Supplementary Material

A C_3 -symmetric chiroptical molecular propeller based on hexakis(phenylethynyl)benzene with a threefold terephthalamide: stereospecific propeller generation through the cooperative transmission of point chiralities on the host and guest upon complexation

Ryo Katoono, Hidetoshi Kawai, Masakazu Ohkita, Kenshu Fujiwara and Takanori Suzuki



Supplementary Figures and Table



Fig. S1 ¹H NMR spectra (400 MHz) of (a) (R,R,R)-**1a**, (b) (R)-**3a**, (c) **1b**, and (d) **3b**, measured in CDCl₃ at room temperature. Nonequivalent phenylene protons [(H^a - H^c)^x and (H^a - H^c)^y] and methylene protons [H^e and H^e] are not assigned in each set, respectively in spectra (a) and (b).



Fig. S2 Energy-minimized structures for **3'** [X = Y = Me] obtained by a conformational search with MacroModel software (v9.9 Monte Carlo Multiple Minimum method, MMFF*, nonsolvated, 20000 steps): (a) a nonhelical conformation (0 kJ mol⁻¹) and (b) a helical conformation (+16.6 kJ mol⁻¹).



Fig. S3 (a) UV-vis spectra of (R,R,R)-1a (bold black), (R,R,R)-4 (thin black), (R)-3a (bold red), and (R)-5 (thin red), and (b) CD spectra of (R,R,R)-1a (bold black), and (R,R,R)-4 (thin black), measured in CH₂Cl₂ at room temperature.



Fig. S4 X-ray structure of **3c** [X = Y = nBu] (*P*2₁, *Z* = 4) in **3c**-chloroform crystal. The crystallization solvent is omitted for clarity.



Fig. S5 (a) CD spectra of **1b** $(7.7 \times 10^{-5} \text{ M})$ upon complexation with (R,R)-**2** [blue lines; i) 3 equiv., ii) 6 equiv., and iii) 11 equiv.] and (S,S)-**2** [red lines; iv) 3 equiv., v) 6 equiv., and vi) 12 equiv.], and CD spectra of (R,R)-**2** [thin blue line, vii] and (S,S)-**2** [thin red line, viii]. (b) CD spectra of **3b** $(3.3 \times 10^{-4} \text{ M})$ upon complexation with (R,R)-**2** [blue lines; i) 1 equiv., ii) 2 equiv., and iii) 4 equiv.] and (S,S)-**2** [red lines; iv) 1 equiv., v) 2 equiv., and vi) 4 equiv.]. All spectra were measured in CH₂Cl₂ at room temperature.



Fig. S6 NMR titration curves for the diastereomeric complexation of (*R*)-**3a** with (a) (*R*,*R*)-**2** ([(*R*)-**3a**] = 1.83 mM, [(*R*,*R*)-**2**] = 0-8.20 mM), and (b) (*S*,*S*)-**2** ([(*R*)-**3a**] = 1.87 mM, [(*S*,*S*)-**2**] = 0-8.02 mM), measured in CDCl₃ at 298 K. We assumed a 1:1 ratio for these complexes, and then curve-fitted the observed data (H^a) to give association constants K_a of 6.6 × 10⁴ M⁻¹ for (*R*)-**3a**·(*R*,*R*)-**2** and 6.4 × 10⁴ M⁻¹ for (*R*)-**3a**·(*S*,*S*)-**2**.



Fig. S7 Continuous changes in the CD spectra of (R,R,R)-1a $(8.1 \times 10^{-5} \text{ M})$ in the presence of (R,R)-2 and (S,S)-2 ([2]/[1] = 12) in various ratios [(R,R)-2/(S,S)-2; i) 0:12 ((S,S)-2 only, red line), ii) 3:9, iii) 6:6, and iv) 12:0 ((R,R)-2 only, blue line)], measured in CH₂Cl₂ at room temperature. Complexation-induced CD signals showed continuous changes in the two saturated CD spectra given by the addition of (S,S)-2 only (**Fig.4a**) or (R,R)-2 only (**Fig. 3a**), with an increase in the ratio of (R,R)-2/(S,S)-2 (matched to mismatched). This can be explained as one of the possibilities if we assume that the association constant was comparable for the two diastereometric complexes.

Table S1 Molar CDs ($\Delta \epsilon$) at 262, 296, and 326 nm induced for (*R*,*R*,*R*)-1a (8 × 10⁻⁵ M) in the presence of (*R*,*R*)-2 and (*S*,*S*)-2 in various ratios, measured in CH₂Cl₂ at room temperature.

equiv.	ratio		Molar CDs ($\Delta \epsilon$)		
[(R,R)-2+(S,S)-2]/[(R,R,R)-1a]	(R,R)- 2 :(S,S)- 2		262 nm	296 nm	326 nm
12 equiv.	0 3 6 12	12 9 6 0	-6.2 -9.3 -11.8 -17.3	-1.2 +0.3 +0.7 +2.1	-3.1 -5.3 -6.5 -10.3
8 equiv.	4	4	-12.1	+0.3	-6.5
6 equiv.	0 3 6	6 3 0	-6.2 -12.0 -18.2	-0.8 +0.3 +2.0	$-3.9 \\ -6.4 \\ -10.0$
3 equiv. ^a	0 1.5 3	3 1.5 0	-5.9 -10.9 -14.9	-1.1 +0.3 +1.0	-4.4 -5.8 -7.9

^{*a.*} not saturated (uncomplexed **1** would be present in a lower-equivalent-solution.

Experimental Details of New Compound Preparation



Scheme S1 Preparation of 1a/b and 3a-c. Reagents and yields; (a) TIPSA, Pd(PPh₃)₄, CuI, Et₃N (79%); (b) CBr₄, PPh₃, Zn, CH₂Cl₂ (95%); (c) ^{*n*}BuLi, THF (49%); (d) 18b, Pd(PPh₃)₄, CuI, THF, ^{*i*}Pr₂NH (73%); (e) i) TFA, CH₂Cl₂ (96% for 10'), ii) 10', 21a'/b', Et₃N, toluene (93% for 11a/96% for 11b); (f) TBAF, Pd(PPh₃)₄, CuI, Et₃N, THF (2.7% for 1a/2.1% for 1b); (g) 18b/c, Pd(PPh₃)₄, CuI, THF, ^{*i*}Pr₂NH (69% for 13b/85% for 13c); (h) i) TFA, CH₂Cl₂ (88% for 13b'/89% for 13c'), ii) 13b'/c', 21a'-c', Et₃N, toluene (97% for 14a/99% for 14b/94% for 14c); (i) TBAF, Pd(PPh₃)₄, CuI, Et₃N, THF (13% for 3a/18% for 3b/11% for 3c). Regarding the new compounds 18 and 21, see Scheme S3.

Preparation of 7

A suspended solution of 6^1 (4.99 g, 12.5 mmol), triisopropylsilylacetylene (10.0 mL, 45.0 mmol), Pd(PPh₃)₄ (433 mg, 375 µmol) and CuI (144 mg, 756 µmol) in Et₃N (470 mL) was refluxed for 2 d under a nitrogen atmosphere. After dilution with diethyl ether, a solid was removed by filtration through a celite pad. The filtrate was cooled down in an ice-bath, and added 1N HCl aq., and then separated. The aqueous layer was

further extracted with diethyl ether. The combined organic layer was washed with brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-20% dichloromethane/hexane) gave 7 (6.91 g) as a yellow solid in 79% yield.

An analytical sample was obtained as orange crystals by recrystallization from hexane.

Data of 7

mp 164.0-164.5 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm}$ 10.75 (3H, s), 1.22-1.13 (63H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm}$ 189.3, 138.6, 128.1, 112.3, 98.1, 18.6, 11.2; IR (KBr) 3396, 2944, 2864, 2749, 2152, 1708, 1524 cm⁻¹; FD-LRMS m/z 704.4 ([M+2]⁺, 32%), 703.4 ([M+1]⁺, 66), 702.4 (M⁺, BP); Anal. Calcd. for C₄₂H₆₆O₃Si₃ C 71.73, H 9.46, Found C 71.63, H 9.64.

Preparation of 8

To an ice-cooled suspended solution of CBr_4 (23.6 g, 71.0 mmol) and Zn powder (4.64 g, 70.9 mmol) in CH_2Cl_2 (490 mL) was added a solution of PPh₃ (18.7 g, 71.1 mmol) in CH_2Cl_2 (120 mL), and the mixture was stirred at 0 °C for 30 min. Then a solution of 7 in CH_2Cl_2 (100 mL) was added to the above solution at room temperature, and the mixture was further stirred for 2 d. After addition of SiO₂ (30 g) to the reaction mixture, a solid was removed by filtration. The filtrate was concentrated by evaporation, and then purified by column chromatography on SiO₂ (0-20% dichloromethane/hexane) to give **8** (6.44 g) as a white solid in 95% yield.

An analytical sample was obtained as a white solid by further purification through GPC (chloroform, detected by UV 254 nm and RI).

Data of 8

mp 81-83 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.53}$ (3H, s), 1.19-1.14 (63H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 141.6}$, 135.0, 122.2, 102.5, 101.2, 96.2, 18.8, 11.2; IR (KBr) 2942, 2889, 2864, 2154, 1601, 1535 cm⁻¹; FD-LRMS m/z 1172.0 ([M+8]⁺, 85%), 1171.0 ([M+7]⁺, 59), 1170.0 ([M+6]⁺, BP), 1168.0 ([M+4]⁺, 69); Anal. Calcd. for C₄₅H₆₆Br₆Si₃ C 46.17, H 5.68, Found C 46.02, H 5.56.

Preparation of 9

To a solution of **8** (3.53 g, 3.02 mmol) in THF (208 mL) was added a 1.6 M *n*BuLi solution in hexane (12.3 mL, 19.1 mmol) at -78 °C, and the mixture was stirred at the temperature for 50 min. After addition of 1N HCl aq. and dilution with hexane, the organic layer was separated and washed with brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (hexane) gave **9** (1.01 g) as a white solid in 49% yield.

Data of 9

mp 156-160 °C (decomp.); ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm } 3.55 (3H, s), 1.20-1.10 (63H, m);$ ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm } 129.7, 127.1, 103.1, 102.2, 87.0, 80.5, 18.6, 11.2; IR (KBr) 3309,$ 2960, 2942, 2889, 2864, 2851, 2162, 2109, 1521 cm⁻¹; FD-LRMS m/z 692.5 ([M+2]⁺, 34%), 691.5 ([M+1]⁺, 66), 690.5 (M⁺, BP).

Preparation of 10

To a solution of **9** (760 mg, 1.10 mmol) and **18b** (1.55 g, 3.73 mmol) in 1:1 THF/ⁱPr₂NH (44 mL) were added

 $Pd(PPh_3)_4$ (114 mg, 0.0987 mmol) and CuI (29 mg, 0.15 mmol) at 60 °C under a nitrogen atmosphere, and the mixture was stirred at the temperature for 36 h. After addition of diethyl ether, the resulting precipitates were removed by filtration. The filtrate was concentrated by evaporation, and then purified by column chromatography on SiO₂ (4:1 chloroform/hexane) to give **10** (1.25 g) as a white solid in 73% yield.

An analytical sample was obtained as colorless crystals by slow evaporation from hexane.

Data of 10 $[X = CH_2(cHex)]$

mp 247-248 °C (decomp.); ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.48}$ (6H, d, J = 8.4 Hz), 7.16 (6H, d, J = 8.4 Hz), 3.54 (6H, d, J = 7.2 Hz), 1.76-1.58 (15H, br.m), 1.51-1.36 (3H, br.m), 1.43 (27H, s), 1.21-0.84 (78H, br.m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 154.6}$, 143.0, 132.1, 128.4, 127.8, 126.4, 120.2, 103.1, 102.3, 98.5, 86.8, 80.1, 55.4, 36.7, 30.7, 28.3, 26.4, 25.8, 18.6, 11.2; IR (KBr) 2926, 2863, 2214, 2154, 1703, 1603, 1508, 1450 cm⁻¹; FD-LRMS m/z 1554.1 ([M+2]⁺, 74%), 1553.1 ([M+1]⁺, BP), 1552.1 (M⁺, 81), 1453.1 ([M+1–BOC+H]⁺, 25), 1353.0 ([M+1–BOC×2+2H]⁺, 15), 1252.9 ([M+1–BOC×3+3H]⁺, 31); Anal. Calcd. for C₉₉H₁₄₁N₃O₆Si₃ C 76.54, H 9.15, N 2.70, Found C 76.58, H 9.45, N 2.52.

Preparation of 11a $[X = CH_2(cHex), Y = (R)-CHMe(cHex)]$

To a refluxed solution of **21a** (1.05 g, 2.20 mmol) and BnNEt₃Cl (6.5 mg, 0.029 mmol) in CH₂Cl₂ (15 mL) was added SOCl₂ (0.23 mL, 3.2 mmol), and the mixture was further refluxed for 1 h. After removal of the solvent by evaporation, the resulting solid (**21a'**) was dried *in vacuo* and dissolved in toluene (10 mL) [acid chloride preparation].

To a solution of **10** (1.06 g, 0.682 mmol) in CH_2Cl_2 (70 mL) was added TFA (6.7 mL), and the mixture was stirred at room temperature for 75 min, and then diluted with CH_2Cl_2 (210 mL). The diluted reaction mixture was quenched by addition of satd. NaHCO₃ aq. The organic layer was separated, and then dried over MgSO₄. Chromatographic separation on SiO₂ (2:3 dichloromethane/hexane) gave 1,3,5-tris[*p*-(*N*-cyclohexylmethylamino)phenylethynyl]-2,4,6-tris(triisopropylsilylethynyl)benzene **10'** (823 mg) as a yellow solid in 96% yield [deprotection of BOC].

To a solution of **10'** (823 mg, 0.657 mmol) and Et_3N (1.4 mL, 10 mmol) in toluene (11 mL) were added the freshly prepared toluene solution (10 mL) containing the acid chloride **21a'** and extra toluene (6+6 mL) at room temperature, and the mixture was stirred at 80 °C for 14 h. After addition of 1N NaOH aq., the organic layer was separated and washed with water and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **11a** (1.60 g) as a white solid in 93% yield.

An analytical sample was obtained as a white solid by further purification through GPC (chloroform, UV detected by 254 nm and RI).

Data of 11a [X = $CH_2(CHex)$, Y = (R)-CHMe(CHex)]

mp 153-155 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.48}$ (6H, d, J = 8.0 Hz), 7.33 (6H, d, J = 8.0 Hz), 7.10 (6H, d, J = 7.6 Hz), 7.03 (6H, d, J = 7.6 Hz), 6.88 (6H, d, J = 8.0 Hz), 6.62 (6H, d, J = 8.0 Hz), 4.41 (3H, br.s), 3.82 (3H, dd, J = 7.2, 13.6 Hz), 3.75 (3H, dd, J = 7.2, 13.6 Hz), 2.03 (3H, br.d), 1.85-1.43 (33H, br.m), 1.27-0.90 (102H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.8}, 169.4, 143.6,$

141.0, 138.3, 138.0, 136.7, 132.5, 131.3, 128.3, 128.3, 128.0, 127.6, 126.8, 121.0, 103.0, 102.5, 97.8, 92.4, 87.7, 58.9, 55.8, 41.2, 36.4, 30.9, 30.9, 30.8, 30.3, 26.3, 26.2, 26.0, 25.9, 25.8, 18.7, 16.7, 11.2; IR (KBr) 2925, 2861, 2211, 2153, 1655, 1650, 1601, 1504, 1484, 1449, 1403 cm⁻¹; FD-LRMS m/z 2632.0 ($[M+3]^+$, 69%), 2631.0 ($[M+2]^+$, BP), 2630.0 ($[M+1]^+$, 95), 2629.0 (M^+ , 57); $[\alpha]_D^{24}$ –37.7 (*c* 0.29 in CHCl₃); Anal. Calcd. for C₁₅₀H₁₈₃N₆O₆I₃Si₃ C 68.47, H 7.01, N 3.19, Found C 68.61, H 7.21, N 3.12.

Preparation of 11b $[X = Y = CH_2(cHex)]$

To a refluxed solution of **21b** (1.11 g, 2.40 mmol) and BnNEt₃Cl (12 mg, 0.053 mmol) in CH₂Cl₂ (18 mL) was added SOCl₂ (0.24 mL, 3.3 mmol), and the mixture was further refluxed for 10 h. After removal of the solvent by evaporation, the resulting solid (**21b'**) was dried *in vacuo* and dissolved in toluene (8 mL) [acid chloride preparation].

To a solution of **10** (1.10 g, 0.710 mmol) in CH_2Cl_2 (72 mL) was added TFA (7.0 mL), and the mixture was stirred at room temperature for 85 min, and then diluted with CH_2Cl_2 (210 mL). The diluted reaction mixture was quenched by addition of satd. NaHCO₃ aq. The organic layer was separated, and then dried over MgSO₄. Chromatographic separation on SiO₂ (2:3 dichloromethane/hexane) gave **10'** (832 mg) as a yellow solid in 93% yield [deprotection of BOC].

To a solution of **10'** (832 mg, 0.664 mmol) and Et_3N (1.4 mL, 10 mmol) in toluene (11 mL) were added the freshly prepared toluene solution (8 mL) containing the acid chloride **21b'** and extra toluene (6+6 mL) at room temperature, and the mixture was stirred at 80 °C for 12 h. After addition of 1N NaOH aq., the organic layer was separated and washed with water and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **11b** (1.65 g) as a white solid in 96% yield.

An analytical sample was obtained as a white solid by further purification through GPC (chloroform, UV detected by 254 nm and RI).

Data of 11b $[X = Y = CH_2(cHex)]$

mp 138-140 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.49} (6H, d, <math>J = 8.4 \text{ Hz})$, 7.33 (6H, d, J = 8.4 Hz), 7.12 (6H, d, J = 8.0 Hz), 7.06 (6H, d, J = 8.0 Hz), 6.90 (6H, d, J = 8.4 Hz), 6.65 (6H, d, J = 8.4 Hz), 3.79 (6H, d, J = 6.8 Hz), 3.70 (6H, d, J = 7.2 Hz), 1.75-1.48 (36H, br.m), 1.22-0.88 (93H, br.m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.4}$, 143.5, 143.2, 138.2, 137.3, 137.1, 132.5, 129.2, 128.3, 128.2, 128.0, 126.9, 121.1, 103.0, 102.5, 97.7, 91.3, 87.6, 55.9, 55.8, 36.4, 36.2, 30.9, 30.8, 26.3, 25.8, 25.7, 18.7, 18.5, 11.2; IR (KBr) 2924, 2861, 2212, 2155, 1654, 1650, 1602, 1505, 1485, 1449, 1406 cm⁻¹; FD-LRMS m/z 2589.9 ([M+3]⁺, 69%), 2588.9 ([M+2]⁺, BP), 2587.9 ([M+1]⁺, 99), 2586.9 (M⁺, 56); Anal. Calcd. for C₁₄₇H₁₇₇N₆O₆I₃Si₃ C 68.20, H 6.89, N 3.25, Found C 68.16, H 6.98, N 3.21.

Preparation of (R,R,R)-1a [X = CH₂(cHex), Y = (R)-CHMe(cHex)]

To a solution of **11a** (217 mg, 82.5 μ mol), Pd(PPh₃)₄ (143 mg, 124 μ mol) and CuI (12 mg, 63 μ mol) in Et₃N (83 mL) was added a solution of TBAF (0.26 mmol) in THF (8.25 mL) at 55 °C over a period of 12 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was further stirred at the temperature for 1.5 h. After removal of a solid by filtration, the filtrate was concentrated by evaporation and dissolved in

chloroform. The solution was washed with 1N HCl aq. and satd. NaHCO₃ aq., and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-20% ethyl acetate/chloroform) gave a mixture containing (R,R,R)-1a, which was further purified by GPC (chloroform, detected by UV 254 nm and RI) and PTLC (SiO₂, 20% ethyl acetate/chloroform) to give (R,R,R)-1a (3.9 mg) as a white solid in 2.7% yield.

Data of (R,R,R)-1a [X = CH₂(cHex), Y = (R)-CHMe(cHex)]

mp > 300 °C; ¹H NMR δ_{H} (400 MHz, CDCl₃, TMS)/ppm 7.34 (6H, d, *J* = 8.4 Hz), 7.28 (6H, d, *J* = 8.4 Hz), 7.11 (6H, d, *J* = 8.4 Hz), 7.08 (6H, d, *J* = 8.4 Hz), 6.88 (6H, d, *J* = 8.4 Hz), 6.84 (6H, d, *J* = 8.4 Hz), 4.36 (3H, br.dq), 3.84 (3H, dd, *J* = 7.2, 13.6 Hz), 3.73 (3H, dd, *J* = 6.8, 13.6 Hz), 2.00 (3H, br.d), 1.83-1.50 (33H, br.m), 1.30-0.88 (30H, br.m), 1.19 (9H, d, *J* = 6.8 Hz); ¹³C NMR δ_{C} (100 MHz, CDCl₃)/ppm 169.4, 169.4, 144.0, 142.8, 138.1, 137.1, 132.2, 131.9, 128.5, 128.4, 128.3, 128.0, 127.7, 126.5, 120.8, 119.9, 99.3, 98.9, 86.7, 55.5, 41.5, 36.3, 30.9, 30.9, 30.7, 30.7, 26.3, 26.2, 26.0, 26.0, 25.7, 16.8; IR (KBr) 2925, 2851, 2199, 1656, 1650, 1600, 1510, 1449 cm⁻¹; FD-LRMS m/z 1778.9 ([M+2]⁺, 81%), 1777.9 ([M+1]⁺, BP), 1776.9 (M⁺, 68); UV-Vis λ_{max} (CH₂Cl₂)/nm (log_E) 315 (5.00); CD λ (CH₂Cl₂)/nm (Δ_{E}) 418 (+0.4), 336 (-3.8), 307 (-0.7), 274 (-7.9); [α]_D²⁴ -62.4 (*c* 0.062 in CHCl₃); FD-HRMS Calcd. for C₁₂₃H₁₂₀N₆O₆ 1776.92693, Found 1776.92978.

Preparation of 1b $[X = Y = CH_2(cHex)]$

To a solution of **11b** (218 mg, 84.2 μ mol), Pd(PPh₃)₄ (145 mg, 126 μ mol) and CuI (11 mg, 58 μ mol) in Et₃N (84 mL) was added a solution of TBAF (0.27 mmol) in THF (8.35 mL) at 55 °C over a period of 12 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was further stirred at the temperature for 1.5 h. After removal of a solid by filtration, the filtrate was concentrated by evaporation and dissolved in chloroform. The solution was washed with 1N HCl aq. and satd. NaHCO₃ aq., and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-20% ethyl acetate/chloroform) gave a mixture containing **1b**, which was further purified by gel permeation chromatography (GPC, chloroform, detected by UV 254 nm and RI) and preparative thin-layer chromatography (PTLC, SiO₂, 20% ethyl acetate/chloroform) to give **1b** (3.0 mg) as a white solid in 2.1% yield.

Data of 1b $[X = Y = CH_2(cHex)]$

mp > 300 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.33}$ (12H, d, J = 8.4 Hz), 7.11 (12H, s), 6.88 (12H, d, J = 8.4 Hz), 3.80 (12H, d, J = 7.2 Hz), 1.76-1.53 (36H, br.m), 1.22-0.94 (30H, br.m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.3}$, 144.0, 137.3, 132.2, 128.5, 127.8, 126.6, 120.1, 99.0, 86.7, 56.7, 36.3, 30.9, 26.3, 25.8; IR (KBr) 2923, 2851, 2200, 1656, 1649, 1600, 1510, 1449 cm⁻¹; FD-LRMS m/z 1736.8 ([M+2]⁺, 91%), 1735.8 ([M+1]⁺, BP), 1734.8 (M⁺, 89); UV-Vis $\lambda_{max}(CH_2Cl_2)/\text{nm}$ (logε) 324 (4.99); FD-HRMS Calcd. for $C_{120}H_{114}N_6O_6$ 1734.87998, Found 1734.87793.

Preparation of 13b [X = CH₂(cHex)]

To a solution of 12^2 (2.12 g, 7.50 mmol) and 18b (3.51 g, 8.46 mmol) in 1:1 THF/ⁱPr₂NH (98 mL) were added Pd(PPh₃)₄ (261 mg, 0.226 mmol) and CuI (64 mg, 0.34 mmol) at 60 °C under a nitrogen atmosphere, and the mixture was stirred at the temperature for 2 d. After addition of hexane, the resulting precipitates were

removed by filtration. The filtrate was concentrated by evaporation, and then purified by column chromatography on SiO₂ (1:1-2:1 dichloromethane/hexane) to give **13b** (2.95 g) as a pale yellow oil in 69% yield.

An analytical sample was obtained as a colorless oil by further purification through GPC (chloroform, detected by UV 254 nm and RI).

Data of 13b $[X = CH_2(cHex)]$

¹H NMR δ_H(400 MHz, CDCl₃, TMS)/ppm 7.54-7.49 (2H, m), 7.48 (2H, d, J = 8.4 Hz), 7.31-7.24 (2H, m), 7.16 (2H, d, J = 8.4 Hz), 3.52 (2H, d, J = 7.2 Hz), 1.74-1.60 (5H, br.m), 1.52-1.41 (1H, m), 1.43 (9H, s), 1.22-1.04 (24H, m), 0.99-0.85 (2H, br.m); ¹³C NMR δ_C(100 MHz, CDCl₃)/ppm 154.7, 142.9, 132.8, 132.0, 132.0, 128.0, 127.8, 126.7, 125.9, 120.5, 105.4, 95.0, 92.8, 88.2, 80.2, 55.5, 36.8, 30.7, 28.3, 26.5, 25.8, 18.7, 11.3; IR (KBr) 2926, 2863, 2220, 2157, 1702, 1604, 1513, 1462 cm⁻¹; EI-LRMS m/z 569 (M⁺, 12%), 513 ([M^{-t}butyl+H]⁺, 13), 469 ([M–BOC+H]⁺, BP); Anal. Calcd. for C₃₇H₅₁NO₂Si C 77.98, H 9.02, N 2.46, Found C 78.10, H 9.33, N 2.43.

Preparation of 13c [X = nBu]

To a solution of **18c** (1.82 g, 4.85 mmol), Pd(PPh₃)₄ (149 mg, 129 μ mol) and CuI (37 mg, 0.19 mmol) in 1:1 THF/^{*i*}Pr₂NH (45 mL) was added a solution of **12**² (0.609 g, 2.15 mmol) in 1:1 THF/^{*i*}Pr₂NH (4 mL) at 50 °C under an argon atmosphere, and the mixture was stirred at 60 °C for 2 h. To the reaction mixture was added the same solution of **12** (0.609 g, 2.15 mmol) in 1:1 THF/^{*i*}Pr₂NH (4 mL), and the mixture was further stirred at 60 °C for 13 h. After removal of a solid by filtration, the filtrate was concentrated by evaporation, and then purified by column chromatography on SiO₂ (1:1 dichloromethane/hexane) to give **13c** (1.93 g) as a pale yellow oil in 85% yield.

An analytical sample was obtained as a pale yellow oil by further purification through GPC (chloroform, detected by UV 254 nm and RI).

Data of 13c [X = nBu]

¹H NMR δ_H(400 MHz, CDCl₃, TMS)/ppm 7.53-7.47 (2H, m), 7.49 (2H, d, *J* = 8.4 Hz), 7.31-7.22 (2H, m), 7.16 (2H, d, *J* = 8.4 Hz), 3.64 (2H, d, *J* = 7.5 Hz), 1.52 (2H, quint, *J* = 7.5 Hz), 1.44 (9H, s), 1.31 (2H, sext, *J* = 7.5 Hz), 1.12 (21H, s), 0.90 (3H, t, *J* = 7.5 Hz); ¹³C NMR δ_C(75 MHz, CDCl₃)/ppm 154.4, 142.6, 132.7, 132.0, 128.0, 127.8, 126.5, 125.8, 125.8, 120.5, 105.4, 95.0, 92.8, 88.2, 80.2, 49.5, 30.5, 28.3, 19.9, 18.7, 13.7, 11.3; IR (KBr) 2960, 2942, 2864, 2218, 2157, 1702, 1604, 1513, 1463 cm⁻¹; EI-LRMS m/z 529 (M⁺, 33%), 473 ([M^{-/b}utyl+H]⁺, 29), 429 ([M–BOC+H]⁺, BP); Anal. Calcd. for C₃₄H₄₇NO₂Si C 77.07, H 8.94, N 2.64, Found C 76.64, H 9.12, N 2.71.

Preparation of 14a $[X = CH_2(cHex), Y = (R)-CHMe(cHex)]$

To a refluxed solution of **21a** (931 mg, 1.95 mmol) and BnNEt₃Cl (4.7 mg, 0.021 mmol) in CH₂Cl₂ (13 mL) was added SOCl₂ (0.19 mL, 2.6 mmol), and the mixture was further refluxed for 3 h. After removal of the solvent by evaporation, the resulting solid (**21a'**) was dried *in vacuo* and dissolved in toluene (10 mL) [acid chloride preparation].

To a solution of **13b** (2.08 g, 3.65 mmol) in CH_2Cl_2 (126 mL) was added TFA (12 mL), and the mixture was stirred at room temperature for 40 min, and then diluted with CH_2Cl_2 (360 mL). The diluted reaction mixture was quenched by addition of satd. NaHCO₃ aq. The organic layer was separated, and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:4 dichloromethane/hexane) gave 1-[p-(N-cyclohexylmethylamino)phenylethynyl]-2-(triisopropylsilylethynyl)benzene**13b'**(830 mg for**14a**, 673 mg for**14b**) as a pale yellow solid in 88% yield [deprotection of BOC].

To a solution of **13b'** (830 mg, 1.77 mmol) and Et_3N (1.2 mL, 8.6 mmol) in toluene (8.2 mL) were added the freshly prepared toluene solution (10 mL) containing the acid chloride **21a'** and extra toluene (4+3 mL) at room temperature, and the mixture was stirred at 80 °C for 1 h. After addition of 1N NaOH aq. and ethyl acetate, the organic layer was separated and washed with water and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **14a** (1.59 g) as a white solid in 97% yield.

An analytical sample was obtained as a white solid by further purification through GPC (chloroform, UV detected by 254 nm and RI).

Data of 14a [X = $CH_2(CHex)$, Y = (R)-CHMe(CHex)]

mp 96-97 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.57-7.45}$ (4H, m), 7.35 (2H, d, J = 8.4 Hz), 7.31-7.24 (2H, m), 7.08 (2H, br.d), 7.04 (2H, br. d), 6.88 (2H, br.d), 6.63 (2H, br.d), 4.42 (1H, br.s), 3.81-3.71 (2H, m), 2.05 (1H, br.d), 1.82-1.50 (11H, br.m), 1.29-0.89 (34H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.8}, 169.6, 143.3, 141.1, 138.1, 137.9, 136.9, 132.8, 132.4, 132.0, 131.4, 128.1, 128.0, 127.6, 127.2, 125.9, 125.5, 121.4, 105.3, 95.1, 92.3, 92.0, 89.3, 58.8, 55.8, 41.3, 36.3, 30.9, 30.8, 30.3, 26.3, 26.2, 26.0, 25.9, 25.8, 18.7, 16.7, 11.3; IR (KBr) 2925, 2861, 2156, 1655, 1650, 1602, 1510, 1449 cm⁻¹; FD-LRMS m/z 930.5 ([M+2]⁺, 25%), 929.5 ([M+1]⁺, 67), 928.5 (M⁺, BP); [<math>\alpha$]_D²³ –53.3 (*c* 0.19 in CHCl₃); Anal. Calcd. for C₅₄H₆₅N₂O₂ISi C 69.81, H 7.05, N 3.02, Found C 69.69, H 6.98, N 3.01.

Preparation of 14b $[X = Y = CH_2(cHex)]$

To a refluxed solution of **21b** (732 mg, 1.58 mmol) and BnNEt₃Cl (4.1 mg, 0.018 mmol) in CH₂Cl₂ (11 mL) was added SOCl₂ (0.16 mL, 2.2 mmol), and the mixture was further refluxed for 20 h. After removal of the solvent by evaporation, the resulting solid (**21b'**) was dried *in vacuo* and dissolved in toluene (7 mL) [acid chloride preparation].

To a solution of **13b'** (673 mg, 1.43 mmol) and Et_3N (1.0 mL, 7.2 mmol) in toluene (6.5 mL) were added the freshly prepared toluene solution (7 mL) containing the acid chloride **21b'** and extra toluene (3+3 mL) at room temperature, and the mixture was stirred at 80 °C for 80 min. After addition of 1N NaOH aq. and ethyl acetate, the organic layer was separated and washed with water and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **14b** (1.30 g) as a white solid in 99% yield.

An analytical sample was obtained as a white solid by further purification through GPC (chloroform, UV detected by 254 nm and RI).

Data of 14b $[X = Y = CH_2(cHex)]$

mp 92-93 °C; ¹H NMR δ_{H} (400 MHz, CDCl₃, TMS)/ppm 7.54-7.49 (2H, m), 7.50 (2H, d, J = 8.4 Hz),

7.35 (2H, d, J = 8.4 Hz), 7.30-7.25 (2H, m), 7.11 (2H, d, J = 8.4 Hz), 7.06 (2H, d, J = 8.4 Hz), 6.90 (2H, d, J = 8.4 Hz), 6.66 (2H, d, J = 8.4 Hz), 3.77 (2H, d, J = 7.2 Hz), 3.70 (2H, d, J = 7.6 Hz), 1.75-1.47 (12H, m), 1.27-0.91 (31H, m); ¹³C NMR $\delta_{C}(100$ MHz, CDCl₃)/ppm 169.7, 169.5, 143.2, 138.2, 137.3, 137.1, 132.7, 132.4, 132.0, 129.3, 128.1, 128.0, 127.2, 125.8, 125.5, 121.5, 105.2, 95.0, 92.0, 91.3, 89.3, 55.9, 55.8, 36.3, 36.2, 30.9, 30.8, 26.3, 26.3, 25.8, 25.7, 18.7, 11.3; IR (KBr) 2924, 2861, 2156, 1655, 1650, 1601, 1510, 1449 cm⁻¹; FD-LRMS m/z 916.5 ([M+2]⁺, 25%), 915.5 ([M+1]⁺, 67), 914.5 (M⁺, BP); Anal. Calcd. for C₅₃H₆₃N₂O₂ISi C 69.56, H 6.94, N 3.06, Found C 69.20, H 6.87, N 3.06.

Preparation of 14c [X = Y = nBu]

To a refluxed solution of **21c** (1.20 g, 2.83 mmol) and BnNEt₃Cl (11 mg, 0.046 mmol) in CH₂Cl₂ (20 mL) was added SOCl₂ (0.28 mL, 3.8 mmol), and the mixture was further refluxed for 12 h. After removal of the solvent by evaporation, the resulting solid (**21c'**) was dried *in vacuo* and dissolved in toluene (15 mL) [acid chloride preparation].

To a solution of **13c** (1.53 g, 2.89 mmol) in CH_2Cl_2 (100 mL) was added TFA (9.4 mL), and the mixture was stirred at room temperature for 40 min, and then diluted with CH_2Cl_2 (290 mL). The diluted reaction mixture was quenched by addition of satd. NaHCO₃ aq. The organic layer was separated, and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:4 dichloromethane/hexane) gave 1-[*p*-(*N*-butylamino)phenylethynyl]-2-(triisopropylsilylethynyl)benzene **13c'** (1.11 g for **9c**) as a pale yellow solid in 89% yield [deprotection of BOC].

To a solution of **13c'** (1.11 g, 2.58 mmol) and Et_3N (2.0 mL, 14 mmol) in toluene (12 mL) were added the freshly prepared toluene solution (15 mL) containing the acid chloride **21c'** and extra toluene (5+4 mL) at room temperature, and the mixture was stirred at 80 °C for 1 h. After addition of 1N NaOH aq. and ethyl acetate, the organic layer was separated and washed with water and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **14c** (2.02 g) as a yellow solid in 94% yield.

An analytical sample was obtained as a white solid by recrystallization from chloroform and hexane.

Data of 14c [X = Y = *n*Bu]

mp 140.0-140.5 °C; ¹H NMR $\delta_{H}(300 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.54-7.49}$ (2H, m), 7.51 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.29-7.25 (2H, m), 7.12 (2H, d, J = 8.4 Hz), 7.07 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.4 Hz), 6.65 (2H, d, J = 8.4 Hz), 3.88 (2H, t, J = 7.5 Hz), 3.81 (2H, t, J = 7.5 Hz), 1.61-1.47 (4H, m), 1.40-1.24 (4H, m), 0.90 (3H, t, J = 7.5 Hz), 0.88 (3H, t, J = 7.5 Hz); ¹³C NMR $\delta_{C}(75 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.3}$, 169.1, 142.9, 138.3, 137.3, 137.0, 132.8, 132.5, 132.1, 129.5, 128.2, 128.1, 128.0, 127.4, 125.9, 125.5, 121.8, 105.3, 95.1, 92.0, 91.5, 89.4, 50.1, 50.0, 29.8, 29.7, 20.1, 20.1, 18.7, 13.8, 13.8, 11.3; IR (KBr) 2955, 2941, 2863, 2155, 1631, 1602, 1511, 1484 cm⁻¹; FD-LRMS m/z 836.4 ([M+2]⁺, 24%), 835.4 ([M+1]⁺, 70), 834.4 (M⁺, BP); Anal. Calcd. for C₄₇H₅₅N₂O₂ISi C 67.61, H 6.64, N 3.36, Found C 67.50, H 6.68, N 3.10.

Preparation of (R)**-3a** [X = CH₂(cHex), Y = (R)-CHMe(cHex)]

To a solution of 14a (183 mg, 197 µmol), Pd(PPh₃)₄ (43 mg, 37 µmol) and CuI (11 mg, 58 µmol) in Et₃N (100

mL) was added a solution of TBAF (0.21 mmol) in THF (9.10 mL) at 54-58 °C over a period of 1 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was further stirred at the temperature for 12 h. After removal of the solvent by evaporation, the resulting solid was dissolved in chloroform and washed with 1N HCl aq. and satd. NaHCO₃ aq., and then dried over MgSO₄. Chromatographic separation on SiO₂ (chloroform) gave a mixture containing (*R*)-**3a**, which was further purified by GPC (chloroform, detected by UV 254 nm and RI) to give (*R*)-**3a** (17 mg) as a white solid in 13% yield.

Data of (R)-3a [X = $CH_2(CHex)$, Y = (R)-CHMe(CHex)]

mp > 300 °C; ¹H NMR δ_H(400 MHz, CDCl₃, TMS)/ppm 7.53-7.49 (2H, m), 7.37-7.32 (2H, m), 7.30 (2H, d, J = 8.4 Hz), 7.25 (2H, d, J = 8.4 Hz), 7.11 (2H, d, J = 8.8 Hz), 7.08 (2H, d, J = 8.8 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.84 (2H, d, J = 8.4 Hz), 4.40 (1H, br.dq), 3.86 (1H, dd, J = 7.6, 13.6 Hz), 3.77 (1H, dd, J = 7.2, 13.6 Hz), 2.00 (1H, br.d), 1.85-1.55 (11H, br.m), 1.30-0.91 (10H, br.m), 1.21 (3H, d, J = 6.8 Hz); ¹³C NMR δ_C(100 MHz, CDCl₃)/ppm 169.5, 169.4, 143.5, 142.2, 138.2, 137.2, 132.0, 131.8, 130.2, 130.0, 128.5, 128.4, 128.3, 128.3, 128.2, 127.0, 126.9, 126.4, 121.4, 120.5, 93.8, 93.4, 88.5, 88.5, 55.6, 41.6, 36.3, 30.9, 30.9, 30.7, 30.7, 26.3, 26.3, 26.1, 26.0, 25.8, 16.8; IR (KBr) 2924, 2851, 2213, 1655, 1649, 1639, 1633, 1599, 1511, 1449, 1446 cm⁻¹; FD-LRMS m/z 646.4 ([M+2]⁺, 15%), 645.4 ([M+1]⁺, 52), 644.4 (M⁺, BP); UV-Vis λ_{max}(CH₂Cl₂)/nm (logε) 277 (4.62); CD λ(CH₂Cl₂)/nm (Δε) 316 (-1.1), 290 (+0.1), 271 (-1.8); [α]_D²⁴ -30.8 (*c* 0.074 in CHCl₃); Anal. Calcd. for C₄₅H₄₄N₂O₂ C 83.82, H 6.88, N 4.34, Found C 83.81, H 6.98, N 4.30.

Preparation of 3b $[X = Y = CH_2(cHex)]$

To a solution of **14b** (104 mg, 114 μ mol), Pd(PPh₃)₄ (14 mg, 12 μ mol) and CuI (4.9 mg, 26 μ mol) in Et₃N (21 mL) was added a solution of TBAF (0.12 mmol) in THF (2.30 mL) at 83 °C over a period of 5 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was further stirred at the temperature for 15 min. After removal of the solvent by evaporation, the resulting solid was dissolved in ethyl acetate and washed with 1N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave a mixture containing **3b**, which was further purified by GPC (chloroform, detected by UV 254 nm and RI) to give **3b** (13 mg) as a white solid in 18% yield.

Data of 3b $[X = Y = CH_2(cHex)]$

mp 287-298 °C (decomp.); ¹H NMR δ_{H} (400 MHz, CDCl₃, TMS)/ppm 7.52 (2H, dd, *J* = 3.2, 6.0 Hz), 7.35 (2H, dd, *J* = 3.2, 6.0 Hz), 7.29 (4H, d, *J* = 8.4 Hz), 7.11 (4H, s), 6.87 (4H, d, *J* = 8.4 Hz), 3.82 (4H, d, *J* = 7.2 Hz), 1.76-1.59 (12H, br.m), 1.22-0.94 (10H, br.m); ¹³C NMR δ_{C} (100 MHz, CDCl₃)/ppm 169.3, 143.5, 137.4, 132.1, 130.2, 128.4, 128.3, 126.9, 126.5, 120.7, 93.5, 88.5, 55.7, 36.3, 30.9, 26.3, 25.8; IR (KBr) 2923, 2850, 2214, 1654, 1649, 1644, 1633, 1599, 1512, 1449, 1446 cm⁻¹; FD-LRMS m/z 632.3 ([M+2]⁺, 15%), 631.3 ([M+1]⁺, 52), 630.3 (M⁺, BP); UV-Vis λ_{max} (CH₂Cl₂)/nm (logε) 280 (4.62); Anal. Calcd. for C₄₄H₄₂N₂O₂ C 83.78, H 6.71, N 4.44, Found C 83.50, H 6.83, N 4.35.

Preparation of 3c [X = Y = nBu]

To a solution of 14c (207 mg, 248 µmol), Pd(PPh₃)₄ (29 mg, 25 µmol) and CuI (12 mg, 63 µmol) in Et₃N (45

mL) was added a solution of TBAF (0.28 mmol) in THF (5.0 mL) at 60 °C over a period of 5 h using a syringe pump under an argon atmosphere, and the reaction mixture was further stirred at the temperature for 30 min. After removal of a solid by filtration, the filtrate was concentrated. The resulting solid was dissolved in ethyl acetate and washed with 1N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (chloroform) gave a mixture containing **3c**, which was further purified by GPC (chloroform, detected by UV 254 nm and RI) to give **3c** (15 mg) as a white solid in 11% yield.

Single-crystals were obtained from a solution of **3c** in chloroform under a hexane-diffusing atmosphere.

Data of 3c [X = Y = nBu]

mp > 208 °C (decomp.); ¹H NMR $\delta_{H}(300 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.52}$ (2H, dd, J = 3.3, 5.7 Hz), 7.35 (2H, dd, J = 3.3, 5.7 Hz), 7.30 (4H, d, J = 8.7 Hz), 7.11 (4H, s), 6.86 (4H, d, J = 8.7 Hz), 3.93 (4H, t, J = 7.5 Hz), 1.59 (4H, quint, J = 7.5 Hz), 1.35 (4H, sext, J = 7.5 Hz), 0.91 (6H, t, J = 7.5 Hz); ¹³C NMR $\delta_{C}(75 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 168.9}, 143.1, 137.2, 132.1, 130.2, 128.5, 128.3, 126.9, 126.6, 120.9, 93.5, 88.5, 50.0, 29.8, 20.2, 13.8; IR (KBr) 2959, 2930, 2870, 2858, 2212, 1647, 1601, 1511 cm⁻¹; FD-LRMS m/z 552.3 ([M+2]⁺, 11%), 551.3 ([M+1]⁺, 44), 550.3 (M⁺, BP); Anal. Calcd. for C₃₈H₃₄N₂O₂ C 82.88, H 6.22, N 5.09, Found C 83.03, H 6.35, N 4.91.$



Scheme S2 Preparation of (R,R,R)-4 and (R)-5. Reagents and yields; (a) 19b, Pd(PPh₃)₄, CuI, THF, Et₃N (55%); (b) 19a, TBAF, Pd(PPh₃)₄, CuI, CH₃CN, Et₂NH, THF (72%); (c) 19b, Pd(PPh₃)₄, CuI, THF, Et₃N (42%); (d) 19a, TBAF, Pd(PPh₃)₄, CuI, THF, Et₃N (82%). Regarding the new compound 19, see Scheme S3.

Preparation of 15

To a solution of **9** (194 mg, 0.281 mmol) and **19b** (529 mg, 1.26 mmol) in 1:2 THF/Et₃N (44 mL) were added Pd(PPh₃)₄ (97.7 mg, 0.0846 mmol) and CuI (18 mg, 0.095 mmol) at room temperature under a nitrogen atmosphere, and the mixture was stirred at 60 °C for 2 d. After dilution with diethyl ether and addition of 1N HCl aq., the organic layer was separated and washed with brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-20% ethyl acetate/chloroform) gave **15** (242 mg) as a white solid in 55% yield.

An analytical sample was obtained as colorless crystals by recrystallization from isopropyl alcohol.

Data of 15

mp 280-281 °C (decomp.); ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.32}$ (6H, d, J = 8.8 Hz), 7.30-7.13 (15H, m), 6.96 (6H, d, J = 8.8 Hz), 3.84 (6H, d, J = 7.2 Hz), 1.77-1.52 (15H, br.m), 1.20-0.82 (81H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 170.6}$, 144.1, 136.3, 132.4, 129.6, 128.7, 128.2, 127.9, 127.8, 127.0, 120.8, 102.9, 102.5, 97.9, 87.2, 55.7, 36.5, 31.0, 26.4, 25.9, 18.6, 11.1; IR (KBr) 2924, 2862, 2216, 2155, 1655, 1650, 1600, 1508 cm⁻¹; FD-LRMS m/z 1565.9 ([M+2]⁺, 75%), 1564.9 ([M+1]⁺, BP), 1563.9 (M⁺, 77); Anal. Calcd. for C₁₀₅H₁₂₉N₃O₃Si₃ C 80.56, H 8.31, N 2.68, Found C 80.69, H 8.50, N 2.61.

Preparation of (R,R,R)-4

To a solution of **15** (199 mg, 127 μ mol), **19a** (189 mg, 436 μ mol), Pd(PPh₃)₄ (44 mg, 38 μ mol) and CuI (14 mg, 74 μ mol) in 1:5 CH₃CN/Et₂NH (20 mL) was added a solution of TBAF (0.40 mmol) in 5:1:1 CH₃CN/Et₂NH/THF (2.30 mL) at 83-85 °C over a period of 10 h using a syringe pump under a nitrogen

atmosphere, and the reaction mixture was further stirred at the temperature for 0.5 h. The mixture was diluted with ethyl acetate and washed with 1N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (chloroform) gave a mixture containing (R,R,R)-4, which was further purified by PTLC (SiO₂, 10% ethyl acetate/chloroform) to give (R,R,R)-4 (185 mg) as a yellow solid in 72% yield.

An analytical sample was obtained as a yellow solid by reprecipitation from ethyl acetate and hexane.

Data of (R,R,R)-4

mp 143-149 °C (decomp.); ¹H NMR δ_{H} (400 MHz, CDCl₃, TMS)/ppm 7.42-7.14 (42H, m), 6.97 (12H, d, J = 8.4 Hz), 4.43 (3H, br.), 3.85 (6H, d, J = 7.2 Hz), 2.16 (3H, br.d), 1.91-1.56 (30H, br.m), 1.34-0.96 (33H, br.m), 1.27 (9H, d, J = 6.8 Hz); ¹³C NMR δ_{C} (100 MHz, CDCl₃)/ppm 170.6, 170.4, 144.8, 143.1, 137.0, 136.1, 132.4, 132.1, 129.8, 129.5, 129.4, 128.8, 128.6, 127.9, 127.8, 127.5, 127.3, 127.1, 121.1, 120.5, 98.9, 98.7, 87.9, 87.7, 60.1, 56.1, 41.5, 36.5, 31.0, 30.9, 30.5, 26.3, 26.3, 26.1, 26.1, 25.9, 17.0; IR (KBr) 2924, 2850, 2201, 1657, 1650, 1599, 1510 cm⁻¹; FD-LRMS m/z 2013.0 ([M+2]⁺, 81%), 2012.0 ([M+1]⁺, BP), 2011.0 (M⁺, 61); UV-Vis λ_{max} (CH₂Cl₂)/nm (logε) 368 (5.20); CD λ (CH₂Cl₂)/nm (Δε) 358 (-3.2), 321 (-2.0), 269 (-5.3); [α]_D²⁴ -53.1 (*c* 0.059 in CHCl₃); FD-HRMS Calcd. for C₁₄₁H₁₃₈N₆O₆ 2011.06778, Found 2011.06341.

Preparation of 16

To a solution of **19b** (1.52 g, 3.62 mmol), $Pd(PPh_3)_4$ (204 mg, 177 µmol) and CuI (33 mg, 0.17 mmol) in THF/Et₃N (80/170 mL) was added a solution of **12**² (977 mg, 3.46 mmol) in THF (10 mL) at 50 °C over a period of 12 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was further stirred at the temperature for 2 h. After removal of the solvents by evaporation, the resulting solid was dissolved in ethyl acetate, and washed with 1N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:1-2:1 dichloromethane/hexane-dichloromethane) gave a colored mixture containing **16**, which was suspended in hexane and collected by filtration to give **16** (828 mg) as a white solid in 42% yield.

An analytical sample was obtained as colorless crystals by recrystallization from methanol.

Data of 16

mp 142.5-143.0 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.53-7.44}$ (2H, m), 7.35 (2H, d, J = 8.8 Hz), 7.31-7.15 (7H, m), 6.98 (2H, d, J = 8.8 Hz), 3.83 (2H, d, J = 7.2 Hz), 1.79-1.59 (5H, br.m), 1.25-0.99 (27H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 170.6}$, 143.8, 136.3, 132.7, 132.3, 131.9, 129.5, 128.6, 128.0, 127.8, 127.2, 125.8, 125.5, 121.1, 105.2, 95.1, 92.1, 88.8, 55.8, 36.4, 30.9, 26.4, 25.8, 18.6, 11.2; IR (KBr) 2923, 2863, 2215, 2158, 1644, 1596, 1510 cm⁻¹; FD-LRMS m/z 575.4 ([M+2]⁺, 17%), 574.4 ([M+1]⁺, 49), 573.4 (M⁺, BP); Anal. Calcd. for C₃₉H₄₇NOSi C 81.62, H 8.25, N 2.44, Found C 81.73, H 8.50, N 2.44.

Preparation of (R)-5

To a solution of **16** (278 mg, 484 μ mol), **19a** (316 mg, 729 μ mol), Pd(PPh₃)₄ (32 mg, 28 μ mol), and CuI (6.1 mg, 32 μ mol) in THF/Et₃N (7.5/24 mL) was added a solution of TBAF (0.51 mmol) in THF (4.8 mL) at 50-55 °C over a period of 10 h using a syringe pump under a nitrogen atmosphere, and the reaction mixture was

further stirred at the temperature for 3.5 h. After removal of the solvents by evaporation, the resulting solid was dissolved in chloroform, and washed with 1N HCl aq. and satd. NaHCO₃ aq., and then dried over MgSO₄. Chromatographic separation on SiO₂ (chloroform) gave a colored mixture containing (*R*)-**5**, which was further purified by GPC (chloroform, detected by UV 254 nm) to give (*R*)-**5** (292 mg) as a white solid in 83% yield.

Data of (R)-5

mp 93-94 °C; ¹H NMR δ_H(400 MHz, CDCl₃, TMS)/ppm 7.53-7.49 (2H, m), 7.35 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 7.32-7.11 (12H, m), 6.97 (2H, d, *J* = 8.4 Hz), 6.96 (2H, d, *J* = 8.4 Hz), 4.47 (1H, br.s), 3.83 (2H, d, *J* = 7.6 Hz), 2.15 (1H, br.d), 1.86-1.60 (10H, m), 1.33-0.94 (11H, m), 1.23 (3H, d, *J* = 6.8 Hz); ¹³C NMR δ_C(100 MHz, CDCl₃)/ppm 170.7, 170.5, 144.0, 142.1, 137.1, 136.2, 132.2, 131.9, 131.8, 131.8, 129.6, 129.4, 129.2, 128.7, 128.4, 128.2, 128.2, 127.8, 127.7, 127.4, 125.4, 125.3, 121.6, 121.0, 92.7, 92.6, 89.2, 88.9, 59.5, 56.0, 41.5, 36.4, 30.9, 30.8, 30.5, 26.3, 26.3, 26.1, 26.0, 25.8, 16.8; IR (KBr) 2925, 2850, 2213, 1649, 1600, 1510 cm⁻¹; FD-LRMS m/z 724.5 ([M+2]⁺, 18%), 723.4 ([M+1]⁺, 58), 722.4 (M⁺, BP); UV-vis λ_{max} (CH₂Cl₂)/nm (logε) 291 (4.69); CD λ (CH₂Cl₂)/nm (Δ ε) 344 (+0.5), 290 (-5.5); [α]_D²³ -58.7 (*c* 0.0510 in CHCl₃); Anal. Calcd. for C₅₁H₅₀N₂O₂ C 84.73, H 6.97, N 3.87, Found C 84.73, H 7.15, N 3.84.



Scheme S3 Preparation of 18-21. Reagents and yields; (a) (*R*)-1-cyclohexylethylamine/aminomethylcyclohexane, CuI, L-proline, K_2CO_3 , DMSO (55% for 17a, 79% for 17b); (b) (BOC)₂O, DMAP, Et₃N, THF (88% for 18b/81% for 18c); (c) benzoyl chloride, DMAP, Et₃N, THF (92% for 19a/95% for 19b) (d) methyl 4-(chloroformyl)benzoate, DMAP, Et₃N, THF (91% for 20a/93% for 20b/95% for 20c); (e) LiOH or NaOH, THF, MeOH, H₂O (92% for 21a/95% for 21b/97% for 21c).

Preparation of 17a [R = (R)-CHMe(cHex)]

A mixture of 1,4-diiodobenzene (5.04 g, 15.3 mmol), (*R*)-1-cyclohexylethylamine (3.3 mL, 23 mmol), CuI (291 mg, 1.53 mmol), L-proline (348 mg, 3.02 mmol), K_2CO_3 (4.19 g, 30.3 mmol) and DMSO (27 mL) was stirred at 84 °C for 19 h. After dilution with ethyl acetate and water, the organic layer was separated and washed with brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:4 dichloromethane/hexane) gave **17a** (2.75 g) as a white solid in 55% yield.

Data of 17a [R = (R)-CHMe(cHex)]

mp 48-49 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.37}$ (2H, d, J = 8.8 Hz), 6.34 (2H, d, J = 8.8 Hz), 3.52 (1H, br.s), 3.25 (1H, br.m), 1.83-1.63 (5H, m), 1.46-1.36 (1H, m), 1.09 (3H, d, J = 6.4 Hz), 1.29-0.95 (5H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 147.5}$, 137.8, 115.1, 76.5, 53.0, 42.9, 29.7, 28.4, 26.6, 26.4, 26.3, 17.3; IR (KBr) 3421, 2977, 2963, 2918, 2846, 1587, 1492 cm⁻¹; EI-LRMS m/z 329 (M⁺, 22%), 246 ([M–cyclohexyl]⁺, BP); $[\alpha]_{D}^{24}$ –1.72 (*c* 0.56 in CHCl₃); Anal. Calcd. for C₁₄H₂₀NI C 51.08, H 6.12, N 4.25, Found C 51.28, H 6.15, N 4.26.

Preparation of 17b [R = CH₂(cHex)]

A mixture of 1,4-diiodobenzene (5.00 g, 15.2 mmol), aminomethylcyclohexane (3.0 mL, 23 mmol), CuI (290 mg, 1.52 mmol), L-proline (353 mg, 3.07 mmol), K_2CO_3 (4.19 g, 30.3 mmol) and DMSO (29 mL) was stirred at 62 °C for 12 h. After dilution with ethyl acetate and water, the organic layer was separated and washed with brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:4 dichloromethane/hexane) gave

17b (3.77 g) as a white solid in 79% yield.

Data of 17b [R = CH₂(cHex)]

mp 62-63 °C; ¹H NMR δ_{H} (400 MHz, CDCl₃, TMS)/ppm 7.39 (2H, d, *J* = 8.8 Hz), 6.37 (2H, d, *J* = 8.8 Hz), 3.74 (1H, br.s), 2.91 (2H, d, *J* = 3.6 Hz), 1.84-1.63 (5H, m), 1.61-1.49 (1H, m), 1.33-1.10 (3H, m), 1.04-0.91 (2H, m); ¹³C NMR δ_{C} (100 MHz, CDCl₃)/ppm 148.1, 137.6, 114.8, 77.0, 50.3, 37.4, 31.2, 26.5, 25.9; IR (KBr) 3412, 2924, 2847, 1595, 1498 cm⁻¹; EI-LRMS m/z 315 (M⁺, 43%), 232 ([M–cyclohexyl]⁺, BP); Anal. Calcd. for C₁₃H₁₈NI C 49.54, H 5.76, N 4.44, Found C 49.47, H 5.65, N 4.41.

Preparation of 18b [R = CH₂(cHex)]

To a solution of **17b** (10.7 g, 33.9 mmol) and DMAP (44 mg, 0.36 mmol) in THF (60 mL) were added $(BOC)_2O$ (14 g, 64 mmol) and Et₃N (9.5 mL, 68 mmol), and the mixture was refluxed for 5 d. During the period, $(BOC)_2O$ was added three times at an appropriate interval (7.6+7.6+7.9 g, total 106 mmol). After dilution with ethyl acetate, the solution was washed with 0.1 N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (3:7 dichloromethane/hexane-dichloromethane) gave **18b** (12.5 g) as a white solid in 88% yield.

An analytical sample was obtained as colorless crystals by recrystallization from hexane.

Data of 18b [R = CH₂(cHex)]

mp 73-74 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.63}$ (2H, d, J = 8.8 Hz), 6.95 (2H, d, J = 8.8 Hz), 3.47 (2H, d, J = 7.2 Hz), 1.73-1.59 (5H, m), 1.50-1.38 (1H, m), 1.42 (9H, s), 1.21-1.06 (3H, m), 0.97-0.84 (2H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 154.7}, 142.7, 137.7, 129.1, 90.2, 80.3, 55.7, 36.7, 30.7, 28.3, 26.4, 25.8; IR (KBr) 2984, 2922, 2852, 1686, 1487, 1449 cm⁻¹; EI-LRMS m/z 415 (M⁺, 13%), 359 ([M-^tbutyl+H]⁺, BP), 315 ([M-BOC+H]⁺, 24), 263 ([M-^tbutyl-cyclohexylmethyl+2H]⁺, 27), 232 ([M-BOC-cyclohexyl+H]⁺, 65), 57 (^tbutyl⁺, 93); Anal. Calcd. for C₁₈H₂₆NO₂I C 52.06, H 6.31, N 3.37, Found C 51.93, H 6.18, N 3.36.$

Preparation of 18c [R = *n*Bu]

To a solution of $17c^3$ (5.16 g, 18.8 mmol), DMAP (22 mg, 0.18 mmol) and Et₃N (5.4 mL, 39 mmol) in THF (40 mL) was added (BOC)₂O (8.18 g, 37.5 mmol), and the mixture was refluxed for 5 d. During the period, (BOC)₂O was added three times at an appropriate interval (4.0+4.5+4.2 g, total 58 mmol). After dilution with ethyl acetate, the solution was washed with 0.1 N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (3:7-8:2 dichloromethane/hexane) gave **18c** (5.72 g) as a white solid in 81% yield.

An analytical sample was obtained as colorless crystals by recrystallization from hexane.

Data of 18c [R = *n*Bu]

mp 64.0-65.0 °C; ¹H NMR $\delta_{H}(300 \text{ MHz}, \text{CDCI}_3, \text{TMS})/\text{ppm 7.63}$ (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.4 Hz), 3.59 (2H, t, J = 7.5 Hz), 1.49 (2H, quint, J = 7.5 Hz), 1.42 (9H, s), 1.29 (2H, sext, J = 7.5 Hz), 0.89 (3H, t, J = 7.5 Hz); ¹³C NMR $\delta_{C}(75 \text{ MHz}, \text{CDCI}_3)/\text{ppm 154.3}$, 142.5, 137.8, 129.0, 90.3, 80.3, 49.6, 30.6, 28.3, 19.9, 13.8; IR (KBr) 2966, 2928, 2862, 1908, 1682, 1585, 1485 cm⁻¹; EI-LRMS m/z 375 (M⁺,

9%), 319 ([M-^tbutyl+H]⁺, 68), 275 ([M-BOC+H]⁺, 13), 232 ([M-BOC-propyl+H]⁺, 34), 57 (^tbutyl⁺, BP); Anal. Calcd. for C₁₅H₂₂NO₂I C 48.01, H 5.91, N 3.73, Found C 47.88, H 5.84, N 3.36.

Preparation of 19a [R = (R)-CHMe(cHex)]

To an ice-cooled solution of **17a** (4.10 g, 12.4 mmol), DMAP (156 mg, 1.28 mmol) and Et₃N (3.6 mL, 26 mmol) in THF (125 mL) was added BzCl (3.0 mL, 26 mmol), and the mixture was refluxed for 27 h. After removal of a solid by filtration and the solvent by evaporation, the residue was dissolved in diethyl ether. The solution was washed with 1N NaOH aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (chloroform) gave **19a** (4.97 g) as a white solid in 92% yield.

An analytical sample was obtained as a white solid by suspending in hexane, followed by collection through filtration.

Data of 19a [R = (R)-CHMe(cHex)]

mp 91.5-92.0 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.52}$ (2H, d, *J* = 8.4 Hz), 7.26-7.12 (5H, m), 6.74 (2H, d, *J* = 8.4 Hz), 4.46 (1H, br.s), 2.12 (1H, br.d), 1.78-1.59 (5H, m), 1.17 (3H, d, *J* = 6.8 Hz), 1.31-0.92 (5H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 170.8}, 141.6, 137.9, 137.0, 131.4, 129.3, 128.3,$ 127.8, 92.0, 59.0, 41.4, 30.8, 30.4, 26.3, 26.1, 26.0, 16.81; IR (KBr) 2976, 2968, 2931, 2919, 2847,1631, 1576 cm⁻¹; EI-LRMS m/z 433 (M⁺, 6%), 350 ([M–cyclohexyl]⁺, 35), 323 ([M–cyclohexylethyl+H]⁺, $25), 105 (PhCO⁺, BP), 77 (Ph⁺, 15); [<math>\alpha$]_D²³ –87.7 (*c* 0.84 in CHCl₃); Anal. Calcd. for C₂₁H₂₄NOI C 58.21, H 5.58, N 3.23, Found C 58.28, H 5.50, N 3.21.

Preparation of 19b [R = CH₂(cHex)]

To an ice-cooled solution of **17b** (2.88 g, 9.14 mmol), DMAP (112 mg, 0.917 mmol) and Et_3N (2.6 mL, 19 mmol) in THF (90 mL) was added BzCl (1.2 mL, 8.3 mmol), and the mixture was refluxed for 2 h. After removal of a solid by filtration, the filtrate was diluted with diethyl ether. The solution was washed with satd. NaHCO₃ aq., and then dried over MgSO₄. Chromatographic separation on SiO₂ (1:1 chloroform/hexane-chloroform-1:9 ethyl acetate/chloroform) gave **19b** (3.65 g) as a white solid in 95% yield.

An analytical sample was obtained as colorless crystals by recrystallization from methanol.

Data of 19b $[R = CH_2(cHex)]$

mp 119.0-119.5 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.52}$ (2H, d, J = 8.4 Hz), 7.24-7.22 (3H, m), 7.21-7.15 (2H, m), 6.77 (2H, d, J = 8.4 Hz), 3.77 (2H, d, J = 7.2 Hz), 1.76-1.60 (6H, m), 1.23-0.97 (5H, m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 170.6}$, 143.8, 138.1, 136.2, 129.6, 129.4, 128.6, 127.9, 91.0, 56.0, 36.3, 30.9, 26.4, 25.8; IR (KBr) 2921, 2916, 2845, 1634, 1577, 1483 cm⁻¹; EI-LRMS m/z 419 (M⁺, 13%), 323 ([M–cyclohexylmethyl+H]⁺, 40), 105 (PhCO⁺, BP), 77 (Ph⁺, 24); Anal. Calcd. for C₂₀H₂₂NOI C 57.29, H 5.29, N 3.34, Found C 57.22, H 5.30, N 3.33.

Preparation of 20a [R = (R)-CHMe(cHex)]

To an ice-cooled solution of **17a** (2.75 g, 8.35 mmol), DMAP (102 mg, 0.836 mmol) and Et_3N (2.4 mL, 17 mmol) in THF (80 mL) was added methyl 4-(chloroformyl)benzoate (1.99 g, 9.99 mmol), and the mixture was

refluxed for 38 h. After dilution with ethyl acetate, the resulting precipitates were removed by filtration, and the filtrate was concentrated by evaporation. The residue was dissolved in ethyl acetate, and the solution was washed with 1N HCl aq. and brine, and then dried over MgSO₄. Chromatographic separation on SiO₂ (0-10% ethyl acetate/chloroform) gave **20a** (3.73 g) as a white solid in 91% yield.

An analytical sample was obtained as colorless crystals by recrystallization from 95% ethanol.

Data of 20a [R = (R)-CHMe(cHex)]

mp 151.0-151.5 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCl}_{3}, \text{TMS})/\text{ppm 7.83}$ (2H, br.d), 7.51 (2H, br.d), 7.28 (2H, br.d), 6.73 (2H, br.d), 4.50 (1H, br.s), 3.87 (3H, s), 2.11 (1H, br.d), 1.87-1.56 (5H, br.m), 1.32-0.92 (5H, br.m), 1.17 (3H, d, J = 7.2 Hz); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCl}_{3})/\text{ppm 169.8}, 166.3, 141.4, 140.9, 138.1, 131.4, 130.5, 129.1, 128.1, 92.5, 58.9, 52.2, 41.3, 30.8, 30.3, 26.2, 26.0, 26.0, 16.8; IR (KBr) 2987, 2974, 2932, 2915, 2849, 2841, 1725, 1633, 1486 cm⁻¹; EI-LRMS m/z 491 (M⁺, 5%), 408 ([M–cyclohexyl]⁺, 24), 381 ([M–cyclohexylethyl+H]⁺, 19), 163 ([M–N(cyclohexylethyl)(4-iodophenyl)]⁺, BP); <math>[\alpha]_{D}^{23}$ –80.9 (*c* 1.4 in CHCl₃); Anal. Calcd. for C₂₃H₂₆NO₃I C 56.22, H 5.33, N 2.85, Found C 56.17, H 5.25, N 2.83.

Preparation of 20b [R = CH₂(cHex)]

To an ice-cooled solution of **17b** (2.23 g, 7.07 mmol) and Et_3N (1.0 mL, 7.2 mmol) in THF (70 mL) was added methyl 4-(chloroformyl)benzoate (1.42 g, 7.16 mmol), and the mixture was stirred at room temperature for 17 h. After removal of the solvent by evaporation, the residue was purified by column chromatography on SiO₂ (0-5% ethyl acetate/chloroform) to give **20b** (3.14 g) as a white solid in 93% yield.

An analytical sample was obtained as colorless crystals by recrystallization from 95% ethanol.

Data of 20b [R = CH₂(cHex)]

mp 179.5-180.0 °C; ¹H NMR $\delta_{H}(400 \text{ MHz}, \text{CDCI}_{3}, \text{TMS})/\text{ppm 7.86}$ (2H, d, J = 8.4 Hz), 7.52 (2H, d, J = 8.4 Hz), 7.31 (2H, d, J = 8.4 Hz), 6.76 (2H, d, J = 8.4 Hz), 3.89 (3H, s), 3.78 (2H, d, J = 7.2 Hz), 1.80-1.58 (6H, br.m), 1.23-0.97 (5H, br.m); ¹³C NMR $\delta_{C}(100 \text{ MHz}, \text{CDCI}_{3})/\text{ppm 169.6}$, 166.3, 140.5, 138.4, 130.8, 129.4, 129.2, 128.4, 91.6, 55.9, 52.3, 36.3, 30.9, 26.3, 25.8; IR (KBr) 2944, 2927, 2915, 2849, 1721, 1683, 1488 cm⁻¹; EI-LRMS m/z 477 (M⁺, 20%), 381 ([M–cyclohexylmethyl+H]⁺, 60), 163 ([M–N(cyclohexylmethyl)(4-iodophenyl)]⁺, BP); Anal. Calcd. for C₂₂H₂₄NO₃I C 55.36, H 5.07, N 2.93, Found C 55.31, H 5.00, N 2.97.

Preparation of 20c [R = nBu]

To a solution of **17c** (5.37 g, 19.5 mmol) and Et_3N (2.7 mL, 19 mmol) in THF (180 mL) was added methyl 4-(chloroformyl)benzoate (3.87 g, 19.5 mmol), and the mixture was refluxed for 12 h. After removal of a solid by filtration, the filtrate was concentrated and the residue was purified by column chromatography on SiO₂ (0-10% ethyl acetate/chloroform) to give **20c** (8.07 g) as a white solid in 95% yield.

An analytical sample was obtained as colorless crystals by recrystallization from 99% ethanol.

Data of 20c [R = *n*Bu]

mp 119.5-120.0 °C; ¹H NMR δ_H(300 MHz, CDCl₃, TMS)/ppm 7.86 (2H, d, *J* = 8.4 Hz), 7.53 (2H, d, *J* =

8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 6.75 (2H, d, J = 8.4 Hz), 3.89 (3H, s), 3.89 (2H, t, J = 7.5 Hz), 1.59 (2H, quint, J = 7.5 Hz), 1.35 (2H, sext, J = 7.5 Hz), 0.91 (3H, t, J = 7.5 Hz); ¹³C NMR $\delta_{C}(75$ MHz, CDCl₃)/ppm 169.2, 166.3, 140.7, 140.3, 138.4, 130.9, 129.6, 129.2, 128.4, 91.8, 52.2, 50.1, 29.7, 20.1, 13.8; IR (KBr) 2950, 2930, 2872, 1934, 1723, 1633, 1485 cm⁻¹; FD-LRMS m/z 438.1 ([M+1]⁺, 45%), 437.1 (M⁺, BP); Anal. Calcd. for C₁₉H₂₀NO₃I C 52.19, H 4.61, N 3.20, Found C 52.14, H 4.59, N 2.92.

Preparation of 21a [R = (R)-CHMe(cHex)]

A mixture of **20a** (228 mg, 0.464 mmol), LiOH·H₂O (67 mg, 1.6 mmol), THF (5 mL), MeOH (2 mL) and water (2 mL) was stirred at room temperature for 2.5 h. After removal of the organic solvents by evaporation, the residue was acidified with 1N HCl aq., and the resulting solid was collected by filtration to give **21a** (204 mg) as a white solid in 92% yield.

An analytical sample was obtained as colorless crystals by recrystallization from 95% ethanol.

Data of 21a [R = (R)-CHMe(cHex)]

mp 271-272 °C (decomp.); ¹H NMR δ_{H} (400 MHz, DMDO-*d*₆, TMS)/ppm 13.08 (1H, br.s), 7.74 (2H, br.d), 7.60 (2H, br.d), 7.32 (2H, br.d), 6.91 (2H, br.d), 4.38 (1H, br.s), 2.11 (1H, br.d), 1.83-1.41 (5H, br.m), 1.30-0.82 (5H, br.m), 1.10 (3H, d, *J* = 6.8 Hz); ¹³C NMR δ_{C} (100 MHz, DMSO-*d*₆)/ppm 169.2, 166.8, 141.6, 140.5, 137.9, 132.2, 131.0, 128.9, 128.0, 93.5, 57.7, 41.0, 30.5, 29.9, 26.0, 25.8, 25.7, 16.7; IR (KBr) 2970, 2934, 2926, 2851, 1713, 1656, 1610, 1566, 1483 cm⁻¹; FAB-LRMS m/z 476 ([M–H]⁻, 85%), 148 ([M–N(cyclohexylethyl)(4-iodophenyl)–H]⁻, BP); [α]_D²⁴ –78.2 (*c* 0.19 in CHCl₃); Anal. Calcd. for C₂₂H₂₄NO₃I C 55.36, H 5.07, N 2.93, Found C 55.14, H 4.99, N 2.89.

Preparation of 21b [R = CH₂(cHex)]

A mixture of **20b** (2.52 g, 5.28 mmol), $\text{LiOH} \cdot \text{H}_2\text{O}$ (562 mg, 13.4 mmol), THF (70 mL), MeOH (20 mL) and water (20 mL) was stirred at room temperature for 1.5 h. After removal of the organic solvents by evaporation, the residue was acidified with 1N HCl aq., and the resulting solid was collected by filtration to give **21b** (2.33 g) as a white solid in 95% yield.

An analytical sample was obtained as colorless crystals by recrystallization from 95% ethanol.

Data of 21b $[R = CH_2(cHex)]$

mp 256-257 °C (decomp.); ¹H NMR δ_H(400 MHz, DMSO-*d*₆, TMS)/ppm 13.10 (1H, br.s), 7.77 (2H, d, J = 8.0 Hz), 7.60 (2H, d, J = 8.4 Hz), 7.34 (2H, d, J = 8.0 Hz), 6.97 (2H, d, J = 8.4 Hz), 3.73 (2H, d, J = 7.2 Hz), 1.77-1.39 (6H, m), 1.20-0.86 (5H, m); ¹³C NMR $\delta_{\rm C}(100 \text{ MHz}, \text{DMSO-}d_{\rm f})/\text{ppm}$ 169.0, 166.8, 142.7, 140.8, 138.1, 131.3, 130.2, 129.0, 128.3, 92.5, 54.9, 35.9, 30.4, 26.1, 25.5; IR (KBr) 2925, 2847, cm⁻¹; 1722, 1599. 1563. 1485 FAB-LRMS m/z 462 ([M–H]⁻, 29%), 148 ([M–N(cyclohexylmethyl)(4-iodophenyl)–H]⁻, BP); Anal. Calcd. for C₂₁H₂₂NO₃I C 54.44, H 4.79, N 3.02, Found C 54.38, H 4.73, N 3.00.

Preparation of 21c [R = nBu]

To a mixture of 17c (3.94 g, 9.02 mmol), THF (95 mL) and MeOH (30 mL) was added a solution of NaOH

(926 mg, 23.2 mmol) in water (30 mL), and the mixture was stirred at room temperature for 4 h. After removal of the organic solvents by evaporation, the residue was acidified with 1N HCl aq., and the resulting solid was collected by filtration to give **21c** (3.71 g) as a white solid in 97% yield.

An analytical sample was obtained as colorless crystals by recrystallization from ethanol and water.

Data of 21c [R = *n*Bu]

mp 151.0-152.0 °C; ¹H NMR $\delta_{H}(300 \text{ MHz}, \text{DMSO-}d_{6}, \text{TMS})/\text{ppm}$ 13.11 (1H, br.s), 7.78 (2H, d, J = 8.1 Hz), 7.61 (2H, d, J = 8.4 Hz), 7.35 (2H, d, J = 8.1 Hz), 6.97 (2H, d, J = 8.4 Hz), 3.82 (2H, d, J = 7.5 Hz), 1.46 (2H, quint, J = 7.5 Hz), 1.29 (2H, sext, J = 7.5 Hz), 0.86 (3H, t, J = 7.5 Hz); ¹³C NMR $\delta_{C}(75 \text{ MHz}, \text{DMSO-}d_{6})/\text{ppm}$ 168.6, 166.8, 142.4, 140.7, 138.1, 131.4, 130.4, 129.0, 128.3, 92.7, 49.0, 29.4, 19.7, 13.9; IR (KBr) 2961, 2932, 2861, 2678, 2559, 2365, 1694, 1647, 1580, 1565, 1508, 1485 cm⁻¹; FD-LRMS m/z 424.1 ([M+1]⁺, 24%), 423.0 (M⁺, BP); Anal. Calcd. for C₁₈H₁₈NO₃I·H₂O C 48.99, H 4.57, N 3.17, Found C 49.20, H 4.50, N 2.77.

Details of X-ray Analysis

Crystal data of 3c: Single-crystalline sample was obtained by recrystallization from chloroform under a hexane-diffusing atmosphere. $C_{39}H_{35}Cl_3N_2O_2$, M = 670.08, colorless needle, $0.60 \times 0.10 \times 0.05 \text{ mm}^3$, monoclinic $P2_1$, a = 9.379(3), b = 24.518(7), c = 14.931(4) Å, $\beta = 94.889(5)^\circ$, V = 3421(2) Å³, ρ_{calcd} (Z = 4) = 1.301 g cm⁻³. A total of 13905 unique data ($2\theta_{max} = 55.0$) were measured at T = 153 K by a Rigaku Mercury70 diffractometer (Mo-K α radiation, $\lambda = 0.71075$ Å). Numerical absorption correction was applied ($\mu = 3.046$ cm⁻¹). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on F^2 with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms are located at the calculated positions. The final R and Rw values are 0.0450 and 0.1333 for 13905 reflections (all reflections) and 829 parameters. Estimated standard deviations for **3c** are 0.003-0.005 Å for bond lengths and 0.2-0.3° for bond angles, respectively.

References

- (a) D. Bruns, H. Miura and K. P. C. Vollhardt, Org. Lett., 2003, 5, 549; (b) J. E. Anthony, S. I. Khan and Y. Rubin, *Tetrahedron Lett.*, 1997, 38, 3499.
- M. L. Bell, R. C. Chiechi, C. A. Johnson, D. B. Kimball, A. J. Matzger, W. B. Wan, T. J. R. Weakley and M. M. Haley, *Tetrahedron*, 2001, 57, 3507.
- 3 D. Ma, Q. Cai and H. Zhang, Org. Lett., 2003, 5, 2453.