 1H), 7.65 (d, J = 12 Hz, 2H), 7.50 (d, J = 1.20 Hz, 3H), 7.43-7.40 (m, 5H), 7.43 (t, J = 9 Hz, 5H), 7.43 (t, J = 9 Hz, 5H).

(E)-4-(2,4-dimethoxyphenyl)-1,2-diphenylbut-2-ene-1,4-dione (2g). Light yellow solid; Yield: 54% 956 mg. m.p. 151-156 °C; 1H NMR (600 MHz, CDCl₃): δ 8.00 (d, J = 12 Hz, 2H), 7.72-7.69 (m, 2H), 7.59-7.56 (m, 2H), 7.50 (t, J = 6 Hz, 1H), 7.42-7.36 (m, 5H), 6.51-6.47 (m, 2H), 3.97 (s, 3H), 3.85 (s, 3H); 13C NMR (600 MHz, CDCl₃): δ 197.84, 187.73, 164.84, 160.73, 152.72, 136.25, 133.19, 130.61, 129.18, 128.72, 128.66, 128.64, 127.25, 125.69, 121.16, 35.15, 31.60, 31.06, 22.67, 14.17; HRMS (ESI) m/z: Calcd. for C₂₆H₂₄O₄Na [M + Na]+ 391.1674; found 391.1667.

(E)-4-(3-nitrophenyl)-1,2-diphenylbut-2-ene-1,4-dione (2h). Cream yellow solid; Yield: 61% 1.04 g. m.p. 152-157 °C; 1H NMR (600 MHz, CDCl₃): δ 8.81 (s, 1H), 8.41 (d, J = 6 Hz, 1H), 8.3 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 12 Hz, 2H), 7.68-7.62 (m, 4H), 7.55 (t, J = 7.4 Hz, 1H), 7.46-7.41 (m, 5H); 13C NMR (600 MHz, CDCl₃): δ 197.84, 187.73, 164.84, 160.73, 152.72, 136.25, 135.33, 133.69, 132.92, 129.99, 128.97, 128.59, 127.18, 121.18, 105.42, 98.45, 55.81, 55.54; HRMS (ESI) m/z: Calcd. for C₂₄H₁₆O₂Na [M + Na]+ 373.1440; found 373.1436.
MHz, CDCl$_3$): $\delta$ 197.06, 186.08, 158.48, 148.33, 138.50, 135.78, 134.25, 134.13, 133.58, 131.30, 130.03, 129.33, 128.84, 127.47, 127.39, 123.28, 119.39; HRMS (ESI) m/z: Calcd. for C$_{22}$H$_{16}$NO$_4$ [M + H]$^+$ 358.1079; found 358.1082.

($E$)-4-(2-nitrophenyl)-1,2-diphenylbut-2-ene-1,4-dione (2i). Yellowish solid; Yield: 63% 1.07 g. m.p. 150-155 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J$ = 12 Hz, 1H), 8.02 (d, $J$ = 4 Hz, 1H), 7.67 (m, 1H), 7.56 (m, 2H), 7.53-7.48 (m, 3H), 7.47-7.41 (m, 3H), 7.36 (m, 3H), 6.93 (s, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$): $\delta$ 196.60, 189.49, 155.34, 136.81, 135.59, 134.46, 134.26, 133.81, 131.14, 131.08, 129.28, 129.25, 128.99, 128.86, 127.44, 124.30, 123.14; HRMS (ESI) m/z: Calcd. for C$_{22}$H$_{16}$NO$_4$ [M + H]$^+$ 358.1079; found 358.1082.

Synthesis of 3-indolyl furanoids

Representative experimental procedure of 3db. To a stirred solution of 2-phenyl indole (1d, 19.4 mg, 0.1 mmol) and ($E$)-1,2,4-triphenylbut-2-ene-1,4-dione (2b, 37.4 mg, 0.12 mmol) in 1 mL dry dichloromethane, was added p-TsOH (9.5 mg, 0.05 mmol). The reaction mixture was then refluxed (40 °C) for 16 h. After completion of reaction (as monitored by TLC), the reaction mixture was diluted with dichloromethane (20 mL) and filtered. The filtrate was washed with water and the extracted organic layer was passed over anhydrous sodium sulphate. The solvent was evaporated to dryness under reduced pressure and the crude reaction mixture was purified by flash chromatography (silica gel 100-200 mesh; eluent: 0.2-0.5% ethyl acetate in hexane) to give the 2-phenyl-3-(2,4,5-triphenylfuran-3-yl)-1H-indole (3db, 39.5 mg, 81% yield) as off-white solid. A similar reaction procedure was followed for the synthesis of all other 3-indolyl furanoids.

2-Phenyl-3-(2,4,5-triphenylfuran-3-yl)-1H-indole (3db). Off-white solid; Yield: 81% 39.5 mg. m.p. 154-156 °C; $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 11.49 (s, 1H), 7.49-7.43 (m, 6H), 7.35 (d, $J$ = 8.0 Hz, 1H), 7.28-7.21 (m, 5H), 7.19-7.09 (m, 5H), 7.07-6.99 (m, 4H), 6.87 (t, $J$ = 8.0 Hz, 2H); $^{13}$C-NMR (100 MHz, DMSO-d$_6$): $\delta$ 148.5, 147.7, 136.7, 135.7, 133.3, 132.8, 130.9, 130.7, 129.7, 129.3, 129.1, 129.1, 128.6, 128.1, 127.9, 127.7, 127.0, 126.9, 125.5, 124.6, 122.5, 120.1, 119.3, 118.7, 112.0, 103.8; HRMS (EI) m/z: Calcd. for C$_{36}$H$_{25}$NO [M]$^+$ 487.1936; found 487.1933. HPLC analysis (Chiralcel OD-H, $\lambda$ = 254 nm, 95:5 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): $[\alpha]_D^{25}$ (+) = 17.1 min, $[\alpha]_D^{25}$ +54.0 (c 0.5, Ethanol) $[\alpha]_D^{25}$ (-) = 34.3 min, $[\alpha]_D^{25}$ -53.0 (c 0.5, Ethanol).

3-(2,5-Diphenylfuran-3-yl)-1H-indole (3aa). Dark yellow solid; Yield: 78% 26.2 mg. m.p. 108-110 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.26 (brs, 1H), 7.81 (d, $J$ = 8.0 Hz, 2H), 7.7 (d, $J$ = 8.0 Hz, 2H), 7.49 (d, $J$ = 8.0 Hz, 1H), 7.46-7.42 (m, 3H), 7.32-7.27 (m, 3H), 7.25-7.17 (m, 3H), 7.11 (t, $J$ = 8.0 Hz, 1H), 6.89 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 152.3, 148.3, 136.2, 131.6, 130.7, 128.8, 128.3, 127.5, 127.1, 126.6, 125.6, 123.9, 122.9, 122.5,
3-(2,5-Diphenylfuran-3-yl)-2-methyl-1H-indole (3ba). Orange-white solid; Yield: 80% 28 mg. m.p. 92-96 ºC; 1H NMR (400 MHz, CDCl₃): δ 8.00 (brs, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.64 (d, J= 8.0 Hz, 2H), 7.45 (t, J = 8.0 Hz, 3H), 7.38-7.28 (m, 3H), 7.10 (t, J = 8.0 Hz, 1H), 6.87 (s, 1H), 2.25 (s, 3H); 13C NMR (100 MHz, CDCl₃): δ 152.2, 148.6, 135.6, 132.5, 131.8, 130.8, 128.8, 128.4, 128.3, 127.4, 126.9, 125.0, 123.8, 121.6, 119.9, 119.4, 116.8, 111.0, 110.3, 106.5, 12.6; HRMS (ESI) m/z: Calcd. for C₂₅H₂₀NO [M+H]⁺ 350.1545; found 350.1537.

Ethyl 3-(2,5-diphenylfuran-3-yl)-1H-indole-2-carboxylate (3ca). Off-white solid; Yield: 69% 28.1 mg. m.p. 109-111 ºC; 1H NMR (300 MHz, CDCl₃): δ 9.12 (brs, 1H), 7.80 (d, J = 9 Hz, 2H), 7.55-7.53 (m, 2H), 7.45 (q, J = 12.0, 6.0 Hz, 4H), 7.38-7.29 (m, 4H), 7.20-7.06 (m, 4H), 6.85 (s, 1H), 4.17 (d, J = 6.0 Hz, 2H), 1.08 (t, J = 6.0 Hz, 3H); 13C NMR (75 MHz, CDCl₃): δ 162.4, 151.8, 149.2, 136.2, 131.4, 130.7, 128.3, 127.5, 127.4, 127.0, 125.8, 124.9, 123.9, 122.1, 120.9, 115.7, 115.4, 111.9, 111.5, 61.1, 13.9; HRMS (ESI) m/z: Calcd. for C₂₇H₂₂NO₃ [M + H]⁺ 408.1600; found 408.1600.

3-(2,5-Diphenylfuran-3-yl)-2-phenyl-1H-indole (3da). White solid; Yield: 81% 33.3 mg. m.p. 115-118 ºC; 1H NMR (400 MHz, CDCl₃): δ 8.4 (brs, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.61-7.55 (m, 4H), 7.47 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 8.0 Hz, 2H), 7.34-7.28 (m, 4H), 7.24-7.00 (m, 6H), 6.68 (s, 1H); 13C NMR (100 MHz, CDCl₃): δ 152.3, 149.1, 136.0, 134.6, 132.3, 131.2, 130.6, 128.7, 128.6, 128.2, 127.6, 127.3, 127.0, 126.8, 124.7, 123.7, 122.8, 120.3, 116.7, 111.2, 110.8, 106.7; HRMS (EI) m/z: Calcd. for C₃₀H₂₁NO [M]⁺ 411.1623; found 411.1621.

3-(2,4,5-Triphenylfuran-3-yl)-1H-indole (3ab). Pale yellow solid; Yield: 75% 31 mg. m.p. 123-125 ºC; 1H NMR (600 MHz, DMSO-d₆): δ 7.50 (dd, J = 12.0, 6.0 Hz, 4H), 7.31 (brs, 2H), 7.24-7.16 (m, 10H), 7.09 (d, J = 6 Hz, 1H), 7.04 (brs, 1H), 6.94 (brs, 1H); 13C NMR (150 MHz, DMSO-d₆): δ 148.1, 147.2, 136.4, 133.5, 131.0, 130.7, 130.3, 129.0, 128.9, 128.8, 127.9, 127.8, 127.7, 127.0, 126.9, 125.6, 125.1, 121.6, 119.4, 118.6, 112.1, 105.9; HRMS (ESI) m/z: Calcd. for C₃₀H₂₂NO [M+H]⁺ 412.1701; found 412.1703.

2-Methyl-3-(2,4,5-triphenylfuran-3-yl)-1H-indole (3bb). Dark brown solid; Yield: 76% 32.5 mg. m.p. 155-157 ºC; 1H NMR (600 MHz, CD₃OD): δ 7.59 (dd, J = 12.0, 6.0 Hz, 4H), 7.34-7.26 (m, 4H), 7.23-7.13 (m, 9H), 7.05 (t, J = 6.0 Hz, 1H), 6.91 (t, J = 9.0 Hz, 1H), 2.00 (s, 3H); 13C NMR (150 MHz, CD₃OD): δ 148.7, 147.2, 136.0, 133.7, 133.5, 131.2, 131.0, 129.5, 128.5, 128.0, 120.4, 120.1, 117.1, 111.3, 110.8, 109.9; HRMS (ESI) m/z: Calcd. for C₂₄H₁₈NO [M + H]⁺ 336.1388; found 336.1383.
127.9, 127.8, 127.0, 126.7, 126.6, 126.5, 125.4, 124.3, 120.2, 118.6, 118.1, 117.6, 110.0, 103.5, 10.6; HRMS (ESI) m/z: Calcd. for C$_{31}$H$_{25}$NO $[M]^+$ 425.1780; found 425.1772. HPLC analysis (Chiralcel OD-H, $\lambda = 254$ nm, 98:2 hexane: isopropanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 15 $^\circ$C): $[\tau_r (+)] = 39.38$ min, $[\tau_r (-)] = 45.01$ min.

2-(Naphthalen-2-yl)-3-(2,4,5-triphenylfuran-3-yl)-1H-indole (3eb). Pale yellow solid; Yield: 76% 41 mg. m.p. 182-184 $^\circ$C; $^1$H NMR (600 MHz, DMSO-d$_6$): $\delta$ 11.7 (s, 1H), 8.01 (s, 1H), 7.81 (t, $J = 6.0$ Hz, 2H), 7.74 (d, $J = 6.0$ Hz, 1H), 7.69 (d, $J = 6.0$ Hz, 1H), 7.55 (d, $J = 6.0$ Hz, 2H), 7.50 (d, $J = 6.0$ Hz, 2H), 7.47-7.43 (m, 3H), 7.31 (t, $J = 6.0$ Hz, 2H), 7.27-7.19 (m, 4H), 7.14 (q, $J = 6.0$ Hz, 2H), 7.06 (t, $J = 6.0$ Hz, 1H), 6.98 (t, $J = 6.0$ Hz, 2H), 6.94 (t, $J = 6.0$ Hz, 1H), 6.87 (d, $J = 6.0$ Hz, 2H), $^{13}$C NMR (150 MHz, DMSO-d$_6$): $\delta$ 148.6, 147.7, 136.8, 135.5, 133.2, 132.3, 132.3, 130.8, 130.6, 130.3, 129.6, 129.3, 129.0, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 127.0, 126.6, 125.5, 125.4, 124.8, 124.6, 122.6, 120.1, 119.3, 118.6, 111.9, 104.3; HRMS (EI) m/z: Calcd. for C$_{30}$H$_{27}$NO $[M]^+$ 537.2093; found 537.2095. HPLC analysis (Chiralcel OD-H, $\lambda = 254$ nm, 95:5 hexane: ethanol, flow rate: 1.0 mL min$^{-1}$, mode: Isocratic, column oven temp.: 20 $^\circ$C): $[\tau_r (+)] = 10.2$ min, $[\alpha]_D^{25}$ +50.0 (c 0.5, Ethanol) $[\tau_r (-)] = 13.6$ min.

Ethyl 2,5-diphenyl-4-(2-phenyl-1H-indol-3-yl)furan-3-carboxylate (3dc). Off-white solid; Yield: 68% (33 mg) m.p. 131-133 $^\circ$C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.39 (s, 1H), 8.00 (d, $J = 6.0$ Hz, 2H), 7.54–7.35 (m, 10H), 7.29 (d, $J = 6.0$ Hz, 1H), 7.23–7.18 (m, 2H), 7.17–7.13 (m, 3H), 7.06 (t, $J = 6$ Hz, 1H), 3.84 (q, $J = 12$ Hz, 2H) 0.66 (t, $J = 6$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 164.2, 154.6, 149.4, 135.9, 135.0, 132.4, 130.2, 129.8, 129.5, 129.0, 128.7, 128.3, 128.24, 127.6, 127.5, 127.4, 126.7, 125.0, 122.5, 120.2, 120.0, 117.8, 116.0, 110.6, 105.3, 60.2, 13.2; HRMS (EI) m/z: Calcd. for C$_{33}$H$_{25}$NO$_3$ $[M]^+$ 483.1834; found 483.1839. HPLC analysis (Chiralcel OD-H, $\lambda = 254$ nm, 95:5:0.1 hexane: isopropanol: TFA, flow rate: 0.8 mL min$^{-1}$, mode: Isocratic, column oven temp.: 20 $^\circ$C): $[\tau_r (+)] = 19.3$ min, $[\alpha]_D^{25}$ +47.0 (c 0.5, Ethanol) $[\tau_r (-)] = 23.1$ min.

3-(4,5-Diphenyl-2-(pyridin-2-yl)furan-3-yl)-2-phenyl-1H-indole (3dd). Dark yellow solid; Yield: 78% 38 mg. m.p. 176-178 $^\circ$C; $^1$H NMR (600 MHz, CD$_2$OD): $\delta$ 8.58 (d, $J = 6.0$ Hz, 1H), 8.07 (d, $J = 6.0$ Hz, 1H), 7.69 (d, $J = 6.0$ Hz, 2H), 7.40 (d, $J = 7.2$ Hz, 3H), 7.36 (d, $J = 6.0$ Hz, 2H), 7.35-7.21 (m, 7H), 7.10 (t, $J = 6.0$ Hz, 2H), 7.01 (t, $J = 6.0$ Hz, 4H), 6.79 (d, $J = 6.0$ Hz, 2H); $^{13}$C NMR (150 MHz, CD$_2$OD): $\delta$ 149.8, 148.7, 148.5, 136.9, 136.7, 133.9, 132.8, 132.6, 132.5, 130.4, 129.4, 128.6, 128.0, 127.9, 127.6, 127.5, 127.0, 126.7, 126.6, 126.5, 125.8, 121.9, 121.8, 120.7, 119.5, 118.7, 111.0; HRMS (EI) m/z: Calcd. for C$_{33}$H$_{24}$N$_2$O $[M]^+$ 488.1889; found 488.1891. HPLC analysis (Chiralcel OD-H, $\lambda = 254$ nm, 0.3% diethylamine in hexane: ethanol = 90:10, flow rate: 1.0 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 $^\circ$C): $[\tau_r (+)] = 7.7$ min, $[\alpha]_D^{25}$ +51.0 (c 0.5, Ethanol) $[\tau_r (-)] = 11.9$ min.

3-(2-(4-Bromophenyl)-4,5-diphenylfuran-3-yl)-2-phenyl-1H-indole (3de). Off-white solid; Yield: 82% (46.5 mg) m.p. 159-161 $^\circ$C; $^1$H NMR (600 MHz, CD$_2$OD): $\delta$ 7.50 (dd, $J = 12.0$ Hz, 6.0 Hz, 4H), 7.40 (d, $J = 12$ Hz, 1H), 7.34 (d, $J = 6$ Hz, 2H), 7.30-7.28 (m, 2H), 7.21-7.17
(m, 6H), 7.15-7.10 (m, 2H), 7.01 (t, J = 12 Hz, 1H), 6.95-6.90 (m, 3H), 6.71 (d, J = 6 Hz, 2H); $^{13}$C NMR (150 MHz, CD$_3$OD): δ 148.0, 147.6, 136.6, 135.8, 133.0, 132.7, 131.1, 130.6, 130.1, 129.3, 128.7, 128.0, 127.5, 127.1, 126.9, 126.7, 126.6, 126.4, 125.9, 125.3, 121.8, 120.3, 119.4, 119.1, 118.9, 110.9, 103.4; HRMS (ESI) m/z: Calcd. for C$_{36}$H$_{24}$BrNONa [M + Na]$^+$ 588.0939; found 588.0938. HPLC analysis (Chiralcel OD-H, λ = 254 nm, 95:5 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): racemic, [t$_R$ (+)] = 18.0 min [α]$_D$ $^{25}$ +56.0 (c 0.5, Ethanol), [t$_R$ (-)] = 30.0 min.

3-(2-(4-(tert-butyl)phenyl)-4,5-diphenylfuran-3-yl)-2-phenyl-1H-indole (3df). Pale yellow solid; Yield: 80% (43.5 mg) m.p. 141-143 °C; $^1$H NMR (600 MHz, CD$_3$OD): δ 7.57 (d, J = 6.0 Hz, 2H), 7.50 (d, J = 6.0 Hz, 2H), 7.39 (q, J = 12 Hz, 3H), 6.93 (q, J = 12 Hz, 2H), 6.72 (d, J = 12.0 Hz, 2H), 1.24 (s, 9H); $^{13}$C NMR (150 MHz, CD$_3$OD): δ 149.8, 149.0, 147.2, 136.6, 135.69, 133.3, 132.9, 131.0, 129.3, 128.7, 127.9, 127.4, 126.8, 126.7, 126.5, 126.3, 125.1, 124.9, 124.1, 121.6, 119.2, 119.0, 117.6 , 110.7, 104.0, 33.9, 30.2; HRMS (ESI) m/z: Calcd. for C$_{40}$H$_{33}$NONa [M + Na]$^+$ 566.2460; found 566.2457. HPLC analysis (Chiralcel OD-H, λ = 254 nm, 95:5 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): racemic, [t$_R$ (+)] = 13.9 min, [α]$_D$ $^{25}$ +48.0 (c 0.5, Ethanol) [t$_R$ (-)] = 32.3 min.

3-(2-(2,4-Dimethoxyphenyl)-4,5-diphenylfuran-3-yl)-2-phenyl-1H-indole (3dg). Off-white solid; Yield: 76% ( 42 mg) m.p. 142-144 °C; $^1$H NMR (600 MHz, CD$_3$OD): δ 7.45 (d, J = 6.0 Hz, 2H), 7.41 (d, J = 6.0 Hz, 2H), 7.28 (d, J = 6.0 Hz, 1H), 7.23-7.11 (m, 8H), 6.99 (t, J = 6.0 Hz, 3H), 6.35- 6.32 (m, 2H), 3.68 (s, 3H), 3.33 (s, 3H); $^{13}$C NMR (150 MHz, CD$_3$OD): δ 161.1, 158.4, 148.3, 147.4, 136.3, 135.1, 133.9, 133.3, 131.4, 130.6, 129.5, 129.4, 127.8, 127.7, 127.4 , 126.9, 126.4, 126.3, 126.0, 125.2, 125.1, 121.1, 119.0, 118.8, 118.6, 113.6, 110.3, 104.9, 98.3, 54.3, 54.2; HRMS (EI) m/z: Calcd. for C$_{38}$H$_{29}$NO$_3$ [M]$^+$ 547.2147; found 547.2139. HPLC analysis (Chiralcel OD-H, λ = 254 nm, 95:5 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): racemic, [t$_R$ (+)] = 11.9 min, [α]$_D$ $^{25}$ +42.0 (c 0.5, Ethanol) [t$_R$ (-)] = 17.0 min.

3-(2-(3-Nitrophenyl)-4,5-diphenylfuran-3-yl)-2-phenyl-1H-indole (3dh). Dark yellow solid; Yield: 82% ( 43.7 mg) m.p. 167-169 °C; $^1$H NMR (600 MHz, DMSO-d$_6$): δ 11.67 (s, 1H), 8.2 (s, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.91 (d, J = 6.0 Hz, 1H), 7.51 (q, J = 12.0 Hz, 5H), 7.42 (d, J = 12.0 Hz, 1H), 7.34 (t, J = 6.0 Hz, 2H), 7.30 (t, J = 6.0 Hz, 3H), 7.20 (q, J = 6.0 Hz, 2H), 7.14-7.07 (m, 4H), 6.91 (t, J = 6.0 Hz, 3H); $^{13}$C NMR (150 MHz, DMSO-d$_6$): 148.8, 148.4, 146.0, 136.7, 136.0, 132.7, 132.5, 132.0, 130.7, 130.2, 130.0, 129.6 , 129.1, 129.0 , 128.7 , 128.0, 127.8, 127.0, 126.9, 125.8 , 122.6, 122.0, 121.0, 120.2, 119.1, 118.6, 112.0, 102.6 ; HRMS (ESI) m/z: Calcd. for C$_{36}$H$_{24}$N$_2$O$_3$Na [M + Na]$^+$ 555.1685; found 555.1698. HPLC analysis (Chiralcel OD-H, λ = 254 nm, 90:10 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): racemic, [t$_R$ (+)] = 17.8 min, [α]$_D$ $^{25}$ +52.0 (c 0.5, Ethanol) [t$_R$ (-)] = 29.0 min.
3-(2-(2-Nitrophenyl)-4,5-diphenylfuran-3-yl)-2-phenyl-1H-indole (3di). Dark yellow solid; Yield: 85% (45.3 mg) m.p. 167-169 °C; $^1$H NMR (600 MHz, CDCl$_3$): δ 8.16 (brs, 1H), 7.68 (d, J = 12.0 Hz, 1H), 7.49-7.46 (m, 2H), 7.40-7.36 (m, 2H), 7.34-7.29 (m, 3H), 7.25-7.15 (m, 9H), 7.07-6.96 (m, 4H), 6.90-6.86 (m, 2H); $^{13}$C NMR (150 MHz, CDCl$_3$): δ 150.0, 148.2, 145.0, 136.0, 135.9, 132.8, 132.3, 131.8, 130.6, 129.8, 129.8, 129.4, 128.7, 128.5, 128.1, 128.0, 127.7, 127.6, 127.0, 126.9, 125.8, 125.7, 124.9, 124.1, 122.6, 120.8, 120.5, 120.0, 110.8, 103.9; HRMS (ESI) m/z: Calcd. for C$_{36}$H$_{25}$N$_2$O$_3$ [M + H]$^+$ 533.1865; found 533.1866. HPLC analysis (Chiralcel OD-H, λ = 254 nm, 90:10 hexane: ethanol, flow rate: 0.5 mL min$^{-1}$, mode: Isocratic, column oven temp.: 25 °C): racemic, [t$_R$ (+)] = 19.1 min, [α]$_D$ $^{25}$ +46.0 (c 0.5, Ethanol) [t$_R$ (-)] = 27.5 min.

Section C: $^1$H NMR, $^{13}$C NMR Spectra, and HPLC profiles

$^1$H NMR, $^{13}$C NMR Spectra of synthesized enediones

Figure S1: $^1$H NMR spectrum of 2b in CDCl$_3$ at 600 MHz
Figure S2: $^1$H NMR spectrum of 2d in CDCl$_3$ at 400 MHz

Figure S3: $^{13}$C NMR spectrum of 2d in CDCl$_3$ at 100 MHz
Figure S4: $^1$H NMR spectrum of 2e in CDCl$_3$ at 300 MHz

Figure S5: $^1$H NMR spectrum of 2f in CDCl$_3$ at 600 MHz
Figure S6: $^{13}$C NMR spectrum of 2f in CDCl$_3$ at 150 MHz

Figure S7: $^1$H NMR spectrum of 2g in CDCl$_3$ at 600 MHz
Figure S8: $^{13}$C NMR spectrum of 2g in CDCl$_3$ at 150 MHz

Figure S9: $^1$H NMR spectrum of 2h in CDCl$_3$ at 600 MHz
Figure S10: $^{13}$C NMR spectrum of $2h$ in CDCl$_3$ at 150 MHz

Figure S11: $^1$H NMR spectrum of $2i$ in CDCl$_3$ at 400 MHz
Figure S12: $^{13}$C NMR spectrum of 2i in CDCl$_3$ at 100 MHz
$^1$H NMR, $^{13}$C NMR Spectra, and HPLC profiles of 3-indolyl furanoids

Figure S13: $^1$H NMR spectrum of 3aa in CDCl$_3$ at 400 MHz

Figure 14: $^{13}$C NMR spectrum of 3aa in CDCl$_3$ at 100 MHz
Figure S15: $^1$H NMR spectrum of 3ba in CDCl$_3$ at 400 MHz

Figure S16: $^{13}$C NMR spectrum of 3ba in CDCl$_3$ at 100 MHz
Figure S17: $^1$H NMR spectrum of 3ca in CDCl$_3$ at 300 MHz

Figure S18: $^{13}$C NMR spectrum of 3ca in CDCl$_3$ at 75 MHz
Figure S19: $^1$H NMR spectrum of 3da in CDCl$_3$ at 400 MHz

Figure S20: $^{13}$C NMR spectrum of 3da in CDCl$_3$ at 100 MHz
Figure S21: $^1$H NMR spectrum of 3ab in DMSO-d$_6$ at 600 MHz

Figure S22: $^{13}$C NMR spectrum of 3ab in DMSO-d$_6$ at 150 MHz
Figure S23: $^1$H NMR spectrum of 3bb in CD$_3$OD at 600 MHz

Figure S24: $^{13}$C NMR spectrum of 3bb in CD$_3$OD at 150 MHz
Figure S25: Chiral HPLC profile of 3bb

Table: HPLC condition for 3bb:

| Peak# | Ret. Time | Area       | Height     | Area %  | Height % |
|-------|-----------|------------|------------|---------|----------|
| 1     | 39.382    | 49244694   | 206290     | 44.671  | 50.076   |
| 2     | 45.015    | 60993752   | 205662     | 55.329  | 49.924   |
| Total |           | 110238446  | 411952     | 100.000 | 100.000  |

Figure S26: 1H NMR spectrum of 3db in DMSO-d$_6$ at 400 MHz
Figure S27: $^{13}$C NMR spectrum of 3db in DMSO-$d_6$ at 100 MHz

Figure S28: Chiral HPLC profile of 3db
Figure S29: $^1$H NMR spectrum of 3eb in DMSO-d6 at 600 MHz

Figure S30: $^{13}$C NMR spectrum of 3eb in DMSO-d6 at 150 MHz
Figure S31: Chiral HPLC profile of 3eb

Figure S32: $^1$H NMR spectrum of 3dc in CDCl$_3$ at 300 MHz
Figure S33: $^{13}$C NMR spectrum of 3dc in CDCl$_3$ at 75 MHz

Figure S34: Chiral HPLC profile of 3dc
Figure S35: $^1$H NMR spectrum of 3dd in CD$_3$OD at 600 MHz

Figure S36: $^{13}$C NMR spectrum of 3dd in CD$_3$OD at 150 MHz
Figure S37: Chiral HPLC profile of 3dd

| Peak# | Ret. Time | Area   | Height | Area % | Height % |
|-------|-----------|--------|--------|--------|----------|
| 1     | 7.727     | 59752360 | 1666302 | 48.082 | 53.669   |
| 2     | 11.937    | 64520060 | 1438502 | 51.918 | 46.331   |
| Total |           | 124272420 | 3104804 | 100.000 | 100.000  |

Figure S38: $^1$H NMR spectrum of 3de in CD$_3$OD at 600 MHz
**Figure S39:** $^{13}$C NMR spectrum of 3de in CD$_3$OD at 150 MHz

**Figure S40:** Chiral HPLC profile of 3de
Figure S41: $^1$H NMR spectrum of 3df in CD$_3$OD at 600 MHz

Figure S42: $^{13}$C NMR spectrum of 3df in CD$_3$OD at 150 MHz
Figure S43: Chiral HPLC profile of 3df

Figure S44: $^1$H NMR spectrum of 3dg in CD$_3$OD at 600 MHz
Figure S45: $^{13}$C NMR spectrum of 3dg in CD$_3$OD at 150 MHz

Figure S46: Chiral HPLC profile of 3dg
Figure S47: $^1$H NMR spectrum of 3dh in DMSO-d6 at 600 MHz

Figure S48: $^{13}$C NMR spectrum of 3dh in DMSO-d6 MHz
Figure S49: Chiral HPLC profile of 3dh

Figure S50: $^1$H NMR spectrum of 3di in CDCl$_3$ at 600 MHz
**Figure S51:** $^{13}$C NMR spectrum of 3di in CDCl$_3$ at 150 MHz

**Figure S52:** Chiral HPLC profile of 3di
Section D: HPLC chromatograms of 3db, 3dg, 3dh and 3di

Representative procedure of HPLC analysis for 3db: \(^{46}\): 1.0 mg of \((S)-3db\) was isolated through chiral HPLC and evaporated in vacuo. The enantiomerically enriched analogue ((S)-3db) was then dissolved in 1.0 mL ethanol and placed in a sealed 2-dram vial to prepare 1.03 mM ethanolic solution. The mother solution was fractionated into ten glass vials containing 100 µL solution of \((S)-3db\) fitted with air tight 2-dram vial and kept inside a preheated incubator at 353 K. The same protocol was followed while studied at 333 K and 300 K. For those, samples were kept inside the preheated incubator at a fixed temperature of 333 K and 300 K respectively. Each sample was taken out from the incubator at indicated time interval and stored at 273 K (to immediately stop the further racemization process). Individual samples were then straight away subjected to chiral HPLC analysis by using following condition:

Column: CHIRALCEL OD-H (4.6 mm x 250.0 mm x 5.0 µm)
Solvent: hexane: ethanol (95: 5)
Flow rate: 0.5 mL/min
Mode: Isocratic
Column oven: 298 K
Sample conc.: 1.0 mg/mL ethanol
Injected volume: 5 µL

[a] Racemization kinetics study of \((S)-3db\) at 353 K

![Figure S53: Chiral HPLC profile of \((S)-3db\) at 0 min(before placing for incubation at 353 K)](image)
Figure S54: Chiral HPLC profile of (S)-3db at 2 min (353 K)

Figure S55: Chiral HPLC profile of (S)-3db at 5 min (353 K)
Figure S56: Chiral HPLC profile of (S)-3db at 10 min (353 K)

Figure S57: Chiral HPLC profile of (S)-3db at 15 min (353 K)
Figure S58: Chiral HPLC profile of (S)-3db at 20 min (353 K)

Figure S59: Plot of ee (%) of (S)-3db as a function of time (min) at 353 K
[b] Racemization kinetics study of (S)-3db at 333 K

Figure S60: Chiral HPLC profile of (S)-3db at 0 min (before placing incubation at 333 K)

Figure S61: Chiral HPLC profile of (S)-3db at 10 min (333 K)
**Figure S62:** Chiral HPLC profile of (S)-3db at 20 min (333 K)

**Figure S63:** Chiral HPLC profile of (S)-3db at 40 min (333 K)
**Figure S64**: Chiral HPLC profile of (S)-3db at 60 min (333 K)

| Peak# | Ret. Time | Area      | Height    | Area % | Height % |
|-------|-----------|-----------|-----------|--------|----------|
| 1     | 17.041    | 39855403  | 600390    | 78.014 | 86.391   |
| 2     | 34.118    | 11232031  | 92772     | 21.986 | 13.509   |
| Total |           | 51087434  | 694161    | 100.00 | 100.00   |

**Figure S65**: Chiral HPLC profile of (S)-3db at 180 min (333 K)

| Peak# | Ret. Time | Area      | Height    | Area % | Height % |
|-------|-----------|-----------|-----------|--------|----------|
| 1     | 17.100    | 11058181  | 161064    | 62.902 | 75.188   |
| 2     | 34.297    | 6904058   | 53151     | 37.098 | 24.812   |
| Total |           | 17563140  | 214235    | 100.00 | 100.00   |
**Figure S66**: Chiral HPLC profile of (S)-3db at 300 min (333 K)

**Figure S67**: Chiral HPLC profile of (S)-3db at 600 min (333 K)
Figure S68: Chiral HPLC profile of (S)-3db at 780 min (333 K)

Figure S69: Plot of ee (%) of (S)-3db as a function of time (min) at 333 K
[c] Racemization kinetics study of (S)-3db at 300 K

Figure S70: Chiral HPLC profile of (S)-3db at 0 day (the moment of placing the sample at 300 K)

Figure S71: Chiral HPLC profile of (S)-3db at 4 days (300 K)
Figure S72: Chiral HPLC profile of (S)-3db at 8 days (300 K)

Figure S73: Chiral HPLC profile of (S)-3db at 10 days (300 K)
Figure S74: Chiral HPLC profile of (S)-3db at 15 days (300 K)

Figure S75: Chiral HPLC profile of (S)-3db at 20 days (300 K)
Figure S76: Chiral HPLC profile of (S)-3db at 23 days (300 K)

| Peak# | Ret. Time | Area     | Height | Area % | Height % |
|-------|-----------|----------|--------|--------|----------|
| 1     | 17.257    | 44631687 | 504903 | 50.868 | 68.466   |
| 2     | 32.548    | 42108591 | 233009 | 46.132 | 31.534   |
| Total | 87740278  | 738912   | 100.000| 100.000|          |

Figure S77: Plot of ee (%) of (S)-3db as a function of time (days) at 300 K
[d] Racemization kinetics study of (S)-3dg at 300 K

Same experimental method employed as in Section D for 3dg. Individual samples were subjected to chiral HPLC analysis by using following condition:

Column: CHIRALCEL OD-H (4.6 mm x 250.0 mm x 5.0 µm)
Solvent: hexane: ethanol (95: 5)
Flow rate: 0.5 mL/min
Mode: Isocratic
Column oven: 298 K
Sample conc.: 1.0 mg/ mL ethanol
Injected volume: 5 µL

Figure S78: Chiral HPLC profile of (S)-3dg at 0 h (moment of placing the sample at 300 K) [during the course of isolating optically pure (S)-3dg from its racemic mixture by HPLC, ee immediately dropped to 91.6%]
**Figure S79:** Chiral HPLC profile of (S)-3dg at 3 h

| Peak# | Ret. Time | Area      | Height   | Area %  | Height % |
|-------|-----------|-----------|----------|---------|----------|
| 1     | 26.424    | 19410755  | 107890   | 76.228  | 73.161   |
| 2     | 37.628    | 6053262   | 39580    | 23.772  | 26.839   |
| Total |           | 25464017  | 147469   | 100.000 | 100.000  |

**Figure S80:** Chiral HPLC profile of (S)-3dg at 8 h (300 K)

| Peak# | Ret. Time | Area      | Height   | Area %  | Height % |
|-------|-----------|-----------|----------|---------|----------|
| 1     | 27.201    | 19668331  | 136492   | 71.923  | 67.816   |
| 2     | 38.166    | 7678178   | 64775    | 28.077  | 32.184   |
| Total |           | 27346509  | 201267   | 100.000 | 100.000  |
**Figure S81**: Chiral HPLC profile of (S)-3dg at 12 h (300 K)

| Peak# | Ret. Time | Area      | Height    | Area %   | Height % |
|-------|-----------|-----------|-----------|----------|----------|
| 1     | 26.301    | 22212913  | 141636    | 65.943   | 60.984   |
| 2     | 37.284    | 11472243  | 90617     | 34.057   | 39.016   |
| Total | 33685156  | 232253    | 100.000   | 100.000  |

**Figure S82**: Chiral HPLC profile of (S)-3dg at 18 h (300 K)

| Peak# | Ret. Time | Area      | Height    | Area %   | Height % |
|-------|-----------|-----------|-----------|----------|----------|
| 1     | 26.358    | 23561871  | 147681    | 59.586   | 54.493   |
| 2     | 37.170    | 159080672 | 123328    | 40.414   | 45.507   |
| Total | 39542543  | 271009    | 100.000   | 100.000  |
Figure S83: Chiral HPLC profile of (S)-3dg at 30 h (300 K)

Figure S84: Chiral HPLC profile of (S)-3dg at 42 h (300 K)
Figure S85: Chiral HPLC profile of (S)-3dg at 48 h (300 K)

Figure S86: Plot of ee (%) of (S)-3dg as a function of time (h) at 300 K
[e] Racemization kinetics study of (S)-3dh at 300 K

Same experimental method was employed as in Section D for 3dh. Individual samples were subjected to chiral HPLC analysis by using following condition:

Column: CHIRALCEL OD-H (4.6 mm x 250.0 mm x 5.0 µm)
Solvent: hexane: ethanol (90: 10)
Flow rate: 0.5 mL/min
Mode: Isocratic
Column oven: 298 K
Sample conc.: 1 mg/ mL ethanol
Injected volume: 5 µL

Figure S87: Chiral HPLC profile of (S)-3dh at 0 day (the moment of placing the sample at 300 K)
Figure S88: Chiral HPLC profile of (S)-3dh at 2 days (300 K)

Figure S89: Chiral HPLC profile of (S)-3dh at 4 days (300 K)
Figure S90: Chiral HPLC profile of (S)-3dh at 6 days (300 K)

Figure S91: Chiral HPLC profile of (S)-3dh at 8 days (300 K)
**Figure S92:** Chiral HPLC profile of (S)-3dh at 10 days (300 K)

| Peak# | Ret. Time | Area     | Height   | Area %  | Height % |
|-------|-----------|----------|----------|---------|----------|
| 1     | 15.936    | 13118432 | 187913   | 51.129  | 59.301   |
| 2     | 26.877    | 12539106 | 128969   | 48.871  | 40.699   |
| Total |           | 25657538 | 316882   | 100.000 | 100.000  |

**Figure S93:** Chiral HPLC profile of (S)-3dh at 12 days (300 K)

| Peak# | Ret. Time | Area     | Height   | Area %  | Height % |
|-------|-----------|----------|----------|---------|----------|
| 1     | 14.510    | 15076071 | 196530   | 51.057  | 60.194   |
| 2     | 25.089    | 14445582 | 128063   | 48.943  | 39.806   |
| Total |           | 29521900 | 326493   | 100.000 | 100.000  |
**Figure S94:** Chiral HPLC profile of (S)-3dh at 14 days (300 K)

**Figure S95:** Plot of ee (%) of (S)-3dh as a function of time (days) at 300 K
Racemization kinetics study of (S)-3di at 300 K

Same experimental method was employed as in Section D for 3di. Individual samples were subjected to chiral HPLC analysis by using following condition:

Column: CHIRALCEL OD-H (4.6 mm x 250.0 mm x 5.0 µm)
Solvent: hexane: ethanol (90: 10)
Flow rate: 0.5 mL/min
Mode: Isocratic
Column oven: 298 K
Sample conc.: 1 mg/ mL ethanol
Injected volume: 5 µL

Figure S96: Chiral HPLC profile of (S)-3di at 0 h (moment of placing the sample at 300 K) [during the course of isolating optically pure (S)-3di from its racemic mixture by HPLC, ee immediately dropped to 91.3%]
**Figure S97:** Chiral HPLC profile of (S)-3di at 1 h (300 K)

**Figure S98:** Chiral HPLC profile of (S)-3di at 2 h (300 K)
**Figure S99:** Chiral HPLC profile of (S)-3di at 3 h (300 K)

| Peak# | Ret. Time | Area   | Height | Area % | Height % |
|-------|-----------|--------|--------|--------|----------|
| 1     | 19.151    | 14939994 | 170684 | 65.705 | 68.384   |
| 2     | 27.595    | 7798058 | 78913  | 34.295 | 31.616   |
| Total |           | 22738052 | 249597 | 100.000| 100.000  |

**Figure S100:** Chiral HPLC profile of (S)-3di at 4 h (300 K)

| Peak# | Ret. Time | Area   | Height | Area % | Height % |
|-------|-----------|--------|--------|--------|----------|
| 1     | 19.164    | 14028625 | 157488 | 60.930 | 63.998   |
| 2     | 27.600    | 8995682 | 88595  | 39.070 | 36.002   |
| Total |           | 23024306 | 246083 | 100.000| 100.000  |
Figure S101: Chiral HPLC profile of (S)-3di at 5 h (300 K)

| Peak# | Ret. Time | Area     | Height   | Area % | Height % |
|-------|-----------|----------|----------|--------|----------|
| 1     | 19.921    | 13594606 | 170715   | 57.236 | 60.804   |
| 2     | 28.350    | 10157035 | 110049   | 42.764 | 39.196   |
| Total |           | 23751641 | 280764   | 100.000| 100.000  |

Figure S102: Chiral HPLC profile of (S)-3di at 6 h (300 K)

| Peak# | Ret. Time | Area     | Height   | Area % | Height % |
|-------|-----------|----------|----------|--------|----------|
| 1     | 19.630    | 10447859 | 132071   | 54.372 | 58.238   |
| 2     | 28.065    | 8767738  | 94706    | 45.628 | 41.762   |
| Total |           | 19215597 | 226778   | 100.000| 100.000  |
Figure S103: Chiral HPLC profile of (S)-3di at 7 h (300 K)

| Peak# | Ret. Time | Area   | Height | Area %  | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1     | 19.913    | 9056158| 113812 | 52.541  | 56.209   |
| 2     | 28.350    | 8180297| 88667  | 47.459  | 43.791   |
| Total |           | 17236455| 202479 | 100.000 | 100.000  |

Figure S104: Chiral HPLC profile of (S)-3di at 8 h (300 K)

| Peak# | Ret. Time | Area   | Height | Area %  | Height % |
|-------|-----------|--------|--------|---------|----------|
| 1     | 20.136    | 10658564| 125466 | 51.013  | 55.226   |
| 2     | 28.580    | 10235402| 109826 | 48.987  | 44.774   |
| Total |           | 20893965| 245293 | 100.000 | 100.000  |
Figure S105: Chiral HPLC profile of (S)-3di at 9 h (300 K)

Figure S106: Plot of ee (%) of (S)-3di as a function of time (h) at 300 K
Section E: Determination of kinetic and thermodynamical parameters of 3db, 3dg, 3dh, and 3di from HPLC analysis

Decrease of enantiomeric excess ($ee$) of (S)-3db as a function of time (min for 353 K and 333 K, days for 300 K) were plotted at different temperatures (fig. S59, fig. S69 and fig. S77). The decay constants ($t_1$), rate constants ($k_{rac}$), and enantiomerisation rate constant ($k_{enant}$) were determined from the exponential decay curves for each of the temperatures by using the following equations Eqn.1 and 2 respectively. \(^5,6\)

**Eqn. 1:** \( y = A_1 \exp(-\frac{x}{t_1}) + y_0 \) (where, \( A_1 \) = amplitude, \( t_1 \) = decay constant and \( y_0 \) = offset)

**Eqn. 2:** \( k_{rac} = \frac{1}{t_1} = 2k_{enant} \) (\( k_{rac} \) = racemization rate constant, \( k_{enant} \) = enantiomerisation rate constant)

The energy ($\Delta G^\neq$) barrier for racemization was further calculated using the following Eyring equation (Eqn. 3).

**Eqn. 3:** \( \Delta G^\neq = -RT\ln\left(\frac{h}{kT\kappa}\right) \) (where \( h \) = Planck constant, \( \kappa \) = transmission coefficient, \( T \) = temperature and \( k_B \) = Boltzmann constant)

The activation enthalpy ($\Delta H^\neq$) and activation entropy ($\Delta S^\neq$) of the isomerization of atropisomer 3db were further determined employing the Eyring equation (Eqn 4).

**Eqn. 4:** \( \ln \frac{k}{T} = -\frac{\Delta H^\neq}{R} \frac{1}{T} + \ln \frac{k_B}{h} + \frac{\Delta S^\neq}{R} \)

**3db at 353K**

decay constant = \( t_1 = 10.23782 \) min = 614.2692 sec  
\( k_{rac} = 1/ t_1 = 0.001627 \)  
\( k_{enant} = 8.13 \times 10^{-4} \)  
\( \Delta G^\neq = 25.758 \) Kcal.mol\(^{-1}\)

**3db at 333K**

decay constant = \( t_1 = 115.4697 \) min = 6928.182 sec  
\( k_{rac} = 1/ t_1 = 1.4433 \times 10^{-4} \)  
\( k_{enant} = 7.21 \times 10^{-4} \)  
\( \Delta G^\neq = 25.86 \) Kcal.mol\(^{-1}\)
3db at 300K

decay constant = $t_1 = 13.43$ day = 1160352 sec

$k_{rac} = 1/ t_1 = 8.61 \times 10^{-7}$

$k_{enant} = 4.305 \times 10^{-7}$

$\Delta G^\neq = 26.29 \text{ Kcal.mol}^{-1}$

This protocol was also applied to determine activation barrier of racemization ($\Delta G^\neq$) for 3dg, 3dh and 3di.

3dg at 300K

decay constant = $t_1 = 10.1247$ hour = 36448.92 sec

$k_{rac} = 1/ t_1 = 2.7435 \times 10^{-5}$

$k_{enant} = 1.371 \times 10^{-5}$

$\Delta G^\neq = 24.22 \text{ Kcal.mol}^{-1}$

3dh at 300K

decay constant = $t_1 = 3.5675$ day = 308232 sec

$k_{rac} = 1/ t_1 = 3.244 \times 10^{-6}$

$k_{enant} = 1.622 \times 10^{-6}$

$\Delta G^\neq = 25.49 \text{ Kcal.mol}^{-1}$

3di at 300K

decay constant = $t_1 = 3.23808$ hour = 11657.088 sec

$k_{rac} = 1/ t_1 = 8.578 \times 10^{-5}$

$k_{enant} = 4.289 \times 10^{-5}$

$\Delta G^\neq = 23.54 \text{ Kcal.mol}^{-1}$

Section F: Temperature dependent CD spectral analysis of 3db

[a] CD spectra of (S)-3db at 353 K with the course of time

To perform the Electronic Circular Dichroism (ECD) analysis, 1.03 mM solution of (S)-3db was prepared by dissolving 1.0 mg of (S)-3db in 1.0 mL EtOH. 400 µL of the above solution was taken in a screw cap quartz cuvette (screw cap is necessary to stop the change of concentration of sample due to solvent evaporation) and placed inside the CD spectrophotometer equipped with thermoelectric temperature controller. Sample was placed inside the preheated CD spectrophotometer at 353 K. CD spectra were recorded with respect to variable time regime up to 30 min at fixed temperature of 353 K. The spectral data was obtained is represented below.
Figure S107: CD spectra of (S)-3db at 353 K in different time scale

Table S1: CD intensities and calculated enantiomeric excess (ee) at 353 K in different time scale.

| Time (min) | 0  | 2  | 5  | 10 | 15 | 20 | 30 |
|------------|----|----|----|----|----|----|----|
| CD_{max} [(-) mdeg] | 29.58 | 27.56 | 20.04 | 10.03 | 5.76 | 2.90 | racemic |
| ee (%)^a | >99.0 | 92.24 | 67.07 | 33.57 | 19.28 | 9.70 | racemic |

^a Calculated from CD_{max} [(-) mdeg] intensity by unitary method considering 29.58 (-) mdeg value of CD_{max} as >99.0% ee of 1.03 mM enantiopure (S)-3db.

[b] CD spectra of (S)-3db at 333 K with the course of time

The above indicated CD spectral analysis was also applied to record at 333 K. Sample was placed inside the preheated CD spectrophotometer at 333 K. CD spectra were recorded with respect to variable time regime up to 10 h at fixed temperature of 333 K. The spectral data was obtained is represented below.
Section G: Verification of kinetic and thermodynamical parameters for 3db by ECD analysis

In order to verify the racemization energy and other kinetic and thermodynamical parameters obtained from HPLC analysis, time dependent CD spectral analysis was recorded on enantiopure (S)-3db following the experimental protocol mentioned in section D. The decrease of negative CD intensity [(−) mdeg] with time at 353 K and 333 K incubation temperature were plotted as a function of variable time regime, as shown in figure S108. From the exponential decay curve (shown in figure S109), activation barrier to racemization (ΔG‡) and other parameters were determined from equations 1-4 described in section E. The results obtained from ECD are in well agreement with the HPLC results performed at different temperatures.
**Figure S109**: Plot of CD [(-) mdeg] of (S)-3db as a function of time (min) at (a) 353 K and (b) 333 K

3db at 353K

decay constant = $t_1 = 11.34$ min $= 680.4$ sec  
k$_{rac} = 1/t_1 = 1.47 \times 10^{-3}$  
k$_{enant} = 7.35 \times 10^{-4}$  
$\Delta G^\ddagger = 25.82$ Kcal.mol$^{-1}$

3db at 333K

decay constant = $t_1 = 128.61$ min $= 7716.6$ sec  
k$_{rac} = 1/t_1 = 1.29 \times 10^{-4}$  
k$_{enant} = 6.45 \times 10^{-5}$  
$\Delta G^\ddagger = 25.93$ Kcal.mol$^{-1}$

**Table S3**: Different kinetic and thermodynamic parameters of 3db, 3dg, 3dh and 3di as a function of temperature.

| Molecule | Mode of analysis | Physical Parameters |
|----------|------------------|---------------------|
|          | **Temp (T, K)** | **Decay Constant (t$_1$)** | **Rate Constant (k$_{rac}$, sec$^{-1}$)** | **Enantimerisation Constant (2K$_{enant}$, k$_{enant}$)** | **Half Life (t$_{1/2}$)** | **Activation Barrier of Racemization (ΔG$^\ddagger$, kcal.mol$^{-1}$)** |
| 3db      | HPLC             |                   |       |               |                |                      |
|          | 353              | 10.61 min         | 1.62 $\times$ 10$^{-3}$ | 8.135$\times$ 10$^{-4}$ | 7.13 min        | 25.75                |
|          | 333              | 115.47 min        | 1.44 $\times$ 10$^{-4}$ | 7.21$\times$ 10$^{-5}$ | 80.20 min       | 25.86                |
|          | 300              | 13.43 days        | 8.62 $\times$ 10$^{-7}$ | 4.305$\times$ 10$^{-7}$ | 9.30 days       | 26.29                |
|          | CD               | 353               | 11.34 min        | 1.47 $\times$ 10$^{-3}$ | 7.35$\times$ 10$^{-4}$ | 7.85 min             |
|          |                  | 333               | 128.61 min       | 1.29 $\times$ 10$^{-4}$ | 6.45$\times$ 10$^{-5}$ | 78.41 min            |
| 3dg      | HPLC             | 300               | 10.12 h          | 2.74 $\times$ 10$^{-5}$ | 1.371$\times$ 10$^{-3}$ | 7.02 h               |
| 3dh      | HPLC             | 300               | 3.56 days        | 3.24 $\times$ 10$^{-6}$ | 1.62$\times$ 10$^{-6}$ | 2.47 days            |
| 3di      | HPLC             | 300               | 3.23 h           | 8.57 $\times$ 10$^{-5}$ | 4.289$\times$ 10$^{-4}$ | 2.24 h               |

**Section H**: Determination of activation enthalpy ($\Delta H^\ddagger$) and activation entropy ($\Delta S^\ddagger$) of racemization:
The activation enthalpy (ΔH\( ^{\neq} \)) and activation entropy (ΔS\( ^{\neq} \)) of the isomerization of atropisomer 3db were further determined employing the Eyring equation:

\[
\text{Eqn. 3: } \ln \frac{k}{T} = -\frac{\Delta H^{\neq}}{R} \frac{1}{T} + \ln \frac{k_B}{h} + \frac{\Delta S^{\neq}}{R}
\]

The values for ΔH\( ^{\neq} \) and ΔS\( ^{\neq} \) were determined from kinetic data obtained from a \( \ln \frac{k_{\text{expt}}}{T} \) vs. \( \frac{1}{T} \) plot considering temperature (T) as 353, 333 and 300 K (based on HPLC results) as well as 353 K and 333 K (based on ECD results). The equation is a straight line with negative slope, \( -\frac{\Delta H^{\neq}}{R} \), and a y-intercept, \( \ln \frac{k_B}{h} + \frac{\Delta S^{\neq}}{R} \). The activation enthalpy (ΔH\( ^{\neq} \)) and activation entropy (ΔS\( ^{\neq} \)) of the racemization process were determined as 28.86 kcal mol\(^{-1}\) and 8.12 cal mol\(^{-1}\) K\(^{-1}\) respectively.

Figure S110: Eyring plot for the racemization of 3db

Section I: X-ray crystal structure determination for 3db, 3dg, 3dh and 3di

[a] X-ray crystal structure determination for 3db (CCDC 1852313)
Suitable single crystal with approximate dimensions of $0.15 \times 0.12 \times 0.04$ mm$^3$ was used for X-ray diffraction analyses by mounting on the tip of a glass fiber in air. Data were collected on a Bruker kappa apex 2 with Mo Kα ($\lambda=0.71073$ Å) at 296.15 K. The structure was solved by direct method using program SHELXL-97 and subsequent Fast Fourier Transform technique. Crystallographic data and experimental details for 3db are summarized in Table S4.

**Table S4.** Crystal data and structure refinement for 3db

| Property                  | Value            |
|---------------------------|------------------|
| Empirical formula         | $2(\text{C}_{36}\text{H}_{35}\text{NO})$ |
| Formula weight            | 975.14           |
Temperature/K 298
Crystal system monoclinic
Space group P 21/n (14)
a/Å 9.8397(15)
b/Å 38.561(6)
c/Å 14.122(2)
α/° 90
β/° 100.382(8)
γ/° 90
Volume/Å³ 5270.6(14)
Z 4
ρ calc g/cm³ 1.229
μ/mm⁻¹ 0.073
F(000) 2048
Crystal size/mm³ 0.04 × 0.12 × 0.15
Radiation MoKα (λ = 0.71073)
2Θ range for data collection/° 1.1 to 28.5
Index ranges -13 ≤ h ≤ 12, -50 ≤ k ≤ 50, -18 ≤ l ≤ 18
Reflections collected 76731
Independent reflections 12254 [R int = 0.073]
Observed data [I> 0.0 σ (I)] 5938
Data/restraints/parameters 12254/1/686
Goodness-of-fit on $F^2$ 0.980
Final R indexes $R_1 = 0.0728$, $wR_2 = 0.2574$
Maximum and average shift/error 0.00/ 0.00
Largest diff. peak/hole / e Å⁻³ -0.26/ 0.26

[b] X-ray crystal structure determination for 3dg (CCDC 1852312)
Suitable single crystal with approximate dimensions of $0.12 \times 0.10 \times 0.05$ mm$^3$ was used for X-ray diffraction analyses by mounting on the tip of a glass fiber in air. Data were collected on a Bruker kappa apex 2 with Mo Kα ($\lambda=0.71073$ Å) at 296.15 K. The structure was solved by direct method using program SHELXL-97 and subsequent Fast Fourier Transform technique. Crystallographic data and experimental details for 3dg are summarized in Table S5.

**Table S5. Crystal data and structure refinement for 3dg**

|                  | 2(C$_{38}$H$_{29}$NO$_3$) |
|------------------|----------------------------|
| **Empirical formula** | 2(C$_{38}$H$_{29}$NO$_3$) |
| **Formula weight**     | 1095.24                    |
| **Temperature/K**      | 298                        |
| **Crystal system**     | triclinic                  |
| **Space group**        | P-1                        |
a/Å  11.7682(9)
b/Å  13.1204(11)
c/Å  19.9515(16)
α/°  77.621(4)
β/°  77.484(3)
γ/°  85.254(4)
Volume/Å³  2935.3(4)
Z  2
ρcalc/g/cm³  1.239
μ/mm⁻¹  0.078
F(000)  1152
Crystal size/mm³  0.05 × 0.10 × 0.12
Radiation  MoKα (λ = 0.71073)
2Θ range for data collection/°  1.1 to 27.6
Index ranges  -15 ≤ h ≤ 15, -17 ≤ k ≤ 16, -25 ≤ l ≤ 26
Reflections collected  60770
Independent reflections  13116 [Rint = 0.045]
Observed data [I> 0.0 σ (I)]  7885
Data/restraints/parameters  13116/1/761
Goodness-of-fit on F²  1.04
Final R indexes  R₁ = 0.0590, wR₂ = 0.1612
Maximum and average shift/error  0.00/ 0.00
Largest diff. peak/hole / e Å⁻³  0.268/-0.181

[c] X-ray crystal structure determination for 3dh (CCDC 1852314)
Suitable single crystal with approximate dimensions of $0.2 \times 0.05 \times 0.05 \text{ mm}^3$ was used for X-ray diffraction analyses by mounting on the tip of a glass fiber in air. Data were collected on a Bruker kappa apex 2 with Mo Kα ($\lambda=0.71073 \text{ Å}$) at 296.15 K. The structure was solved by direct method using program SHELXL-97 and subsequent Fast Fourier Transform technique. Crystallographic data and experimental details for 3dh are summarized in Table S6.
Table S6. Crystal data and structure refinement for 3dh

| Property                  | Value                                      |
|---------------------------|--------------------------------------------|
| Empirical formula         | C\textsubscript{36}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3} |
| Formula weight            | 532.57                                     |
| Temperature/K             | 296.15                                     |
| Crystal system            | monoclinic                                 |
| Space group               | P \textit{2} \textsubscript{1}/\textit{n} (14) |
| a/Å                       | 24.204(3)                                  |
| b/Å                       | 12.6309(13)                                |
| c/Å                       | 18.083(2)                                  |
| α/°                       | 90                                         |
| β/°                       | 90.124(7)                                  |
| γ/°                       | 90                                         |
| Volume/Å\textsuperscript{3} | 5528.3(11)                               |
| Z                         | 8                                          |
| \(\rho_{\text{calc}}\)/cm\textsuperscript{3} | 1.280                                      |
| \(\mu\)/mm\textsuperscript{-1} | 0.082                                      |
| F(000)                    | 2224                                       |
| Crystal size/mm\textsuperscript{3} | 0.05 × 0.05 × 0.2                          |
| Radiation                 | MoKα (λ = 0.71073)                         |
| 2Θ range for data collection/° | 0.841 to 24.997                           |
| Index ranges              | -28 ≤ h ≤ 28, -14 ≤ k ≤ 15, -21 ≤ l ≤ 21 |
| Reflections collected     | 119377                                     |
| Independent reflections   | 9638 \ ([R\text{int} = 0.132]        |
| Observed data [I > 0.0 σ (I)] | 5127                                 |
| Data/restraints/parameters| 9638/1/740                                 |
| Goodness-of-fit on \(F^2\) | 1.018                                     |
| Final R indexes           | \(R_1 = 0.0536, wR_2 = 0.1562\)           |
| Maximum and average shift/error | 0.00/ 0.00                           |
Suitable single crystal with approximate dimensions of $0.8 \times 0.7 \times 0.12$ mm$^3$ was used for X-ray diffraction analyses by mounting on the tip of a glass fiber in air. Data were collected on a 'Bruker APEX-II CCD' diffractometer with Mo Kα ($\lambda=0.71073$ Å) at 296.15 K. Using Olex2, the structure was solved with the ShelXT structure solution program using Intrinsic Phasing and refined with the ShelXL refinement package using Least Squares minimization. Crystallographic data and experimental details for 3di are summarized in Table S7.
Table S7. Crystal data and structure refinement for 3di

| Property                        | Value                      |
|---------------------------------|----------------------------|
| Empirical formula               | C36H24N2O3                 |
| Formula weight                  | 532.57                     |
| Temperature/K                   | 296.15                     |
| Crystal system                  | triclinic                  |
| Space group                     | P-1                        |
| a/Å                             | 10.259(7)                  |
| b/Å                             | 11.282(7)                  |
| c/Å                             | 13.341(9)                  |
| α/°                             | 70.807(8)                  |
| β/°                             | 84.165(9)                  |
| γ/°                             | 71.005(8)                  |
| Volume/Å³                       | 1378.9(16)                 |
| Z                               | 2                          |
| ρcalcg/cm³                      | 1.283                      |
| μ/mm 1                          | 0.082                      |
| F(000)                          | 556.0                      |
| Crystal size/mm³                | 0.8 × 0.7 × 0.12           |
| Radiation                       | MoKα (λ = 0.71073)         |
| 2Θ range for data collection/° | 4.828 to 54.696            |
| Index ranges                    | -13 ≤ h ≤ 13, -14 ≤ k ≤ 14, -17 ≤ l ≤ 16 |
| Reflections collected           | 24460                      |
| Independent reflections         | 6030 [Rint = 0.0517, Rsigma = 0.0526] |
| Data/restraints/parameters      | 6030/0/371                 |
| Goodness-of-fit on F2           | 1.092                      |
Final R indexes \([I\geq 2\sigma (I)]\)  
\[R1 = 0.0963, \text{wR2} = 0.3352\]

Final R indexes [all data]  
\[R1 = 0.1389, \text{wR2} = 0.3580\]

Largest diff. peak/hole / e Å\(^{-3}\)  
0.34/-0.30

Section J: Additional computational details and results

Methods: All modelling for this work was done with Gaussian09 or Gaussian16 (citations at the end of this section). The CD spectra were optimised and predicted at the B3LYP/6-311+G\(^{**}\) level of theory in PCM solvent ethanol, and used the TD=(nstates=18) and IOP(9/40=2) options. All energies and optimizations given below are at the M062X/6-311G\(^{**}\) level of theory. Transition states were optimized with the Opt=(TS, NoEigenTest, CalcAll) settings. Transition states and minima were verified with frequency calculations. Free energies are predicted at 298.15 K. All axial torsions were measured from furan C2 to indole C3 (highlighted below). All models below are optimized in vacuo, save for the solvated 3db models (Table S8) which used default PCM solvent representations.

Table S8. Predicted axial torsions, relative energies, and thermodynamic parameters various models of optimized and transition state structures for 3da-3di. For structures of core-1, core-2, and 3da-variant, see below.

| molecule    | structure | Axial Torsion (degrees) | Relative Energy (kcal/mol) | Relative Free Energy (kcal/mol) | Relative Enthalpy (kcal/mol) |
|-------------|-----------|-------------------------|----------------------------|--------------------------------|------------------------------|
| core-1      | min       | -147                    | 0.0                        | 0.0                            | 0.0                          |
|             | TS3       | 180                     | 0.7                        | 1.5                            | 0.1                          |
|             | TS2       | 0                       | 2.1                        | 2.8                            | 1.4                          |
|             | TS2       | -96                     | 1.6                        | 2.2                            | 1.0                          |
| core-2      | min       | -146                    | 0.0                        | 0.0                            | 0.0                          |
|             | TS1       | 180                     | 0.8                        | 1.5                            | 0.0                          |
|             | TS1       | 0                       | 2.2                        | 3.1                            | 1.6                          |
|             | TS2       | -98                     | 1.6                        | 2.2                            | 0.8                          |
|             | TS3       | 180                     | 0.8                        | 1.5                            | 0.0                          |
| 3da variant | min       | -46                     | 0.0                        | 0.0                            | 0.0                          |
|             | TS-0      | 15                      | 11.9                       | 13.4                           | 11.3                         |
|             | TS-180    | 180                     | 12.6                       | 12.4                           | 12.1                         |
|     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|
| **3bb** | min | -130 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 6 | 23.8 | 25.1 | 23.2 |
|     | TS-180 | 176 | 22.9 | 24.4 | 22.3 |
| **3db** | min | -132 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 8 | 27.2 | 28.2 | 26.3 |
|     | TS-180 | -173 | 25.5 | 26.0 | 24.3 |
| **3db-water** | min | -131 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 8 | 26.6 | 28.2 | 25.8 |
|     | TS-180 | -174 | 25.1 | 26.7 | 24.2 |
| **3db-ethanol** | min | -131 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 8 | 26.6 | 28.2 | 25.9 |
|     | TS-180 | -174 | 25.1 | 26.7 | 24.3 |
| **3dc** | min | -48 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | -8 | 22.6 | 23.1 | 21.7 |
|     | TS-180 | -179 | 21.7 | 22.4 | 20.9 |
| **3dd** | min | -131 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 8 | 26.1 | 28.3 | 25.6 |
|     | TS-180 | 175 | 25.4 | 26.4 | 24.4 |
| **3de** | min | -132 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 7 | 26.3 | 26.6 | 25.0 |
|     | TS-180 | -175 | 25.5 | 25.6 | 24.1 |
| **3dg** | min-1 | -132 | 0.0 | 0.0 | 0.0 |
|     | min-2 | -133 | 3.6 | 3.4 | 4.0 |
|     | TS-0 | 1 | 23.7 | 25.2 | 22.7 |
|     | TS-180 | -173 | 26.9 | 27.6 | 26.2 |
| **3dh** | min | -130 | 0.0 | 0.0 | 0.0 |
|     | TS-0 | 3 | 21.4 | 25.3 | 20.8 |
|     | TS-180 | -174 | 25.5 | 27.7 | 24.6 |
| **3di** | min-1 | -132 | 0.0 | 0.0 | 0.0 |
|     | min-2 | 134 | 2.2 | 0.7 | 2.2 |
|     | TS-0 | 8 | 22.5 | 23.4 | 21.7 |
|     | TS-180 | -175 | 25.2 | 25.4 | 24.3 |
**Figure S111:** Left: structures of core-1, highlighting the carbons used to measure the axial torsions in the above table; Middle: core-2; Right: 3da variant missing the furan C5 phenyl group.

**Comparative study of isomerization energy barrier of 2-methyl indole substitution (3bb) with 2-phenyl indole substitution (3db) through DFT modelling**

The predicted isomerization energy barrier of Molecule 3bb, which has a methyl group at the 2-indole position, is 22.9 kcal/mol (24.4 kcal/mol $\Delta G^\ddagger$). This is 2.6 kcal/mol lower than the barrier of 3db, which has a phenyl at the same position (1.6 kcal/mol lower in $\Delta G^\ddagger$). That the methyl substituted species presents a lower barrier might seem counterintuitive, as a methyl is sterically bulkier than a phenyl (when measured normal to the plane of the aromatic ring). However, the furan bond angles at the 2 and 4 positions orient the phenyl groups towards the indole. The predicted transition states show the phenyl groups acting as rigid leaver arms, which must pass the indole to allow axial inversion. In the more favourable of the two 3bb transition states, the 4-furan phenyl slides over the 2-indole methyl group causing the angle between the 4-furan carbon, 1-phenyl carbon, and 4-phenyl carbon to bend out of plane to 175.7° (Figure S112). By comparison, in the corresponding 3db transition state, nonplanarity of the matching atoms increases to 170.5° (Figure S112 right).
Figure S112. Transition states of 3bb (left, 22.9 kcal/mol) and 3db (right, 25.5 kcal/mol), highlighting the nonplanarity of relevant phenyl groups.

Additional analysis regarding the barrier of rotation of 3dg

Molecule 3dg interconverts relatively rapidly compared to similar species. However, its overall barrier height is predicted to be in the same range as the more stable molecules (predicted $\Delta G^\ddagger$ of 27.6 kcal/mol vs. 26.0 for 3db $\Delta G^\ddagger$). A notable observation from 3dg modelling is that the 2-methoxy phenyl substitution leads to a second local minimum pose which is ~4 kcal/mol above the predicted global minimum (Figure S113, bottom). In the higher energy structure, the methoxy oxygen sits proximal to the furan ring oxygen. The higher energy structure is predicted to be metastable—a potential energy surface for rotation around the furan-dimethoxyphenyl bond shows a barrier in the range of 2 kcal/mol (Figure S113, top).
Figure S113. Top: Potential energy surface of rotation about 3dg furan-dimethoxyphenyl bond calculated at the M062X/6-311G** level of theory. Bottom: Structures of the higher (left) and lower (right) energy local minima.
Predicted low barrier of rotation for 3di

Figure S114. Local minima (left, middle) and the lowest energy transition state (right) of molecule 3di. Also shown are the closest furan oxygen to nitro oxygen distance (for the minima) and the relative $\Delta G$ of the poses left to right are: 0.0, 0.7, and 23.4 kcal/mol, respectively. The nitro orientation in the middle structure resembles that of the crystal structure.

Tables of selected atom coordinates and absolute energies:

Optimized coordinates of 3db min in vacuo (Ground State):

Table S9. Cartesian coordinates (in Å) of the M062X/6-311G** optimized structure of the electronic ground state of 3db. (Total energy: M062X/6-311G**: -1516.64146655 Hartrees, 0 imaginary frequencies)

| Atom | x     | y     | z     |
|------|-------|-------|-------|
| N    | -2.27295 | -2.75756 | 0.06073 |
| C    | -1.83811 | 2.50829  | 0.64232 |
| C    | -2.93182 | 4.64912  | 0.90832 |
| C    | -4.04842 | 4.02039  | 1.44965 |
| C    | -4.05589 | 2.63656  | 1.5931 |
| C    | -2.96017 | 1.88207  | 1.19717 |
| C    | -0.67291 | 1.73506  | 0.21858 |
| C    | 2.79404  | 2.14006  | -0.49771 |
| C    | 1.46529  | 1.56279  | -0.2933 |
| C    | 0.94594  | 0.30364  | -0.40401 |
| C    | -0.4576  | 0.41639  | -0.08059 |
| C    | 3.14608  | 3.3181   | 0.16939 |
| C    | 4.40169  | 3.8808   | -0.01515 |
| C    | 5.32114  | 3.27792  | -0.86672 |
| Element | X-coordinate | Y-coordinate | Z-coordinate |
|---------|--------------|--------------|--------------|
| C       | 4.97279      | 2.11166      | -1.54121     |
| C       | 3.71759      | 1.54585      | -1.36501     |
| C       | -1.41838     | -0.68814     | -0.11533     |
| C       | -2.61991     | -0.76        | -0.90535     |
| C       | -3.13688     | -2.06556     | -0.75856     |
| C       | -1.25296     | -1.92289     | 0.46925      |
| C       | -0.18877     | -2.39837     | 1.36085      |
| C       | 0.28245      | -1.57562     | 2.38809      |
| C       | 1.30775      | -2.01078     | 3.21624      |
| C       | 1.87178      | -3.27011     | 3.03049      |
| C       | 1.40782      | -4.09194     | 2.00943      |
| C       | 0.38436      | -3.65892     | 1.17597      |
| C       | 1.65336      | -0.94699     | -0.74133     |
| C       | 2.76981      | -1.34382     | -0.00129     |
| C       | 3.42179      | -2.53427     | -0.29252     |
| C       | 2.96158      | -3.34813     | -1.32312     |
| C       | 1.84544      | -2.96436     | -2.05985     |
| C       | -3.29652     | 0.16187      | -1.71526     |
| C       | -4.46507     | -0.23551     | -2.3368      |
| C       | -4.97182     | -1.53755     | -2.16876     |
| C       | -4.31898     | -2.46908     | -1.38164     |
| C       | 1.19228      | -1.77095     | -1.77048     |
| C       | -1.83388     | 3.90166      | 0.50642      |
| O       | 0.48859      | 2.42798      | 0.08342      |
| H       | 5.67854      | 1.64517      | -2.2182      |
| H       | -2.44538     | -3.66555     | 0.4607       |
| H       | -2.9101      | 1.16812      | -1.83454     |
| H       | -5.89242     | -1.81606     | -2.6672      |
| H       | -2.91682     | 5.72658      | 0.79443      |
| H       | -4.91833     | 2.14002      | 2.02121      |
| H       | -2.96816     | 0.80668      | 1.32407      |
| H       | 2.42899      | 3.78217      | 0.8353       |
| H       | 4.66345      | 4.79127      | 0.51067      |
| H       | 6.30136      | 3.71715      | -1.00908     |
| H       | 3.4454       | 0.6496       | -1.90863     |
| H       | -0.1653      | -0.59854     | 2.53157      |
| H       | 1.66464      | -1.36771     | 4.01192      |
Optimized coordinates of 3db T.S.-I in vacuo (~0 degree axial torsion):

Table S10. Cartesian coordinates (in Å) of the M062X/6-311G**: optimized structure of the electronic transition state-I of 3db. (Total energy M062X/6-311G**: -1516.59816795 Hartrees, 1 imaginary frequency)

| Atom | x     | y     | z     |
|------|-------|-------|-------|
| N    | -2.37663 | 2.80878 | 0.27814 |
| C    | -1.72726 | -1.93864 | 0.19188 |
| C    | -3.03762 | -3.02736 | 1.90852 |
| C    | -3.87800 | -3.55335 | 0.93386 |
| C    | -3.64455 | -3.27216 | -0.40829 |
| C    | -2.56851 | -2.47454 | -0.77958 |
| C    | -0.46214 | -1.23680 | -0.13685 |
| C    | 2.92639  | -2.32161 | -0.22168 |
| C    | 1.72303  | -1.48154 | -0.18825 |
| C    | 1.49086  | -0.13952 | -0.10576 |
| C    | 0.04064  | 0.04685  | -0.11502 |
| C    | 4.10456  | -1.96138 | 0.44151 |
| C    | 5.21358  | -2.79570 | 0.39724 |
| C    | 5.16434  | -3.99993 | -0.29730 |
| C    | 3.99038  | -4.37194 | -0.94338 |
| C    | 2.87880  | -3.54144 | -0.90530 |
| C    | -0.70573 | 1.32881 | -0.07384 |
| C    | -0.18094 | 2.69799 | -0.15842 |
| C    | -1.25788 | 3.57421 | 0.10998  |
| C    | -2.07369 | 1.47790 | 0.10718  |
| C    | -3.27670 | 0.63327 | -0.11125 |
| C    | -3.71846 | 0.48953 | -1.42889 |
| C    | -4.93407 | -0.12590| -1.70088 |
| C    | -5.71847 | -0.60141| -0.65624 |
| C    | -5.28286 | -0.46197| 0.65746  |
| C    | -4.07199 | 0.16312 | 0.93162  |
| C    | 2.58898 | 0.82269 | 0.11710  |
| C    | 2.65365 | 1.53966 | 1.31241  |
| C    | 3.69598 | 2.42856 | 1.54330  |
| C    | 4.69126 | 2.60079 | 0.58635  |
| C    | 4.64514 | 1.87190 | -0.59884 |
| C    | 1.01997 | 3.31180 | -0.56940 |
| C    | 1.12901 | 4.68936 | -0.58517 |
| C    | 0.05999 | 5.52022 | -0.21415 |
| C    | -1.15675| 4.96706 | 0.12275  |
| C    | 3.60095 | 0.98515 | -0.83112 |
| C    | -1.96465| -2.22668| 1.53772  |
| O    | 0.55047 | -2.14295| -0.22051 |
| H    | 3.93916 | -5.31171| -1.48029 |
| H    | -3.32186| 3.15331 | 0.32241  |
| H    | 1.85840 | 2.73428 | -0.91704 |
| H    | 0.18137 | 6.59658 | -0.22558 |
| H    | -3.21047| -3.24909| 2.95520  |
| H    | -4.30185| -3.67593| -1.16943 |
| H    | -2.37716| -2.26173| -1.82481 |
| H    | 4.14846 | -1.03804| 1.00441  |
| H    | 6.11819 | -2.50644| 0.91876  |
| H    | 6.03274 | -4.64717| -0.32736 |
| H    | 1.96156 | -3.83120| -1.40298 |
| H    | -3.10020| 0.87259 | -2.23334 |
| H    | -5.26985| -0.22947| -2.72599 |
| H    | -6.66661| -1.08377| -0.86324 |
| H    | -5.88668| -0.84269| 1.47271  |
Optimized coordinates of 3db TS-II in vacuo (~180 degrees axial torsoin):

**Table S11.** Cartesian coordinates (in Å) of the M062X/6-311G**: optimized structure of the electronic transition state-II of 3db. (Total energy M062X/6-311G**: -1516.60077176 Hartrees, 1 imaginary frequency)

| Atom | x     | y     | z     |
|------|-------|-------|-------|
| N    | -1.78017 | -3.19480 | 0.18459 |
| C    | -2.41734 | 2.12824 | 0.23313 |
| C    | -4.12677 | 3.76054 | -0.26543 |
| C    | -4.87577 | 3.31088 | 0.81805 |
| C    | -4.38602 | 2.28529 | 1.62042 |
| C    | -3.15968 | 1.69948 | 1.33517 |
| C    | -1.10539 | 1.53794 | -0.06036 |
| C    | 2.21959  | 2.77282 | -0.28243 |
| C    | 1.06347  | 1.87214 | -0.17335 |
| C    | 0.89129  | 0.52215 | -0.03685 |
| C    | -0.54773 | 0.27691 | -0.03796 |
| C    | 2.02312  | 4.03284 | -0.86435 |
| C    | 3.07441  | 4.92846 | -0.99202 |
| C    | 4.34437  | 4.58768 | -0.53916 |
| C    | 4.54655  | 3.34515 | 0.04982 |
| C    | 3.49901  | 2.44217 | 0.18224 |
| C    | -1.27741 | -1.00687 | -0.05865 |
| C    | -2.72103 | -1.20395 | -0.23041 |
| C    | -2.98224 | -2.57676 | -0.02477 |
| C    | -0.75194 | -2.28260 | 0.09003 |
| Element | X         | Y         | Z         |
|---------|-----------|-----------|-----------|
| C       | 0.56834   | -2.92563  | -0.13922  |
| C       | 1.30950   | -3.51688  | 0.88131   |
| C       | 2.43265   | -4.27820  | 0.57685   |
| C       | 2.81000   | -4.47262  | -0.74752  |
| C       | 2.06971   | -3.89150  | -1.77081  |
| C       | 0.95328   | -3.12236  | -1.46813  |
| C       | 2.04226   | -0.33906  | 0.33366   |
| C       | 2.29751   | -0.53129  | 1.69397   |
| C       | 3.47307   | -1.14153  | 2.11430   |
| C       | 4.40662   | -1.56895  | 1.17586   |
| C       | 4.14732   | -1.40319  | -0.18110  |
| C       | -3.80335  | -0.42385  | -0.68272  |
| C       | -5.06181  | -0.98630  | -0.79304  |
| C       | -5.29727  | -2.33430  | -0.48016  |
| C       | -4.25113  | -3.15258  | -0.10728  |
| C       | 2.97293   | -0.78901  | -0.60007  |
| C       | -2.90023  | 3.17754   | -0.55291  |
| O       | -0.14068  | 2.48261   | -0.20917  |
| H       | 5.52825   | 3.07240   | 0.41851   |
| H       | -1.62603  | -4.18990  | 0.17028   |
| H       | -3.67178  | 0.60196   | -0.98530  |
| H       | -6.29718  | -2.74196  | -0.56680  |
| H       | -4.50011  | 4.56473   | -0.88818  |
| H       | -4.96075  | 1.94047   | 2.47156   |
| H       | -2.77603  | 0.89521   | 1.95222   |
| H       | 1.03508   | 4.30331   | -1.21386  |
| H       | 2.90069   | 5.89614   | -1.44791  |
| H       | 5.16609   | 5.28658   | -0.63906  |
| H       | 3.68316   | 1.49190   | 0.66286   |
| H       | 1.01136   | -3.36574  | 1.91242   |
| H       | 3.01479   | -4.71892  | 1.37762   |
| H       | 3.68208   | -5.07235  | -0.98081  |
| H       | 2.35769   | -4.04051  | -2.80485  |
| H       | 0.36171   | -2.67142  | -2.25734  |
| H       | 1.57934   | -0.16251  | 2.41853   |
| H       | 3.66784   | -1.26797  | 3.17305   |
| H       | 5.33017   | -2.03482  | 1.49947   |
|   |          |          |          |
|---|----------|----------|----------|
| H | 4.86518  | -1.74761 | -0.91653 |
| H | -5.88106 | -0.37016 | -1.14313 |
| H | -4.39489 | -4.20920 | 0.08611  |
| H | 2.78025  | -0.63456 | -1.14313 |
| H | -2.31381 | 3.51708  | 1.08963  |
| H | -5.83460 | 3.76395  | 1.03996  |

**Gaussian citations:**

Gaussian 09, Revision D.01,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria,
M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci,
G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian,
A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada,
M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima,
Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr.,
J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers,
K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand,
K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi,
M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross,
V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann,
O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski,
R. L. Martin, K. Morokuma, G. V. Zakrzewski, G. A. Voth,
P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels,
O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski,
and D. J. Fox, Gaussian, Inc., Wallingford CT, 2013.

Gaussian 16, Revision B.01,
M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria,
M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone,
G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich,
J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian,
J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young,
F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone,
T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega,
G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda,
J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai,
T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta,
F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin,
V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand,
K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar,
J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi,
J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas,
J. B. Foresman, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2016.
Section K: References

1. R.N. Gupta, V.A. Vaidya, N.M. Bhatia, C.R. Kokare, I. Singhvi and M.S. Bhatia. Asian Journal of Chemistry. 2006, 18, 937.

2. Y. Yang, M. Gao, L. M. Wu, C. Deng, D. X. Zhang, Y. Gao, Y. P. Zhu, A. X. Wu. Tetrahedron, 2011, 67, 5142.

3. H. S. P. Rao, B. K. Gorityala, and K. Vasantham, Ind. Journal of Heterocyclic Chem, 2006, 15, 331

4. D. E. Smith, I. Marquez, M. E. Lokensgard, A. L. Rheingold, D. A. Hecht, and J. L. Gustafson , Angew. Chem.Int.Ed. 2015, 54, 11754.

5. E. Kumarasamy, R. Raghunathan, M. P. Sibi, and J. Sivaguru, Chem. Rev. 2015, 115, 20, 11239.

6. S. Chatterjee, G. L. Butterfoss, M. Mandal, B. Paul, S. Gupta, R. Bonneau and P. Jaisankar, RSC Adv., 2016, 6, 71245

7. D. V. Kosynkin, A. L. Higginbotham, A. Sinitskii, J. R. Lomeda, A. Dimiev, B. K. Price and J. M. Tour, Nature, 2009, 458, 872.

8. E. Marsili, D. B. Baron, I. D. Shikhare, D. Coursolle, J. A. Gralnick and D. R. Bond, Proc. Natl. Acad. Sci. U.S.A, 2008, 105, 3968.

9. W. Verstraete and K. Rabaey, Environ. Sci. Technol., 2006, 40, 5181.

10. A. J. Bard and L. R. Faulkner, Electrochemical Methods: Fundamentals and Applications, 2 edn., John Wiley and Sons, 2001.