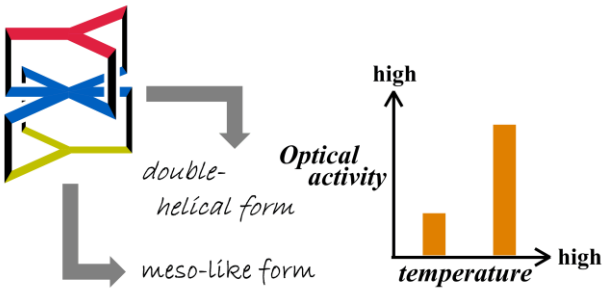
Supplementary Information

Enhanced circular dichroism at elevated temperatures through complexation-induced transformation of a three-layer cyclophane with dualistic dynamic helicity

Ryo Katoono,* Yudai Obara, Kenshu Fujiwara and Takanori Suzuki

Department of Chemistry, Faculty of Science, Hokkaido University



Contents

Supplementary Figures (Fig. S1-Fig. S9)

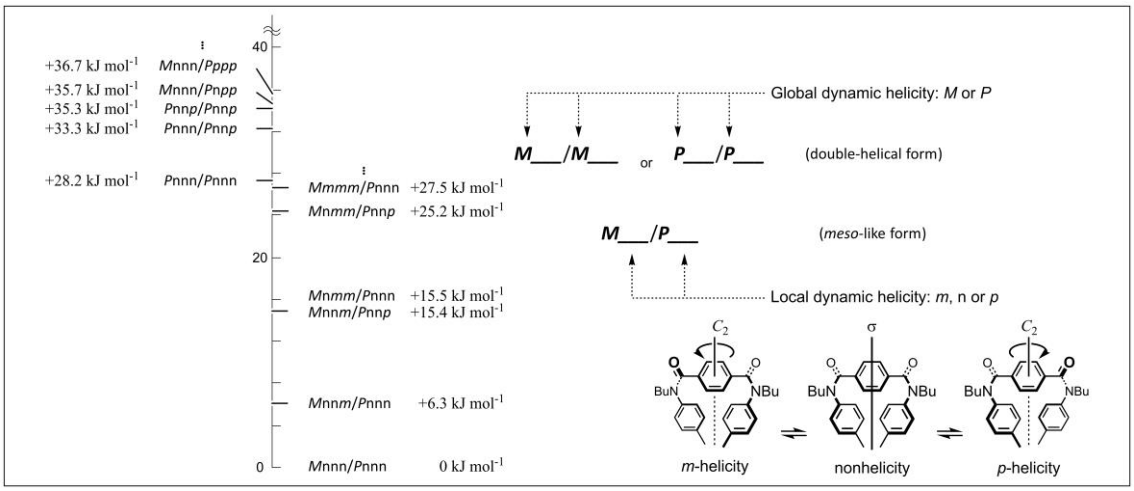


Fig. S1 Energy diagram for **1'** [NMe], obtained by a conformational search with MacroModel software (v9.9 Monte Carlo Multiple Minimum method, OPLS_2005, nonsolvated, 50 000 steps). Uppercase *M* or *P* denotes the global conformation of the molecule, and lowercase *m*, n or *p* denotes a local conformation of the terephthalamide units.

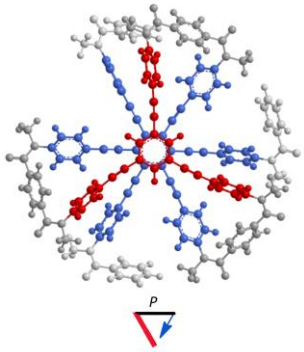


Fig. S2 The most energy-minimized structure for model **2'** [NMe], obtained by a conformational search using MacroModel software (v9.9 OPLS_2005, Monte Carlo Multiple Minimum method, nonsolvated, 20 000 steps). View from a plane of 1,3,5-tris(phenylethynyl)benzene (red). Only one enantiomeric form with (*P*)-helicity is depicted.

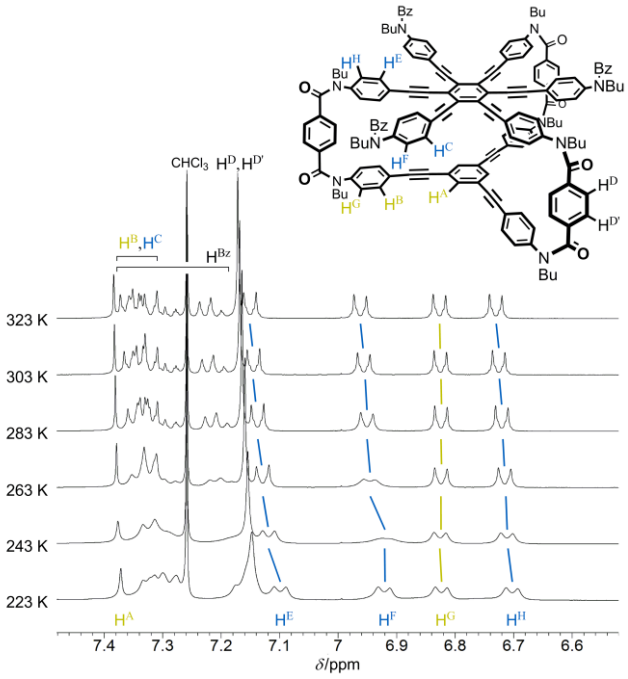


Fig. S3 Partial VT ^{1}H NMR spectra (400 MHz) of **2**, measured in chloroform-*d* at 223-323 K.

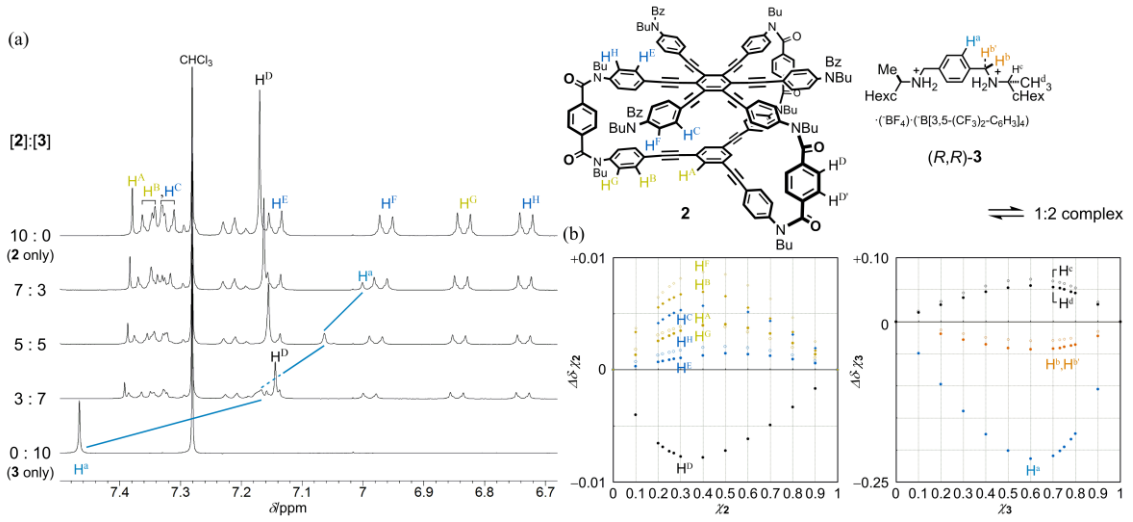
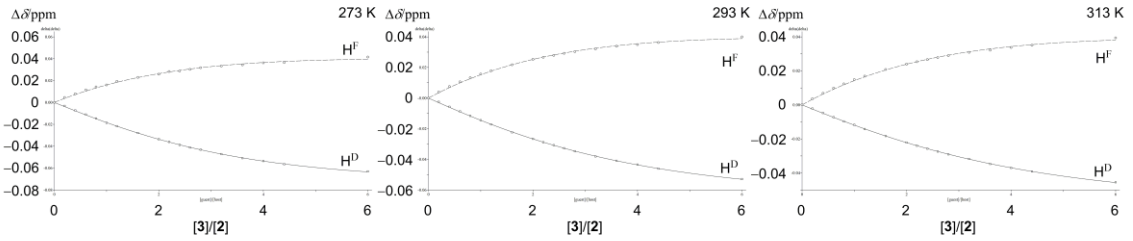


Fig. S4A (a) Partial ^{1}H NMR spectra (400 MHz) of **2** in the presence or absence of a chiral ditopic guest (*R*,*R*)-**3**; (b) Job plots for the complexation of **2** with (*R*,*R*)-**3** ([**2**] + [**3**] = 2 mM), based on continuous changes in the chemical shift induced for **2** (left) and **3** (right). All spectra were measured in chloroform-*d* containing 3vol% acetonitrile-d_3 at 303 K.



(a)

		273 K	293 K	313 K
	K_1/M	515.1	466.8	428.8
	K_2/M	817.2	540.5	492.3
	ln $K_{1:2}$	12.95	12.44	12.26
H^D	δ_b/ppm	7.180	7.172	7.167
	$\Delta\delta_{max1:1}$/ppm	7.105	7.108	7.112
	$\Delta\delta_{max1:2}$/ppm	7.104	7.104	7.106
H^F	δ_b/ppm	6.969	6.963	6.961
	$\Delta\delta_{max1:1}$/ppm	7.045	7.040	7.037
	$\Delta\delta_{max1:2}$/ppm	7.004	6.994	6.992

(b)

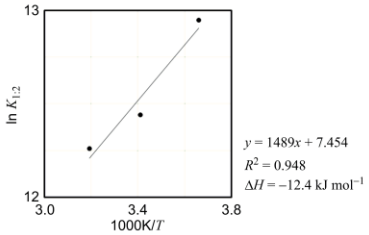


Fig. S4B (a) Titration curves for the complexation of **2** ([**2**] = 0.67 mM) with (*R*,*R*)-**3**, based on continuous changes in the chemical shift induced for protons H^D and H^F in **2**, measured at 273, 293 and 313 K; (b) plot of ln $K_{1:2}$ versus 1/*T*. All spectra were measured in chloroform-*d* containing 3vol% acetonitrile-d_3.

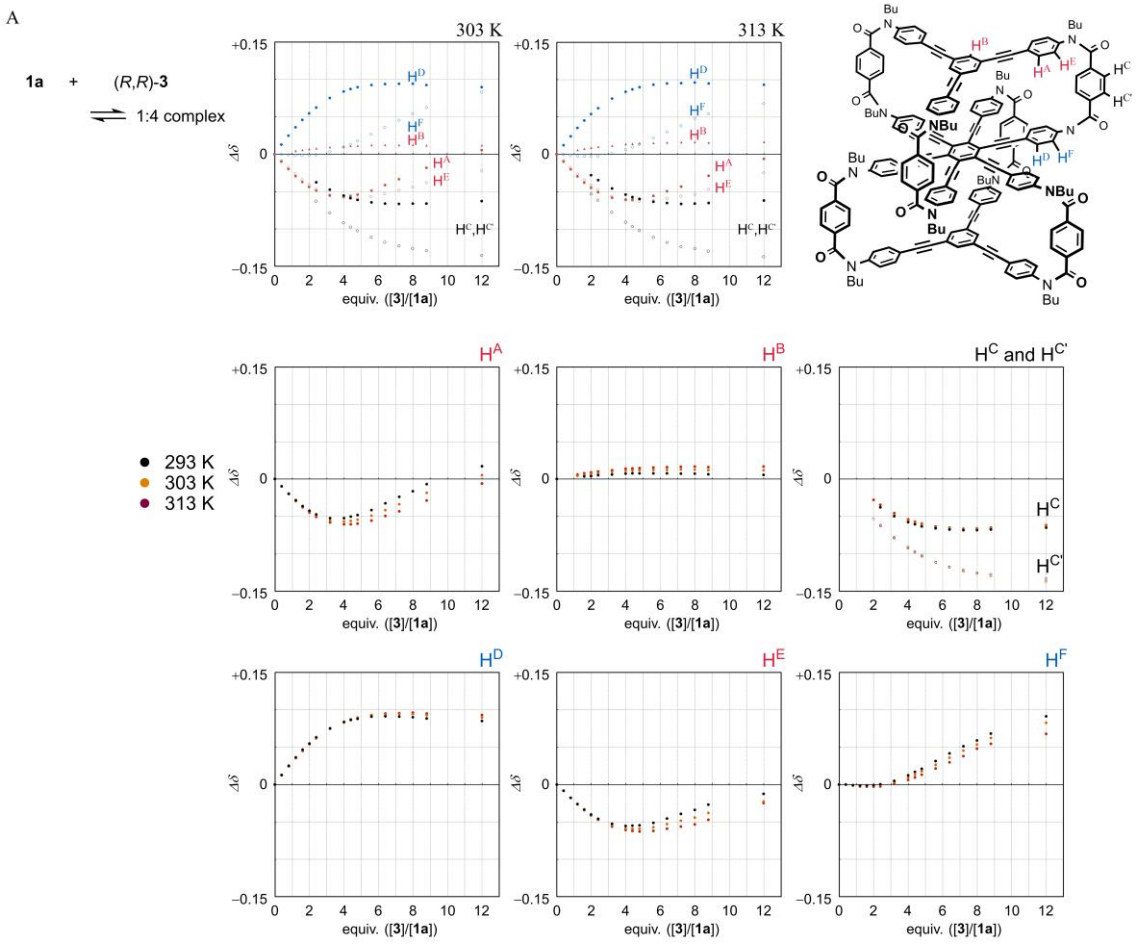


Fig. S5A Titration curves for the complexation of **1a** with (*R*,*R*)-**3** based on changes in the chemical shift ($\Delta\delta$), measured at 303 K and 313 K. All spectra were measured in chloroform-*d* containing 3vol% acetonitrile-d_3. Conditions: [**1a**] = 3.3×10^{-4} M and [**3**] = 4.0×10^{-3} M.

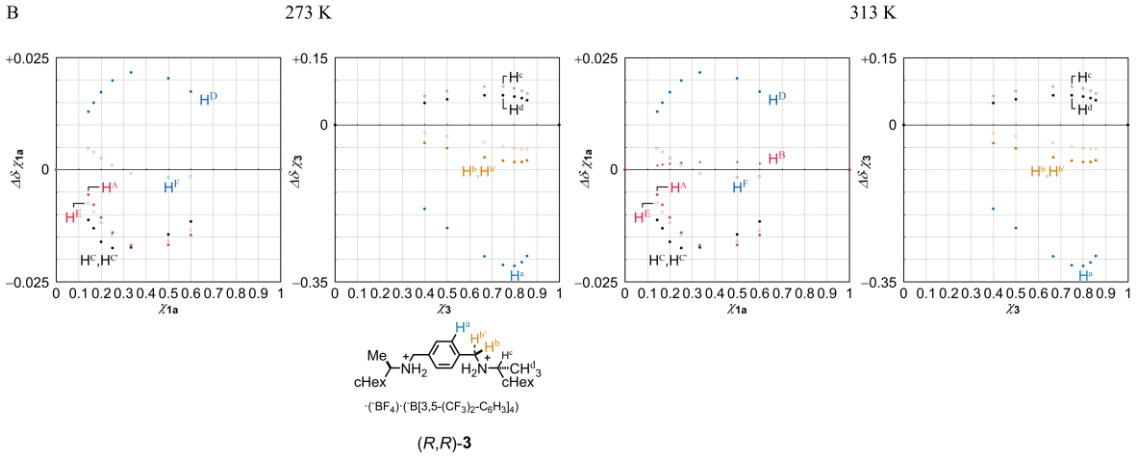


Fig. S5B Job plots for the complexation of **1a** with (*R*,*R*)-**3** based on changes in the chemical shift ($\Delta\delta$), measured at 273 K and 313 K. All spectra were measured in chloroform-*d* containing 3vol% acetonitrile-d_3. Conditions: [**1a**] + [**3**] = 2 mM.

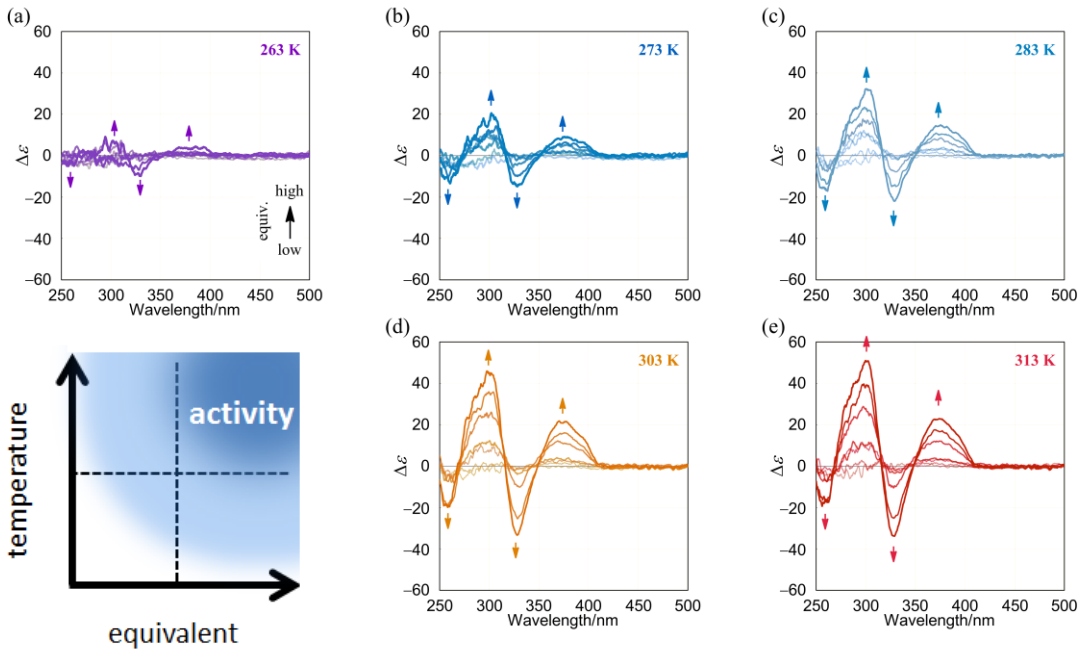


Fig. S6 CD spectra of **1a** (7.4×10^{-5} M) in the presence of (*R*,*R*)-**3** under conditions that differed with respect to equivalents (1, 2, 3, 4, 6, 9 and 12 equiv.) or temperature [(a) 263 K; (b) 273 K; (c) 283 K; (d) 303 K; (e) 313 K]. All spectra were measured in dichloromethane.

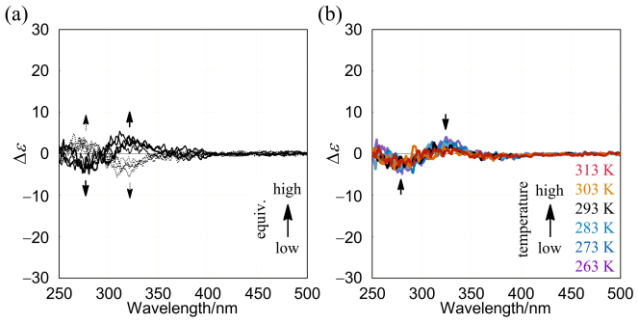


Fig. S7 (a) CD spectra of **2** (1.3×10^{-4} M) in the presence of a chiral guest [1, 2, 4 and 6 equiv. of (*S*,*S*)-**3** (dashed lines) or (*R*,*R*)-**3** (solid lines)], measured at 263 K; (b) VT CD spectra of **2** (1.3×10^{-4} M) in the presence of (*R*,*R*)-**3** (6 equiv.), measured at 263-313 K. All spectra were measured in dichloromethane.

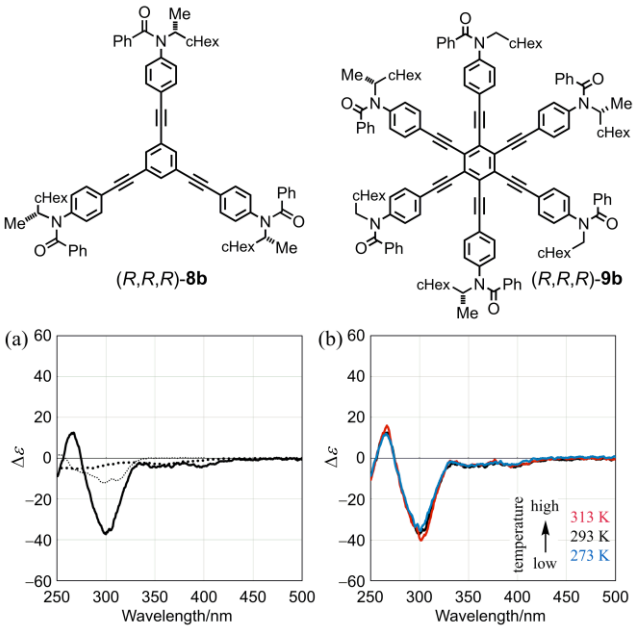


Fig. S8 Chemical structures of (*R*,*R*,*R*)-**8b**[2] and (*R*,*R*,*R*)-**9b**[3], and (a) CD spectra of (*R*,*R*,*R*)-**1b** (bold solid line), (*R*,*R*,*R*)-**8b** (thin dashed line) and (*R*,*R*,*R*)-**9b** (bold dashed line), measured at 293 K; (b) VT CD spectra of (*R*,*R*,*R*)-**1b**, measured at 273, 293 and 313 K. All spectra were measured in dichloromethane.

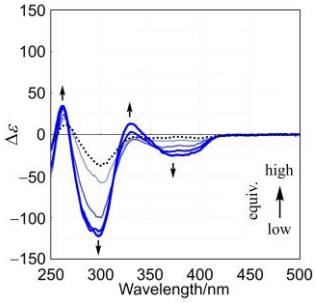
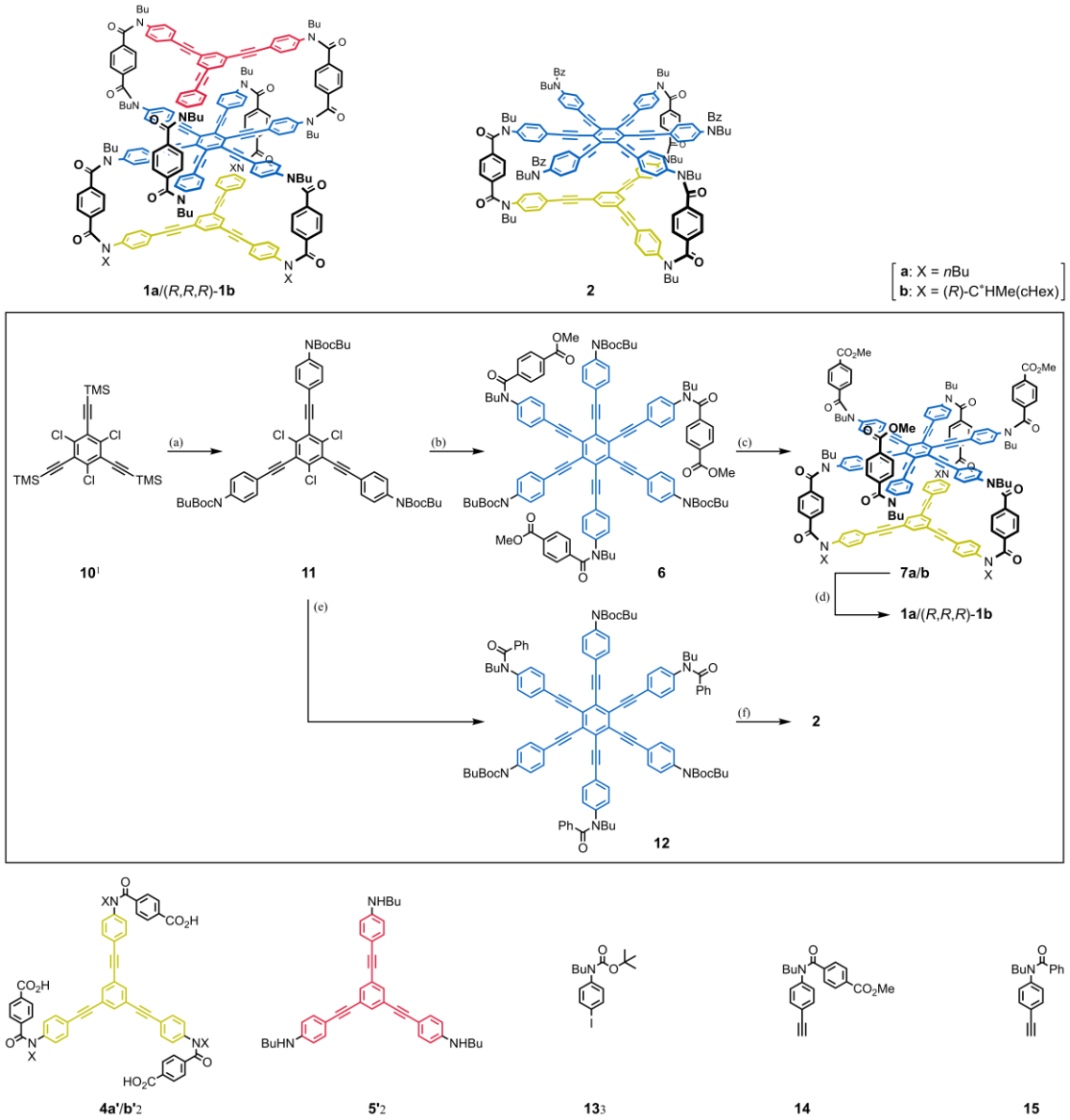


Fig. S9 CD spectra of (*R*,*R*,*R*)-**1b** (6.3×10^{-5} M) in the presence of (*R*,*R*)-**3** [0 (**1b** only, black dashed line), 1, 3, 6 and 12 equiv. (blue solid lines)], measured in dichloromethane at 293 K.

Experimental Details of New Compound Synthesis



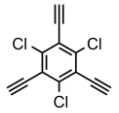
Scheme S1 Synthesis of **1a**, (*R*,*R*,*R*)-**1b** and **2**. Reagents and yields: (a) i) K_2CO_3, MeOH, THF (100%), ii) **13**, $Pd(PPh_3)_4$, CuI, iPr_2NH, THF (86%); (b) **14**, $PdCl_2(CH_3CN)_2$, X-Phos[4], CuI, iPr_2NH, dioxane (75%); (c) i) TFA, CH_2Cl_2 (93% for **6'**), ii) **4a''**/**4b''**, Et_3N, THF, toluene (53% for **7a**, 57% for **7b**); (d) i) LiOH, THF, MeOH, H_2O, ii) **7a'**/**7b'**, $SOCl_2$, $BnNEt_3Cl$, CH_2Cl_2, iii) **5'**, Et_3N, THF, toluene (26% for **1a**, 22% for **1b**, 3 steps); (e) **15**, $PdCl_2(CH_3CN)_2$, X-Phos, CuI, iPr_2NH, dioxane (61%); (f) i) TFA, CH_2Cl_2 (94% for **12'**), ii) **4a''**, Et_3N, THF, toluene (65%). Regarding the compounds **13**, **14** and **15**, see **Scheme S2**.

Preparation of 11

To a solution of 1,3,5-trichloro-2,4,6-triiodobenzene[5] (1.41 g, 2.53 mmol) and **16** (2.13 g, 7.81 mmol) in $^iPr_2NH$/THF (51 mL/51 mL) were added $Pd(PPh_3)_4$ (198 mg, 0.171 mmol) and CuI (66 mg, 0.35 mmol) at 60 °C under an argon atmosphere, and the mixture was stirred at the temperature for 5 days. To the reaction mixture was added **16** (109 mg, 0.399 mmol), and the mixture was further stirred

for 4 days. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (3:7 dichloromethane/hexane-dichloromethane) to give a mixture containing **11**, which was further purified by washing with hexane to give **11** (1.48 g) as a white solid in 59% yield. This was a poorly-reproducible result. Then, we adopted the following two-step procedure.

To a solution of **10**[1] (600 mg, 1.28 mmol) in THF/MeOH (6.3 mL/2.2 mL) was added K_2CO_3 (527 mg, 3.82 mmol), and the mixture was stirred at room temperature for 25 min. The reaction mixture was diluted with dichloromethane, and which was acidified with aq. 1M HCl, and then separated. The organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on SiO_2 (1:9 dichloromethane/hexane) to give **10'** (323 mg) as a white solid in 100% yield.



10'

To a solution of **10'** (323 mg, 1.27 mmol) and **13**[3] (4.31 g, 11.5 mmol) in $^{i}Pr_2NH$/THF (26 mL/13 mL) were added $Pd(PPh_3)_4$ (177 mg, 0.153 mmol) and CuI (82 mg, 0.43 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at 80 °C for 35 min. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (6:4 dichloromethane/hexane-dichloromethane-2:9 ethyl acetate/dichloromethane) to give **11** (1.09 g) as a brown solid in 86% yield. An analytical sample was obtained as a white solid by further purification through GPC (chloroform), followed by recrystallization from 1:9 dichloromethane/methanol. **11**: mp 151-152 °C; elemental analyses Found: C, 68.60; H, 6.53; N, 4.26. Calc. for $C_{57}H_{66}Cl_3N_3O_6$: C, 68.77; H, 6.68; N 4.22%; IR (KBr) ν_{max}/cm^{-1} 3044, 2963, 2931, 2873, 2218, 1701, 1604, 1537, 1507; ^1H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.59 (6H, d, J = 8.4 Hz), 7.24 (6H, d, J = 8.4 Hz), 3.66 (6H, t, J = 7.6 Hz), 1.57-1.49 (6H, m), 1.45 (27H, s), 1.36-1.27 (6H, m), 0.90 (9H, t, J = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 154.3, 143.7, 137.8, 132.3, 126.7, 123.0, 119.3, 100.6, 83.2, 80.5, 49.5, 30.6, 28.3, 19.9, 13.8; FD-LRMS m/z 996.39 ($[M+3]^+$, 60%), 995.38 ($[M+2]^+$, 100), 994.39 ($[M+1]^+$, 57), 993.39 (M^+, 86).

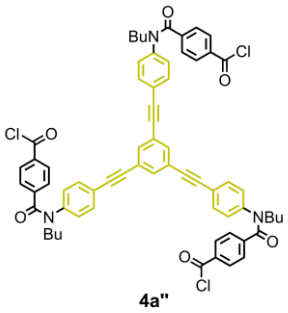
Preparation of 6

To a solution of **11** (757 mg, 0.760 mmol) and **14** (1.02 g, 3.04 mmol) in $^{i}Pr_2NH$/dioxane (5.8 mL/10.1 mL) were added X-Phos[4] (2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl, 20 mg, 0.042 mmol), $PdCl_2(CH_3CN)_2$ (8 mg, 0.03 mmol) and CuI (2 mg, 0.01 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at 92 °C for 23 h, and then diluted with ethyl acetate. The diluted solution was washed with water and brine, dried over magnesium sulfate, and then concentrated. The residue was purified by column chromatography on SiO_2 (1:19-3:7 ethyl acetate/dichloromethane) to give **6** (1.08 g) as a yellow solid in 75% yield. An analytical sample was suspended in refluxed methanol, and collected as a yellow solid by filtration. **6**: mp 205-212 °C (dec); elemental analyses Found: C, 76.05; H, 6.66; N, 4.37. Calc. for $C_{120}H_{126}N_6O_{15}$: C, 76.17; H, 6.71; N,

4.44%; IR (KBr) ν_{max}/cm^{-1} 3044, 2957, 2930, 2872, 2202, 1726, 1698, 1649, 1599, 1511; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.87 (6H, d, J = 8.4 Hz), 7.53 (6H, d, J = 8.4 Hz), 7.42 (6H, d, J = 8.4 Hz), 7.37 (6H, d, J = 8.4 Hz), 7.24 (6H, d, J = 8.4 Hz), 7.00 (6H, d, J = 8.4 Hz), 3.94 (6H, t, J = 7.6 Hz), 3.85 (9H, s), 3.69 (6H, t, J = 7.6 Hz), 1.66-1.53 (12H, m), 1.50 (27H, s), 1.43-1.30 (12H, m), 0.93 (9H, t, J = 7.6 Hz), 0.93 (9H, t, J = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.2, 166.2, 154.3, 143.5, 143.5, 140.3, 132.7, 132.0, 131.0, 129.2, 128.5, 127.7, 127.6, 127.0, 126.6, 121.5, 119.8, 99.3, 98.4, 88.2, 87.0, 80.6, 52.2, 50.1, 49.6, 30.8, 29.9, 28.4, 20.1, 19.9, 13.8; FD-LRMS m/z 1893.82 ([M+3]$^+$, 35%), 1892.81 ([M+2]$^+$, 72), 1891.81 ([M+1]$^+$, 100), 1890.81 (M$^+$, 75).

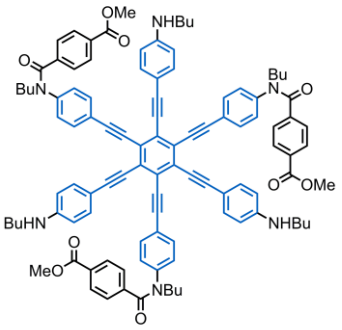
Preparation of 7a [X = *n*Bu]

To a refluxed solution of **4a'**[2] (210 mg, 0.203 mmol) and $BnNEt_3Cl$ (3 mg, 0.01 mmol) in CH_2Cl_2 (14 mL) was added $SOCl_2$ (0.12 mL, 1.7 mmol), and the mixture was further refluxed for 1 h. After removal of the solvent by evaporation, the resulting solid (**4a''**) was dried *in vacuo* and dissolved in THF (10 mL) [acid chloride preparation].



4a''

To a solution of **6** (625 mg, 0.330 mmol) in CH_2Cl_2 (29 mL) was added TFA (3.3 mL), and the mixture was stirred at room temperature for 45 min, and then diluted with dichloromethane. The diluted reaction mixture was washed with satd. aq. $NaHCO_3$. The organic layer was separated, dried over magnesium sulfate, and then concentrated. The residue was purified by column chromatography on SiO_2 (ethyl acetate/dichloromethane) to give **6'** (489 mg) as a yellow solid in 93% yield [deprotection of BOC].



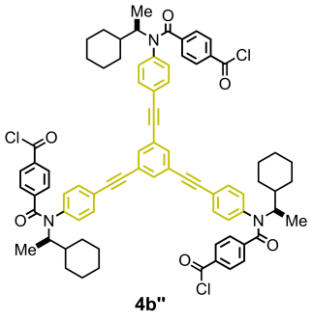
6'

To a solution of **6'** (207 mg, 0.130 mmol) and Et_3N (0.56 mL, 4.0 mmol) in toluene (25 mL) were added the freshly prepared THF solution (10 mL) containing the acid chloride **4a''** and THF (15 mL) at 80 °C, and the mixture was stirred at the temperature for 1 h. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (1:3-2:1 ethyl acetate/dichloromethane) to give **7a** (179 mg) as a yellow solid in 53% yield. An analytical sample was further purified through GPC (chloroform), and recrystallization from ethanol. **7a**: mp >300 °C (dec); elemental analyses Found: C, 79.25; H, 5.99; N, 4.87. Calc. for $C_{171}H_{153}N_9O_{15}$·(EtOH): C, 79.30; H, 6.12; N, 4.81%; IR (KBr) ν_{max}/cm^{-1} 3042, 2956, 2931, 2871, 2201, 1725, 1654, 1650, 1600, 1579, 1510; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.87 (6H, d, J = 8.4 Hz), 7.39 (3H, s), 7.38 (6H, d, J = 8.4 Hz), 7.34 (6H, d, J = 8.4 Hz), 7.33 (6H, d, J = 8.4 Hz), 7.17 (12H, s), 7.16 (6H, d, J = 8.4 Hz), 6.92 (6H, d, J = 8.4 Hz), 6.85 (6H, d, J = 8.4 Hz), 6.74 (6H, d, J = 8.4 Hz), 3.92-3.84 (18H, m), 3.86 (9H, s), 1.65-1.49 (18H, m), 1.41-1.26 (18H, m), 0.93 (9H, t, J = 7.2 Hz), 0.92 (9H, t, J = 7.2

Hz), 0.88 (9H, t, J = 7.2 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.1, 168.9, 168.8, 166.1, 143.9, 143.5, 143.4, 140.0, 137.2, 137.0, 133.8, 132.7, 132.1, 132.1, 131.2, 129.2, 128.5, 128.4, 128.3, 127.5, 127.4, 127.3, 127.1, 126.9, 123.4, 121.5, 120.9, 120.9, 98.6, 98.3, 89.4, 89.1, 88.3, 88.0, 52.3, 50.5, 50.1, 50.0, 30.0, 29.7, 29.7, 20.1, 20.1, 13.8, 13.8, 13.7; FD-LRMS m/z 2576.00 ([M+4]$^+$, 37%), 2575.00 ([M+3]$^+$, 71), 2574.00 ([M+2]$^+$, 99), 2573.00 ([M+1]$^+$, 100), 2572.00 (M$^+$, 57).

Preparation of (*R*,*R*,*R*)-7b [X = (*R*)-CHMe(cHex)]

To a refluxed solution of **4b'**[2] (408 mg, 0.341 mmol) and $BnNEt_3Cl$ (7 mg, 0.03 mmol) in dichloromethane (11 mL) was added $SOCl_2$ (0.15 mL, 2.1 mmol), and the mixture was further refluxed for 1 h. After removal of the solvent by evaporation, the resulting solid (**4b''**) was dried *in vacuo* and dissolved in THF (10 mL) [acid chloride preparation].



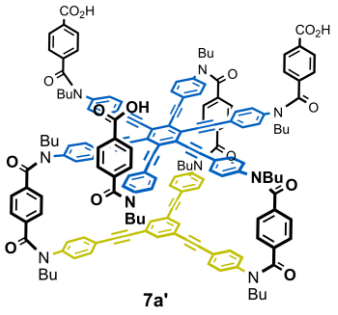
4b''

To a solution of **6'** (489 mg, 0.307 mmol) and Et_3N (1.25 mL, 8.99 mmol) in THF/toluene (20 mL/40 mL) were added the freshly prepared THF solution (10 mL) containing the acid chloride **4b''** and THF (10 mL) at 75-82 °C, and the mixture was stirred at the temperature for 1 h. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (1:3-2:1 ethyl acetate/dichlorometane) to give (*R*,*R*,*R*)-**7b** (479 mg) as a yellow solid in 57% yield. An analytical sample was further purified through GPC (chloroform), and recrystallization from ethanol. (*R*,*R*,*R*)-**7b**: mp >300 °C (dec); elemental analyses Found: C, 79.98; H, 6.26; N, 4.55. Calc. for $C_{183}H_{171}N_9O_{15}$·(EtOH): C, 79.86; H, 6.41; N, 4.53%; $[\alpha]_D^{24}$ –123 (*c* 0.134 in $CHCl_3$); IR (KBr) ν_{max}/cm^{-1} 3042, 2930, 2854, 2201, 1725, 1654, 1650, 1600, 1579, 1510; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.88 (6H, d, J = 8.4 Hz), 7.38 (3H, s), 7.37 (6H, d, J = 8.4 Hz), 7.33 (6H, d, J = 8.4 Hz), 7.30 (6H, d, J = 8.8 Hz), 7.19 (6H, d, J = 8.4 Hz), 7.15 (12H, s), 6.90 (6H, d, J = 8.4 Hz), 6.82 (6H, d, J = 8.8 Hz), 6.76 (6H, d, J = 8.4 Hz), 4.40-4.30 (3H, br.m), 3.96-3.83 (12H, m), 3.87 (9H, s), 2.03 (3H, br.d), 1.83-1.52 (27H, m), 1.36 (12H, sext, J = 7.6 Hz), 1.26-0.91 (15H, m), 1.09 (9H, d, J = 6.8 Hz), 0.92 (18H, t, J = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.4, 169.3, 168.9, 166.1, 143.8, 143.5, 142.1, 140.0, 138.1, 137.0, 133.8, 132.7, 132.0, 131.8, 131.3, 129.2, 128.8, 128.5, 128.1, 128.1, 127.4, 127.4, 127.3, 127.2, 123.3, 121.5, 121.4, 120.7, 98.6, 98.3, 89.4, 89.4, 88.4, 88.0, 52.3, 50.5, 49.9, 41.5, 30.7, 30.5, 30.0, 29.7, 26.2, 26.0, 20.1, 20.1, 16.7, 13.9, 13.8; FD-LRMS m/z 2738.14 ([M+4]$^+$, 48%), 2737.14 ([M+3]$^+$, 79), 2736.14 ([M+2]$^+$, 100), 2735.13 ([M+1]$^+$, 87), 2734.13 (M$^+$, 43).

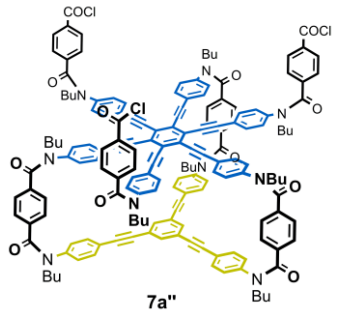
Preparation of 1a [X = *n*Bu]

To a solution of **7a** (318 mg, 0.124 mmol) in THF/MeOH (6 mL/2 mL) was added a solution of $LiOH·H_2O$ (44 mg, 1.0 mmol) in H_2O (2 mL), and the mixture was stirred at room temperature for 1h. After removal of the organic solvents by evaporation, the residue was acidified with aq. 1M HCl, and

extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and then concentrated to give **7a'** (298 mg) as an amorphous in 95% yield. The product was subjected to the next reaction without purification [hydrolysis of methyl ester].



To a refluxed solution of as-obtained **7a'** (298 mg, 0.118 mmol) and $BnNEt_3Cl$ (5 mg, 0.02 mmol) in CH_2Cl_2 (13 mL) was added $SOCl_2$ (0.18 mL, 2.5 mmol), and the mixture was further refluxed for 2 h. After removal of the solvent by evaporation, the resulting solid (**7a''**) was dried *in vacuo* and dissolved in THF (2 mL) [acid chloride preparation].



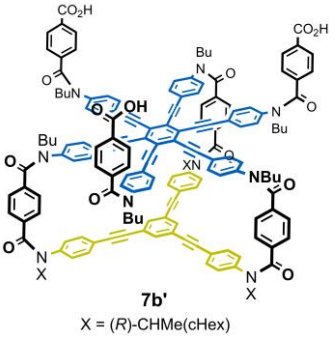
To a solution of **5'**[2] (65 mg, 0.11 mmol) and Et_3N (0.44 mL, 3.2 mmol) in toluene (4.8 mL) were added the freshly prepared THF solution (2 mL) containing the acid chloride **7a''** and THF (4 mL) at 80 °C, and the mixture was stirred at the temperature for 2 h. After removal of the solvents by evaporation, the residue was dissolved in dichloromethane, and which was washed with satd. aq. $NaHCO_3$, dried over magnesium sulfate, and then concentrated. The residue was purified by column chromatography on SiO_2 (3:7-4:1 ethyl acetate/chloroform) to give **1a** (98 mg) as a yellow solid in 26% yield (based on **7a**). An analytical sample was suspended in refluxed ethyl acetate, and collected as a yellow solid by filtration. **1a**: mp >300 °C (dec); elemental analyses Found: C, 81.76; H, 6.19; N, 5.42. Calc. for $C_{210}H_{186}N_{12}O_{12}\cdot$(EtOH): C, 81.72; H, 6.21; N, 5.39%; IR (KBr) ν_{max}/cm^{-1} 3041, 2956, 2930, 2871, 2202, 1654, 1650, 1601, 1579, 1510; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm [303 K] 7.31 (12H, d, J = 8.4 Hz), 7.29 (6H, s), 7.16 (24H, s) , 7.06 (12H, d, J = 8.4 Hz) , 6.78 (12H, d, J = 8.4 Hz) , 6.68 (12H, d, J = 8.4 Hz), 3.89-3.84 (24H, m), 1.65-1.50 (24H, m), 1.43-1.30 (24H, m), 0.94 (18H, t, J = 7.2 Hz) , 0.91 (18H, t, J = 7.2 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.0, 168.5, 144.0, 143.5, 137.1, 137.0, 133.6, 132.2, 132.0, 128.5, 128.2, 127.2, 126.9, 126.8, 123.2, 121.2, 120.9, 98.2, 89.3, 89.1, 88.4, 50.4, 50.2, 30.1, 29.8, 20.2, 20.1, 13.9, 13.8; MALDI-TOF-MS *m/z* 3094.8 ([M+5+Na]$^+$, 67%), 3093.9 ([M+4+Na]$^+$, 88), 3092.9 ([M+3+Na]$^+$, 100), 3091.9 ([M+2+Na]$^+$, 96), 3090.9 ([M+1+Na]$^+$, 72), 3090.0 ([M+Na]$^+$, 25); UV-vis λ_{max}(CH_2Cl_2)/nm (log ε) 373 (4.94), 301 (5.35).

Preparation of (*R*,*R*,*R*)-1b [X = (*R*)-CHMe(cHex)]

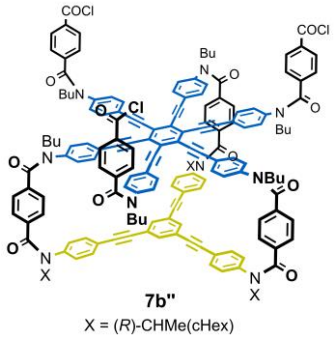
To a solution of **7b** (479 mg, 0.175 mmol) in THF/MeOH (16 mL/5 mL) was added a solution of $LiOH\cdot H_2O$ (64 mg, 1.5 mmol) in H_2O (5 mL), and the mixture was stirred at room temperature for 2 h. After removal of the solvents by evaporation, the residue was acidified with aq. 1M HCl, and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and then concentrated to give **7b'** (489 mg) as a yellow solid. The product was subjected to the next

reaction without purification [hydrolysis of methyl ester].

To a refluxed solution of as-obtained **7b'** and $BnNEt_3Cl$ (12 mg, 0.053 mmol) in CH_2Cl_2 (12 mL) was added $SOCl_2$ (0.16 mL, 2.2 mmol), and the mixture was further refluxed for 1 h. After removal of the solvent by evaporation, the resulting solid (**7b''**) was dried *in vacuo* and dissolved in THF (10 mL) [acid chloride preparation].



To a solution of **5'** (112 mg, 0.189 mmol) and Et_3N (0.73 mL, 5.2 mmol) in THF/toluene (3.6 mL/22 mL) were added the freshly prepared THF solution (10 mL) containing the acid chloride **7b''** and THF (8 mL) at 80 °C, and the mixture was stirred at the temperature for 40 min. After removal of the solvents by evaporation, the residue was purified by column chromatography on SiO_2 (4:6-9:1 ethyl acetate/dichloromethane) to give (*R*,*R*,*R*)-**1b** (125 mg) as a yellow solid in 22% yield (based on **7b**). An analytical sample was suspended in refluxed *n*-butyl alcohol, and collected as a yellow solid by filtration.



(*R*,*R*,*R*)-**1b**: mp >300 °C (dec); elemental analyses Found: C, 82.14; H, 6.41; N, 5.21. Calc. for $C_{222}H_{204}N_{12}O_{12}\cdot$(EtOH): C, 82.07; H, 6.46; N, 5.13%; $[\alpha]_D^{25}$ –64.8 (*c* 0.209 in $CHCl_3$); IR (KBr) ν_{max}/cm^{-1} 3041, 2955, 2929, 2857, 2201, 1655, 1650, 1601, 1579, 1509; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm [303 K] 7.31 (6H, d, *J* = 8.4 Hz), 7.29 (6H, d, *J* = 8.4 Hz), 7.29 (3H, s), 7.28 (3H, s), 7.17 (12H, s), 7.14 (12H, s), 7.09 (6H, d, *J* = 8.4 Hz), 7.08 (6H, d, *J* = 8.4 Hz), 6.79 (6H, d, *J* = 8.4 Hz), 6.75 (6H, d, *J* = 8.4 Hz), 6.72 (6H, d, *J* = 8.4 Hz), 6.71 (6H, d, *J* = 8.4 Hz), 4.34 (3H, br.dq), 3.92-3.80 (18H, m), 2.01 (3H, br.d), 1.82-1.49 (33H, m), 1.44-1.31 (18H, m), 1.28-0.86 (15H, m), 1.13 (9H, d, *J* = 6.8 Hz), 0.95 (9H, t, *J* = 7.2 Hz) , 0.94 (9H, t, *J* = 7.2 Hz) , 0.91 (9H, t, *J* = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.2, 169.1, 169.0, 168.5, 144.1, 144.0, 143.5, 142.4, 138.1, 137.1, 137.0, 136.9, 133.6, 132.2, 132.1, 132.0, 131.7, 128.7, 128.6, 128.3, 128.2, 128.1, 127.2, 126.9, 126.8, 123.2, 123.2, 121.4, 121.2, 121.1, 120.9, 98.3, 98.2, 89.5, 89.4, 89.3, 89.2, 88.5, 88.4, 50.4, 50.3, 50.2, 41.5, 30.8, 30.6, 30.1, 29.8, 26.2, 26.0, 20.2, 20.2, 20.1, 16.7, 13.9, 13.8; MALDI-TOF-MS *m*/*z* 3257.9 ($[M+5+Na]^+$, 40%), 3256.9 ($[M+4+Na]^+$, 61), 3255.9 ($[M+3+Na]^+$, 82), 3254.9 ($[M+2+Na]^+$, 100), 3254.0 ($[M+1+Na]^+$, 92), 3253.0 ($[M+Na]^+$, 63); UV-vis λ_{max}(CH_2Cl_2)/nm (log ε) 373 (4.95), 301 (5.37); CD λ(CH_2Cl_2)/nm ($\Delta\varepsilon$) [293 K] 300 (−37.2), 267 (+12.5).

Preparation of **12**

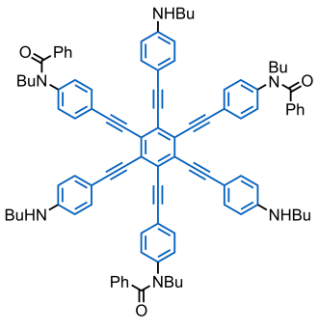
To a solution of **11** (321 mg, 0.322 mmol) and **14** (535 mg, 1.93 mmol) in ^{i}Pr$_2$NH/dioxane (2.6 mL/4.4 mL) were added X-Phos (8 mg, 0.02 mmol), $PdCl_2(CH_3CN)_2$ (2 mg, 0.008 mmol) and CuI (2 mg, 0.01 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at 90 °C for 24 h. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and

purified by column chromatography on SiO_2 (1:19-15:85 ethyl acetate/dichloromethane), followed by HPLC with a standard normal-phase column (1:9 ethyl acetate/dichloromethane; YMC-Pack SIL, SIL-06, YMC Co., Ltd.) to give **12** (338 mg) as a yellowish brown amorphous solid in 61% yield. An analytical sample was obtained as a yellow solid by further purification through GPC (chloroform), followed by recrystallization from methanol. **12**: mp 202-204 °C (dec); elemental analyses Found: C, 79.39; H, 7.02; N, 4.87. Calc. for $C_{114}H_{120}N_6O_9$: C, 79.69; H, 7.04; N, 4.89%; IR (KBr) ν_{max}/cm^{-1} 3058, 3043, 2957, 2929, 2871, 2201, 1698, 1648, 1599, 1510; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.50 (6H, d, J = 8.4 Hz), 7.45 (6H, d, J = 8.4 Hz), 7.32 (6H, d, J = 8.4 Hz), 7.29-7.25 (3H, m), 7.22-7.19 (12H, m), 7.02 (6H, d, J = 8.4 Hz), 3.95 (6H, t, J = 7.6 Hz), 3.68 (6H, t, J = 7.6 Hz), 1.67-1.53 (12H, m), 1.43-1.30 (12H, m), 0.93 (18H, t, J = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 170.1, 154.3, 144.2, 143.4, 136.0, 132.5, 132.1, 129.8, 128.8, 127.9, 127.6, 127.5, 127.0, 126.7, 121.0, 119.9, 99.3, 98.6, 87.9, 87.1, 80.6, 50.2, 49.6, 30.8, 29.9, 28.4, 20.2, 19.9, 13.8, 13.8; FD-LRMS *m/z* 1721.91 ([M+5]$^+$, 3%), 1720.91 ([M+4]$^+$, 11), 1719.90 ([M+3]$^+$, 30), 1718.90 ([M+2]$^+$, 66), 1717.90 ([M+1]$^+$, 100), 1716.89 (M$^+$, 78), 1619.85 ([M+3−BOC]$^+$, 2), 1618.85 ([M+2−BOC]$^+$, 4), 1617.84 ([M+1−BOC]$^+$, 7), 1616.84 ([M−BOC]$^+$, 6), 860.95 ([M+5]$^{2+}$, 1), 860.44 ([M+4]$^{2+}$, 4), 859.94 ([M+3]$^{2+}$, 12), 859.44 ([M+2]$^{2+}$, 27), 858.94 ([M+1]$^{2+}$, 39), 858.44 (M^{2+}, 32), 809.90 ([M+3−BOC]$^{2+}$, 2), 809.41 ([M+2−BOC]$^{2+}$, 4), 808.91 ([M+1−BOC]$^{2+}$, 6), 808.41 ([M−BOC]$^{2+}$, 6).

Preparation of **2**

To a refluxed solution of **4a'** (176 mg, 0.170 mmol) and $BnNEt_3Cl$ (5 mg, 0.02 mmol) in CH_2Cl_2 (13 mL) was added $SOCl_2$ (0.19 mL, 2.6 mmol), and the mixture was further refluxed for 1 h. After removal of the solvent by evaporation, the resulting solid (**4a''**) was dried *in vacuo* and dissolved in THF (10 mL) [acid chloride preparation].

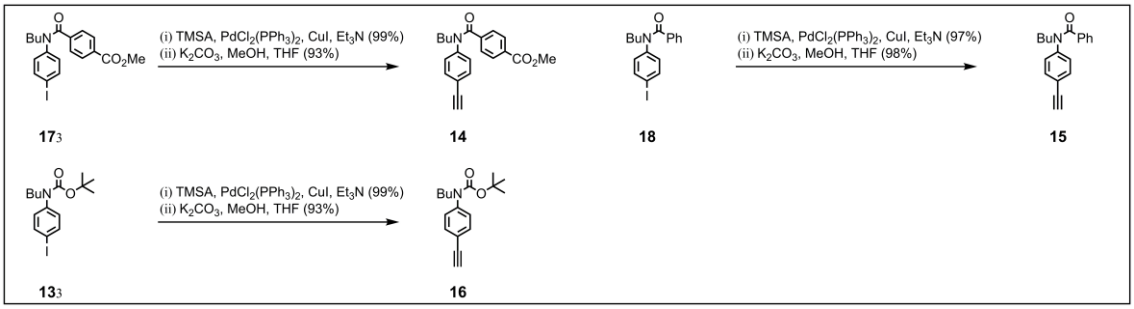
To a solution of **12** (559 mg, 0.325 mmol) in CH_2Cl_2 (29 mL) was added TFA (3.3 mL), and the mixture was stirred at room temperature for 1.5 h, and then diluted with dichloromethane. The diluted reaction mixture was quenched with aq. 1M NaOH and separated. After extraction with dichloromethane, the combined organic layer was dried over magnesium sulfate and concentrated. The residue was purified by column chromatography on SiO_2 (8:92 ethyl acetate/dichloromethane), followed by washing with ethanol to give **12'** (432 mg) as an orange solid in 94% yield [deprotection of BOC].



12'

To a solution of **12'** (240 mg, 0.169 mmol) and Et_3N (0.70 mL, 5.0 mmol) in toluene/THF (17 mL/7 mL) was added the freshly prepared THF solution (10 mL) containing the acid chloride **4a''** at 80 °C, and the mixture was stirred at the temperature for 1 h, and then concentrated. The residue was dissolved in chloroform, and which was washed with aq. 1M NaOH and separated. The organic layer

was dried over magnesium sulfate and purified by column chromatography on SiO_2 (dichloromethane-15:85-7:3 ethyl acetate/dichloromethane) to give **2** (264 mg) as a yellow solid in 65% yield. An analytical sample was obtained as a pale-yellow solid by further purification through GPC (chloroform) and HPLC (5:95 methanol/dichloromethane), and recrystallization from *t*-butyl alcohol. **2**: mp >300 °C; elemental analyses Found: C, 81.69; H, 6.08; N, 5.19. Calc. for $C_{171}H_{153}N_9O_{15}\cdot$(MeOH): C, 81.98; H, 6.26; N, 5.18%; IR (KBr) ν_{max}/cm^{-1} 3041, 2956, 2929, 2871, 2200, 1650, 1599, 1579, 1510; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.39 (3H, s), 7.36 (6H, d, J = 8.4 Hz), 7.35-7.28 (9H, m), 7.32 (6H, d, J = 8.4 Hz), 7.23-7.20 (6H, m), 7.17 (12H, s), 7.15 (6H, d, J = 8.4 Hz), 6.82 (6H, d, J = 8.4 Hz), 6.83 (6H, d, J = 8.4 Hz), 6.73 (6H, d, J = 8.4 Hz), 3.93-3.84 (18H, m), 1.67-1.50 (18H, m), 1.42-1.27 (18H, m), 0.93 (18H, t, J = 7.2 Hz), 0.89 (9H, t, J = 7.2 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.9, 169.1, 168.8, 144.2, 143.9, 143.4, 137.1, 137.0, 135.9, 133.8, 132.6, 132.1, 132.1, 129.9, 128.8, 128.4, 128.3, 127.9, 127.4, 127.3, 127.3, 127.1, 127.0, 123.4, 121.0, 121.0, 120.9, 98.5, 89.4, 89.2, 88.1, 50.5, 50.2, 50.1, 30.1, 29.8, 29.7, 20.1, 20.1, 20.1, 13.9, 13.8; FD-LRMS m/z 2404.12 ([M+6]$^+$, 5%), 2403.12 ([M+5]$^+$, 13), 2402.11 ([M+4]$^+$, 33), 2401.11 ([M+3]$^+$, 62), 2400.10 ([M+2]$^+$, 95), 2399.10 ([M+1]$^+$, 100), 2398.09 (M$^+$, 58), 2372.09 ([M+1−(C=O)]$^+$, 6), 2371.09 ([M−(C=O)]$^+$, 6), 2295.04 ([M+1−Bz]$^+$, 5), 2294.06 ([M−Bz]$^+$, 6), 1202.06 ([M+6]$^{2+}$, 2), 1201.54 ([M+5]$^{2+}$, 4), 1201.05 ([M+4]$^{2+}$, 10), 1200.55 ([M+3]$^{2+}$, 19), 1200.05 ([M+2]$^{2+}$, 29), 1199.54 ([M+1]$^{2+}$, 31), 1199.05 (M^{2+}, 18); UV-vis λ_{max}(CH_2Cl_2)/nm (log ε) 369 (5.08), 319 (sh. 5.09), 293 (5.14).



Scheme S2 Preparation of acetylenes **14**, **15** and **16**.

Preparation of 14

To a suspended solution of **17**[3] (3.19 g, 7.29 mmol), $PdCl_2(PPh_3)_2$ (76 mg, 0.11 mmol) and CuI (34 mg, 0.18 mmol) in Et_3N (60 mL) was added TMSA (trimethylsilylacetylene, 1.1 mL, 7.9 mmol) at room temperature under an argon atmosphere, and the reaction mixture was stirred at the temperature for 21 h. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (dichloromethane-1:19-1:9 ethyl acetate/dichloromethane) to give TMS-protected **14** (2.94 g) as a pale yellow oil in 99% yield.

To a solution of TMS-protected **14** (2.94 g, 7.23 mmol) in THF/MeOH (35 mL/35 mL) was added K_2CO_3 (974 mg, 7.06 mmol), and the mixture was stirred at room temperature for 25 min, and then diluted with ethyl acetate. The diluted solution was washed with water and brine, dried over magnesium sulfate, and then purified by column chromatography on SiO_2 (dichloromethane-1:19-1:9 ethyl acetate/dichloromethane) to give **14** (2.26 g) as a white solid in 93% yield. An analytical sample was obtained as a white solid by precipitation in ethyl acetate. **14**: mp 123-124 °C; elemental analyses Found: C, 75.19; H, 6.17; N, 4.19. Calc. for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18%; IR (KBr) ν_{max}/cm^{-1} 3285, 3060, 2951, 2872, 2106, 1721, 1637, 1598, 1504; ^1H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.80 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.4 Hz), 7.32 (2H, d, J = 8.4 Hz), 6.96 (2H, d, J = 8.4 Hz), 3.92 (2H, t, J = 7.6 Hz), 3.88 (3H, s), 3.07 (1H, s), 1.63-1.56 (2H, m), 1.41-1.32 (2H, m), 0.92 (3H, t, J = 7.2 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 169.2, 166.3, 143.3, 140.4, 133.0, 130.9, 129.1, 128.5, 127.6, 120.7, 82.5, 78.2, 52.2, 50.0, 29.8, 20.1, 13.8; FD-LRMS m/z 337.16 ($[M+2]^+$, 3.2%), 336.16 ($[M+1]^+$, 23), 335.15 (M^+, 100).

Preparation of 15

To a solution of **18** (1.60 g, 4.21 mmol), $PdCl_2(PPh_3)_2$ (45 mg, 0.064 mmol) and CuI (22 mg, 0.12 mmol) in Et_3N (32 mL) was added TMSA (0.65 mL, 4.6 mmol) at room temperature under an argon atmosphere, and the mixture was stirred at the temperature for 25 hours. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (8:2 dichloromethane/hexane-dichloromethane-2:98 ethyl acetate/dichloromethane) to give TMS-protected **15** (1.43 g) as a yellow oil in 97% yield. An analytical sample was obtained as a pale

yellow oil by further purification through GPC (chloroform). TMS-protected **15**: elemental analyses Found: C, 75.65; H, 7.88; N, 4.02. Calc. for $C_{22}H_{27}NOSi$: C, 75.59; H, 7.79; N, 4.01%; IR (neat) ν_{max}/cm^{-1} 3085, 3061, 3040, 2958, 2931, 2872, 2157, 1649, 1600; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.31 (2H, d, J = 8.4 Hz), 7.27-7.21 (3H, m), 7.17-7.14 (2H, m), 6.94 (2H, d, J = 8.4 Hz), 3.91 (2H, t, J = 7.6 Hz), 1.62-1.54 (2H, m), 1.40-1.30 (2H, m), 0.90 (3H, t, J = 7.6 Hz), 0.22 (9H, s); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 170.2, 143.7, 136.1, 132.7, 129.6, 128.6, 127.8, 127.4, 121.1, 104.1, 95.1, 50.0, 29.8, 20.2, 13.8; FD-LRMS *m*/*z* 699.34 ([2M+1]$^+$, 4%), 698.34 ([2M]$^+$, 7), 351.17 ([M+2]$^+$, 8), 350.17 ([M+1]$^+$, 30), 349.17 (M$^+$, 100).

To a solution of TMS-protected **15** (150 mg, 0.429 mmol) in THF/MeOH (1.1 mL/1.1 mL) was added K_2CO_3 (59 mg, 0.43 mmol), and the mixture was stirred at room temperature for 10 min, and then diluted with ethyl acetate. The diluted reaction mixture was washed with water and brine, dried over magnesium sulfate, and then concentrated. The residue was purified by column chromatography on SiO_2 (dichloromethane-1:19 ethyl acetate/dichloromethane) to give **15** (117 mg) as a white solid in 98% yield. An analytical sample was obtained as a white solid by further purification through GPC (chloroform), followed by recrystallization from benzene/hexane. **15**: mp 81-82 °C; elemental analyses Found: C, 82.23; H, 6.93; N, 5.06. Calc. for $C_{19}H_{19}NO$: C, 82.28; H, 6.90; N, 5.05%; IR (KBr) ν_{max}/cm^{-1} 3224, 3079, 3056, 3023, 2969, 2955, 2928, 2870, 2102, 1629, 1596, 1504; ^{1}H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.33 (2H, d, J = 8.4 Hz), 7.28-7.22 (3H, m), 7.19-7.15 (2H, m), 6.97 (2H, d, J = 8.4 Hz), 3.91 (2H, t, J = 7.6 Hz), 3.06 (1H, s), 1.63-1.56 (2H, m), 1.40-1.31 (2H, m), 0.91 (3H, t, J = 7.2 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 170.2, 144.0, 136.0, 132.9, 129.7, 128.6, 127.8, 127.5, 120.1, 82.7, 77.9, 50.1, 29.8, 20.2, 13.8; FD-LRMS *m*/*z* 555.27 ([2M+1]$^+$, 2%), 554.27 ([2M]$^+$, 6), 279.14 ([M+2]$^+$, 3), 278.14 ([M+1]$^+$, 22), 277.14 (M$^+$, 100).

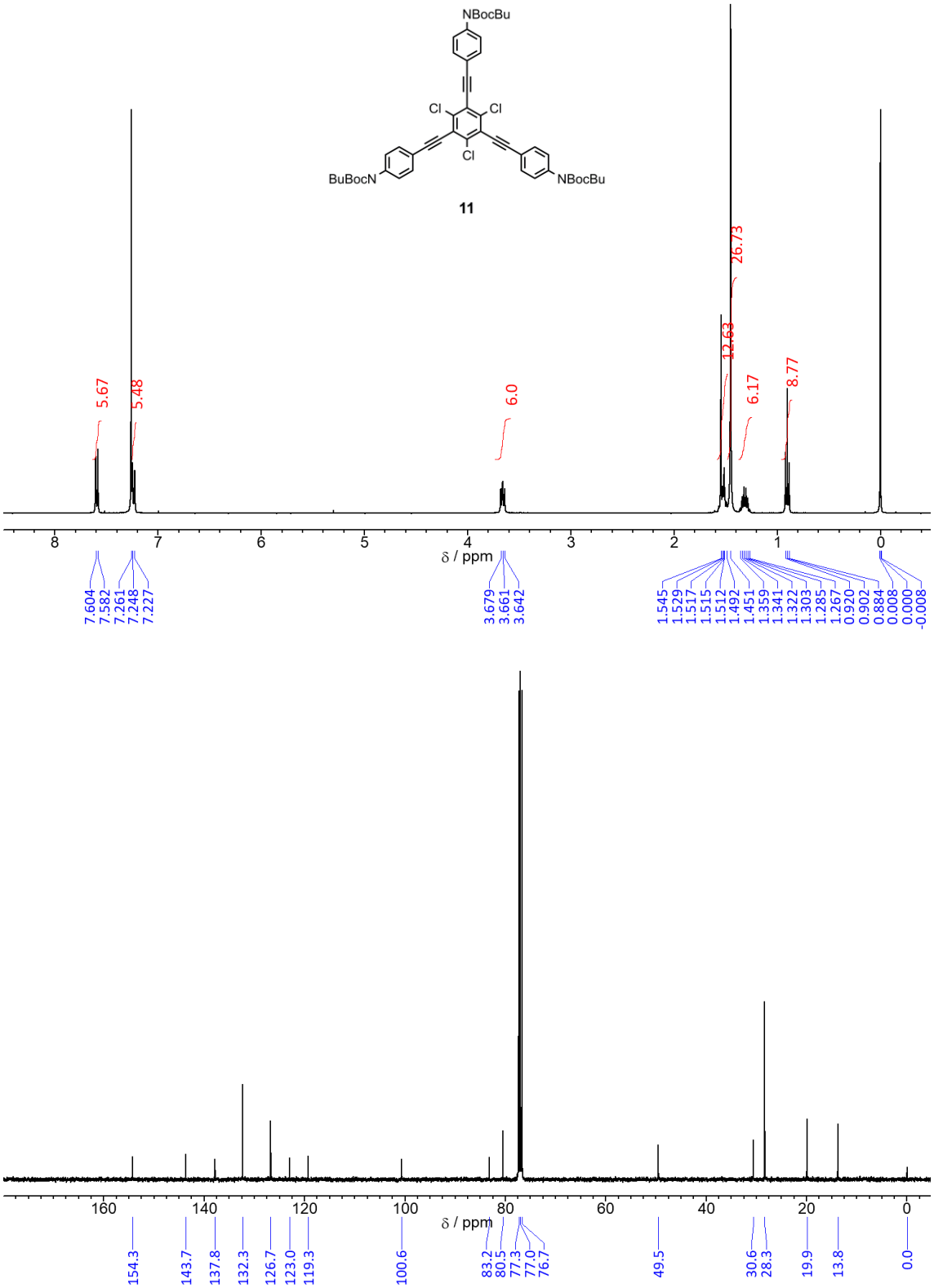
Preparation of 16

To a solution of **13**[3] (5.16 g, 13.8 mmol), $PdCl_2(PPh_3)_2$ (136 mg, 0.194 mmol) and CuI (65 mg, 0.34 mmol) in Et_3N (100 mL) was added TMSA (2.0 mL, 14 mmol) at room temperature under an argon atmosphere, and the reaction mixture was stirred at the temperature for 22 h. After removal of a solid by filtration through a Celite pad, the filtrate was concentrated and purified by column chromatography on SiO_2 (3:7-2:1 dichloromethane/hexane) to give TMS-protected **16** (4.69 g) as a white solid in 99% yield.

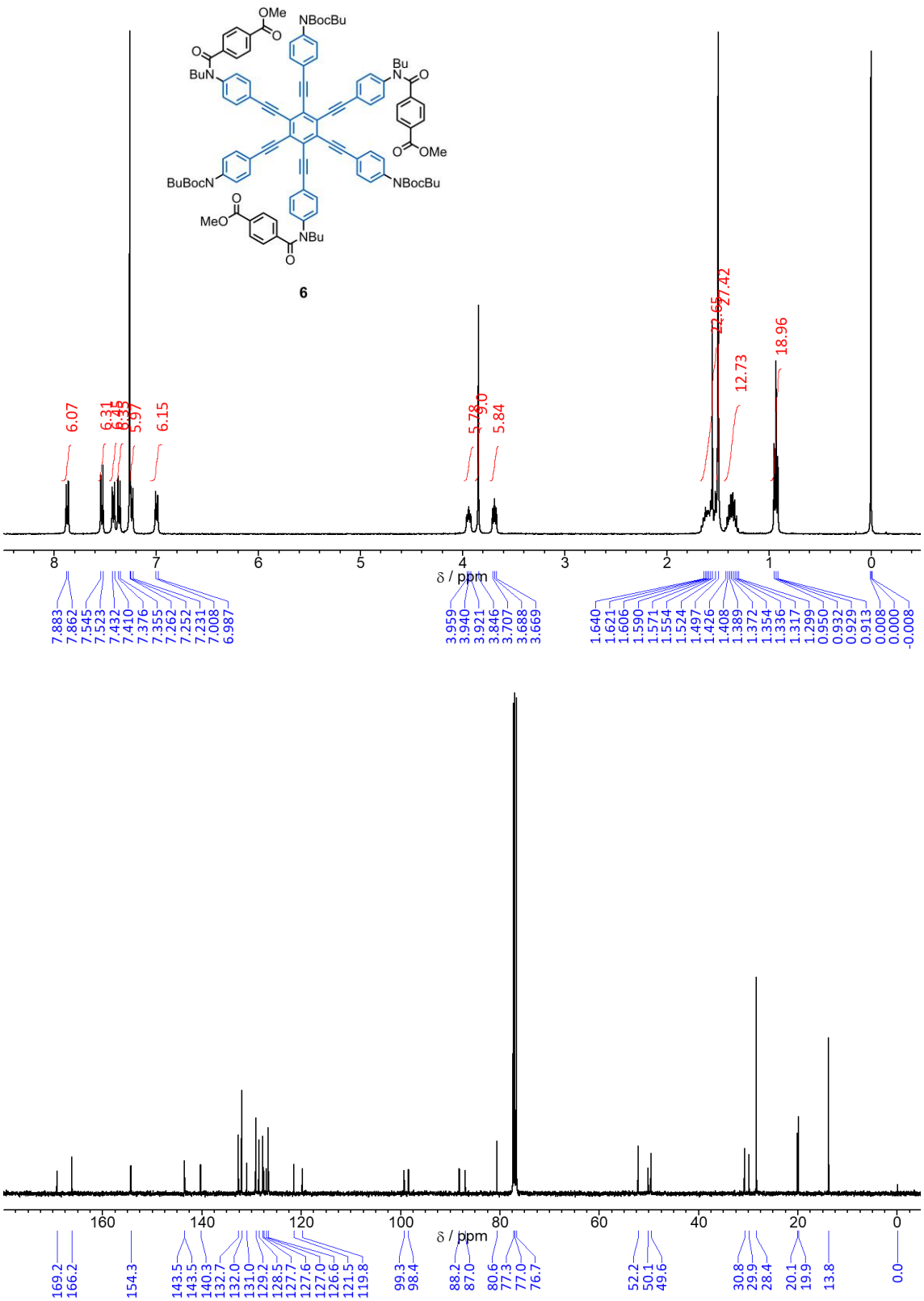
To a solution of TMS-protected **16** (4.69 g, 13.6 mmol) in THF/MeOH (66 mL/66 mL) was added K_2CO_3 (1.87 g, 13.6 mmol), and the mixture was stirred at room temperature for 40 min, and then diluted with ethyl acetate. The diluted reaction mixture was washed with water and brine, dried over magnesium sulfate, and then purified by column chromatography on SiO_2 (3:7-2:1 dichloromethane/hexane) to give **16** (3.44 g) as a white solid in 93% yield. An analytical sample was obtained as colorless crystals by recrystallization from dichloromethane/hexane. **16**: mp 71-72 °C;

elemental analyses Found: C, 74.66; H, 8.66; N, 4.97. Calc. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%; IR (KBr) ν_{max}/cm^{-1} 3241, 2954, 2929, 2872, 2103, 1915, 1683, 1602, 1506; ^1H NMR δ_H(400 MHz, $CDCl_3$, Me_4Si)/ppm 7.45 (2H, d, J = 8.4 Hz), 7.15 (2H, d, J = 8.4 Hz), 3.62 (2H, t, J = 7.6 Hz), 3.06 (1H, s), 1.54-1.47 (2H, m), 1.43 (9H, s), 1.34-1.25 (2H, m), 0.89 (3H, t, J = 7.6 Hz); ^{13}C NMR δ_C(100 MHz, $CDCl_3$)/ppm 154.3, 143.1, 132.5, 126.7, 119.3, 83.3, 80.3, 77.1, 49.5, 30.6, 28.3, 19.9, 13.7; FD-LRMS m/z 274.17 ($[M+1]^+$, 20%), 273.17 (M^+, 100).

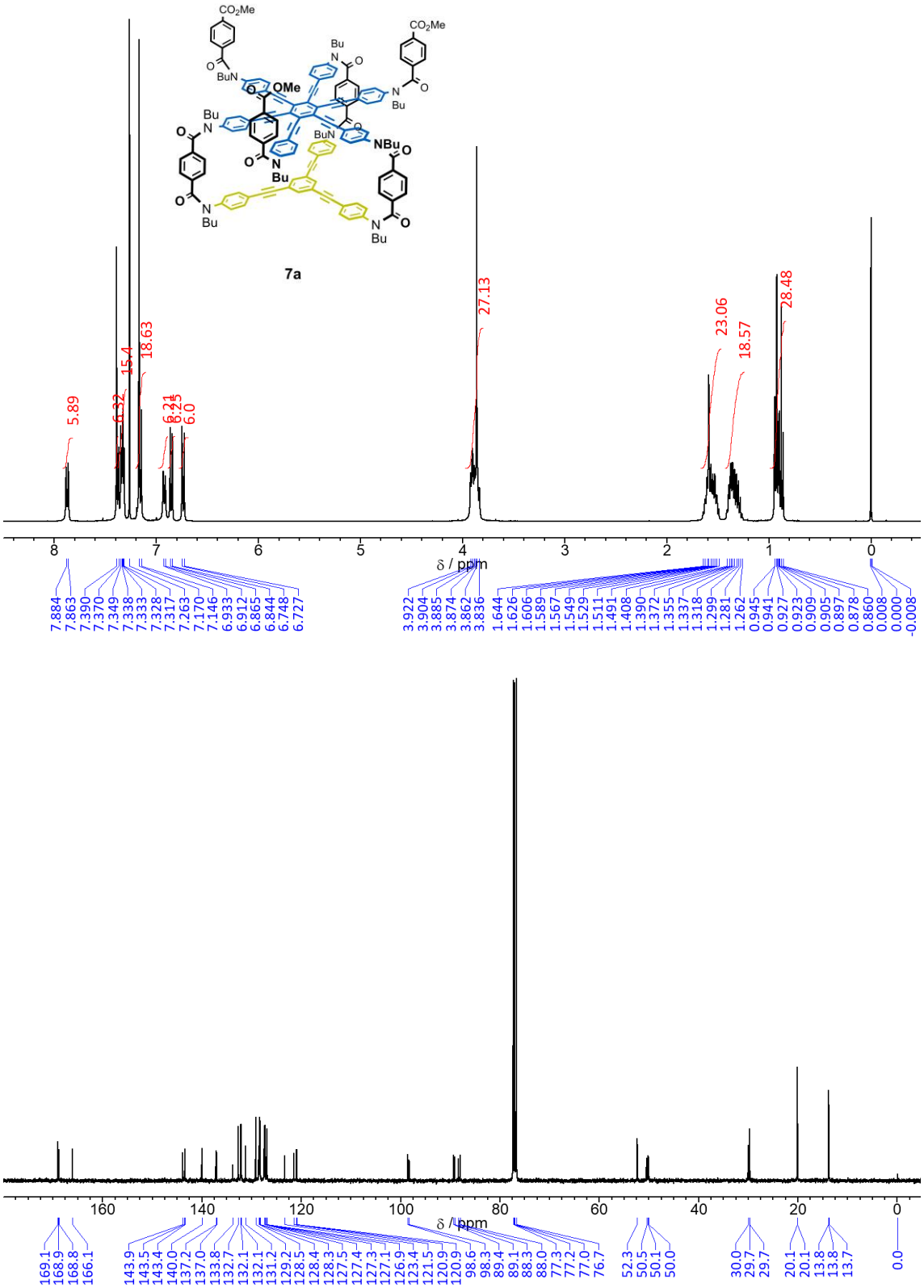
^{1}H and ^{13}C NMR spectra of new compounds



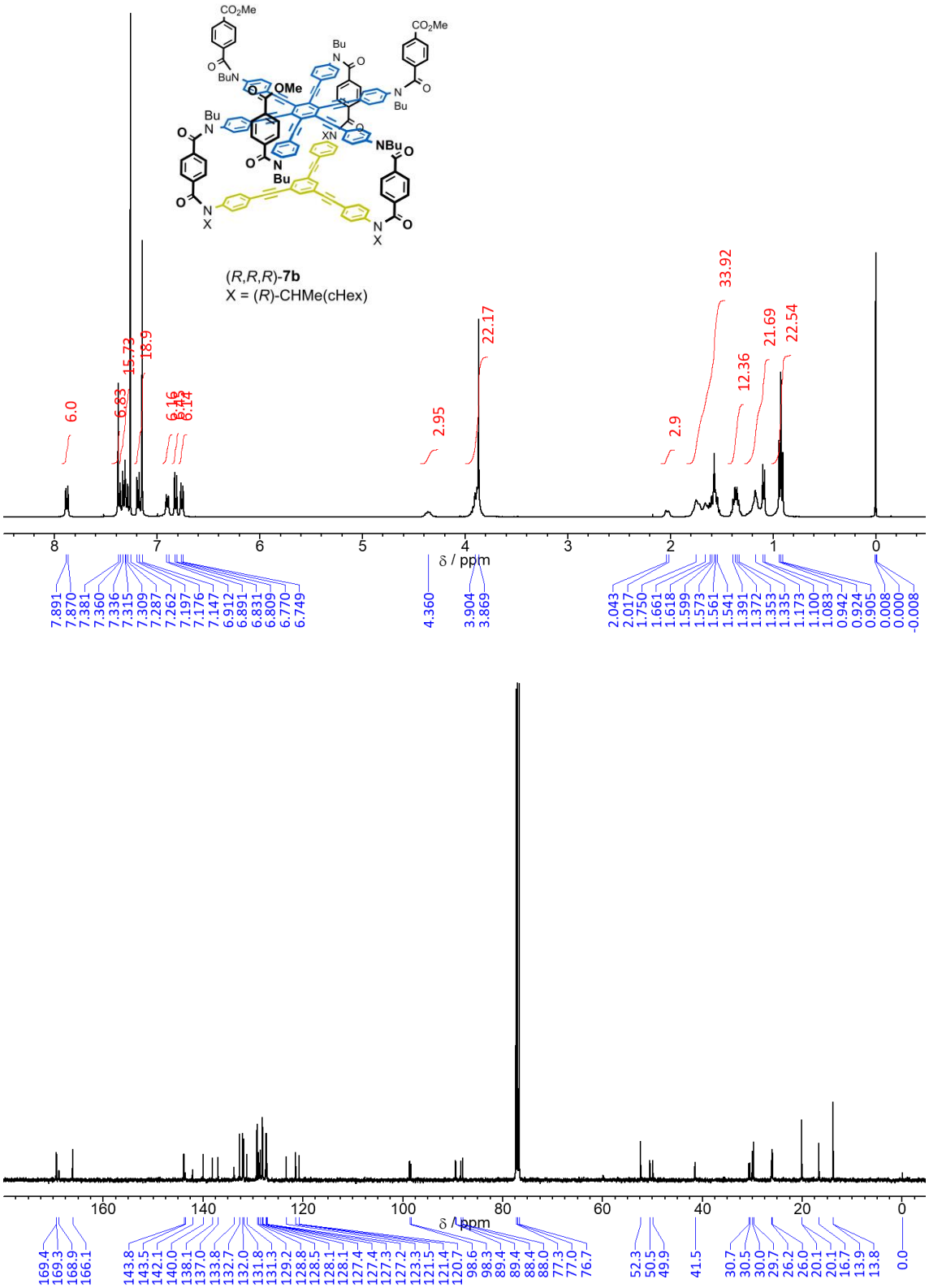
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **11**, measured in chloroform-*d* at room temperature.



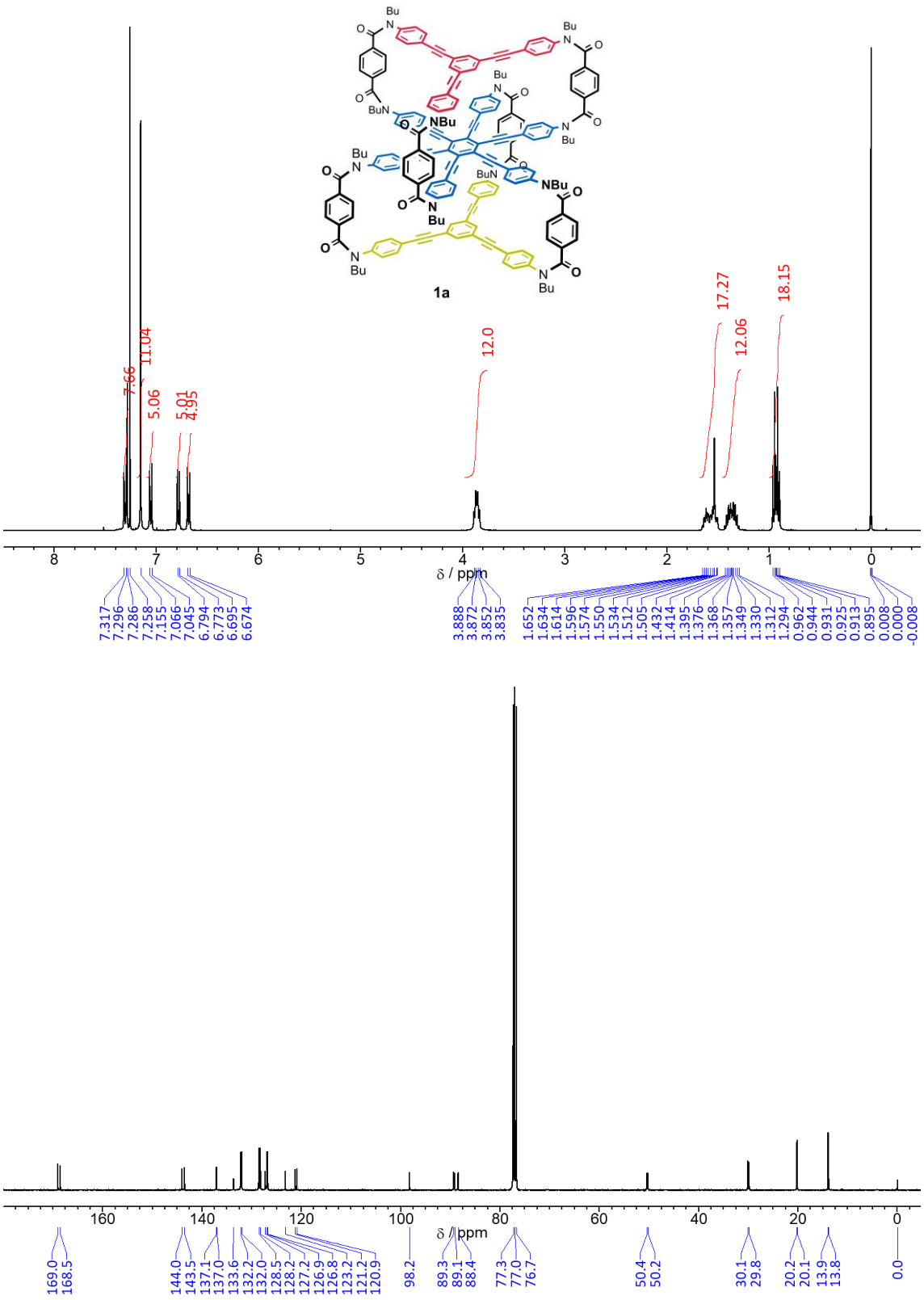
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **6**, measured in chloroform-*d* at room temperature.



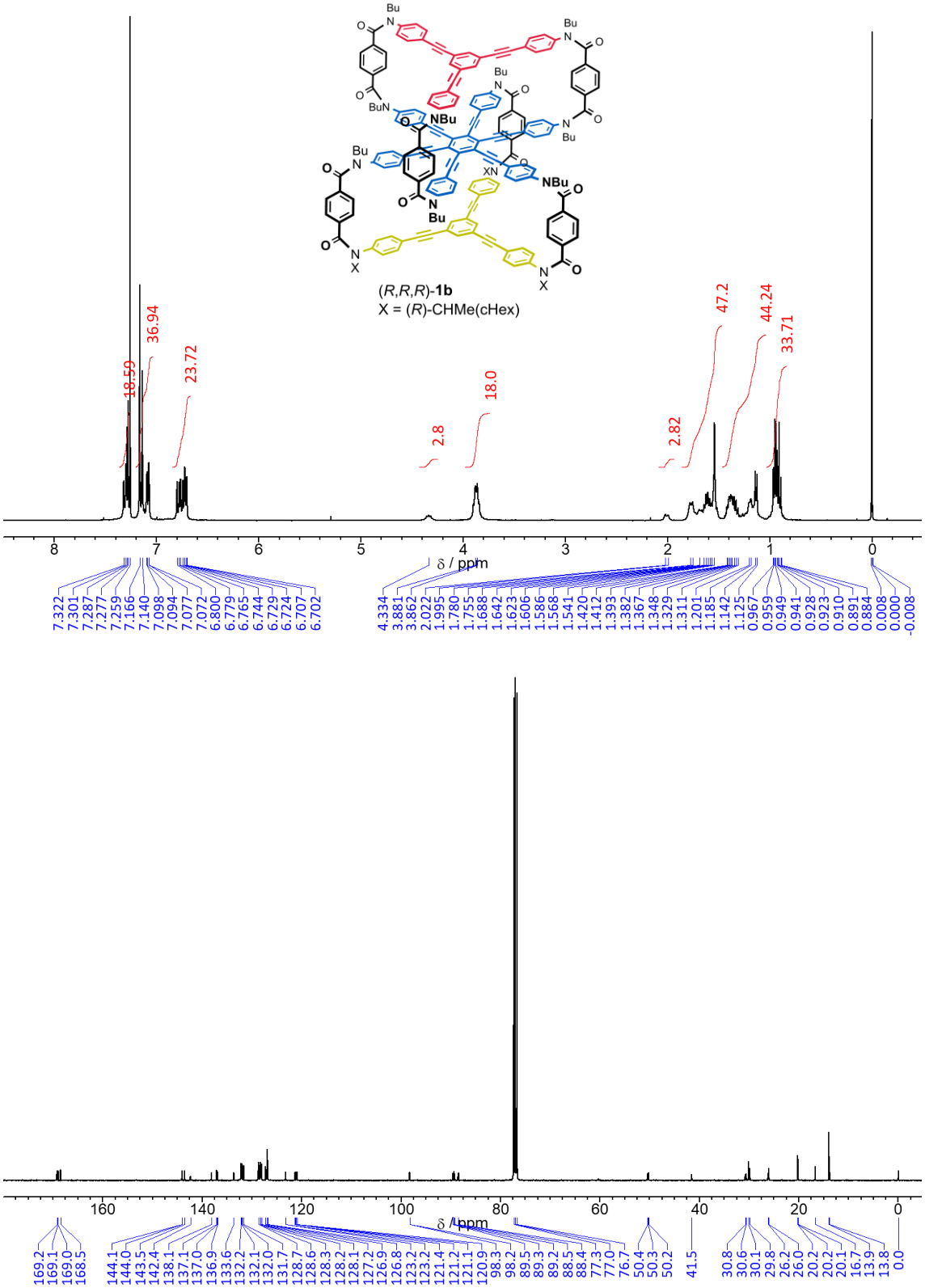
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **7a**, measured in chloroform-*d* at room temperature.



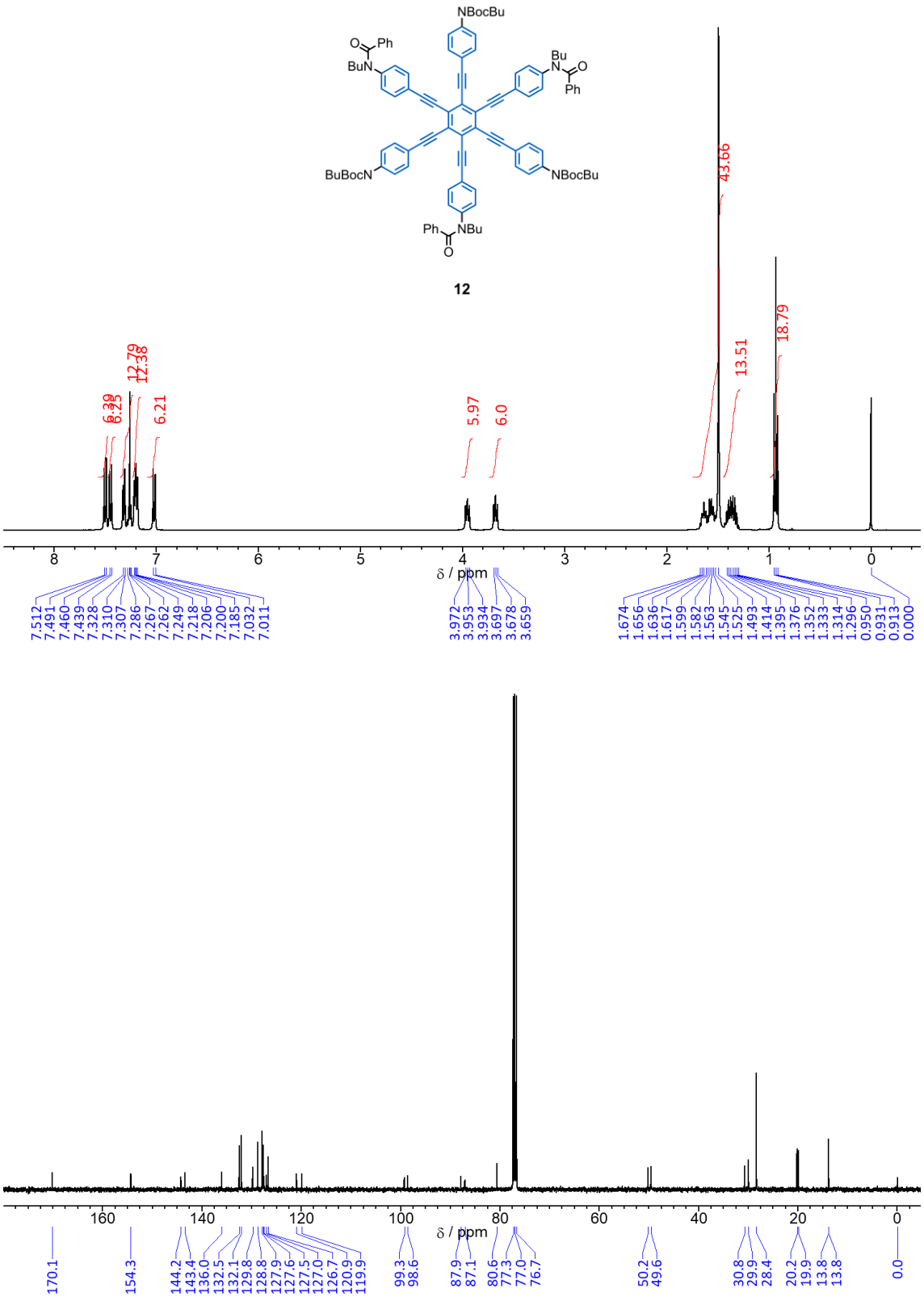
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of (*R*,*R*,*R*)-**7b**, measured in chloroform-*d* at room temperature.



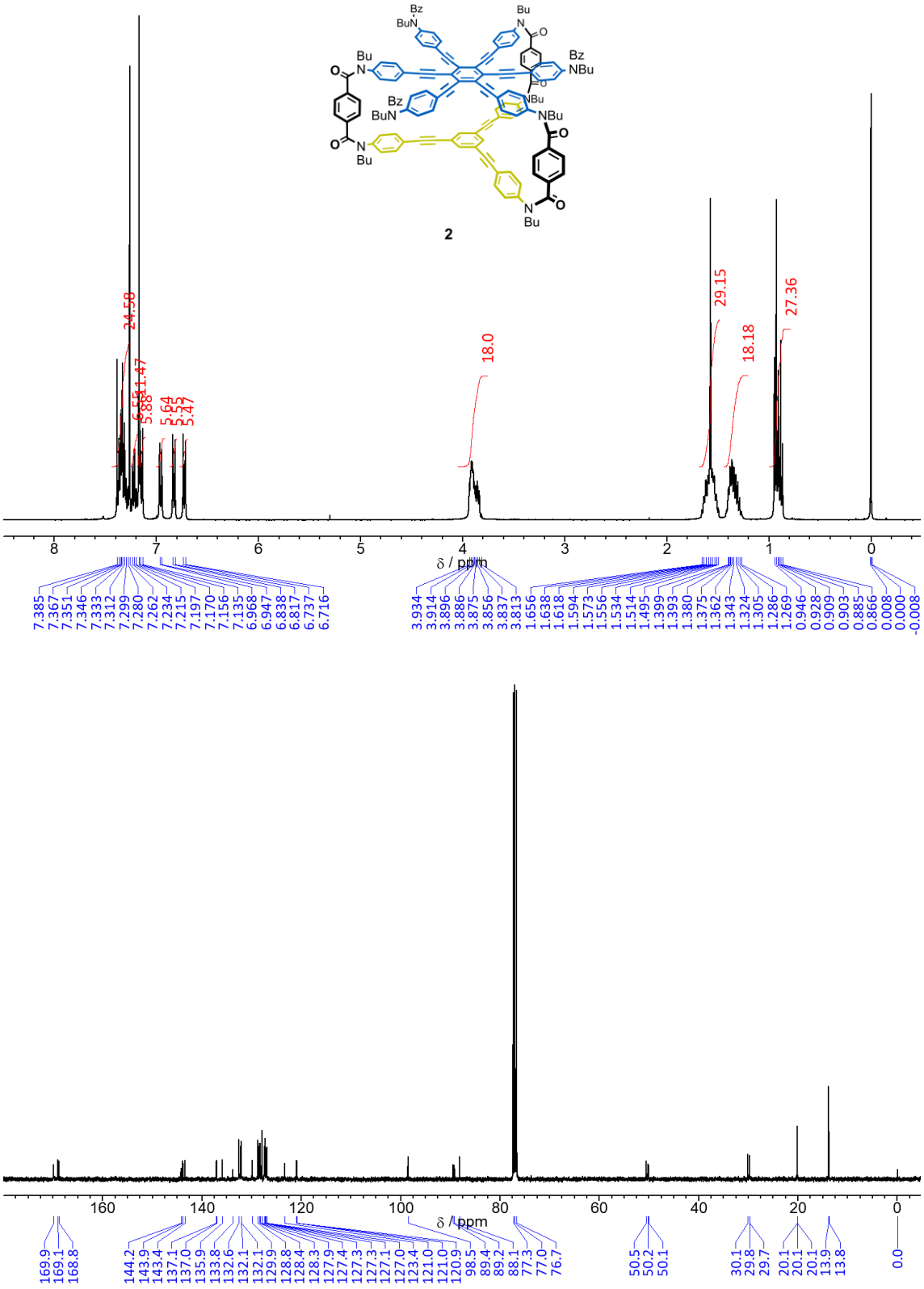
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **1a**, measured in chloroform-*d* at room temperature.



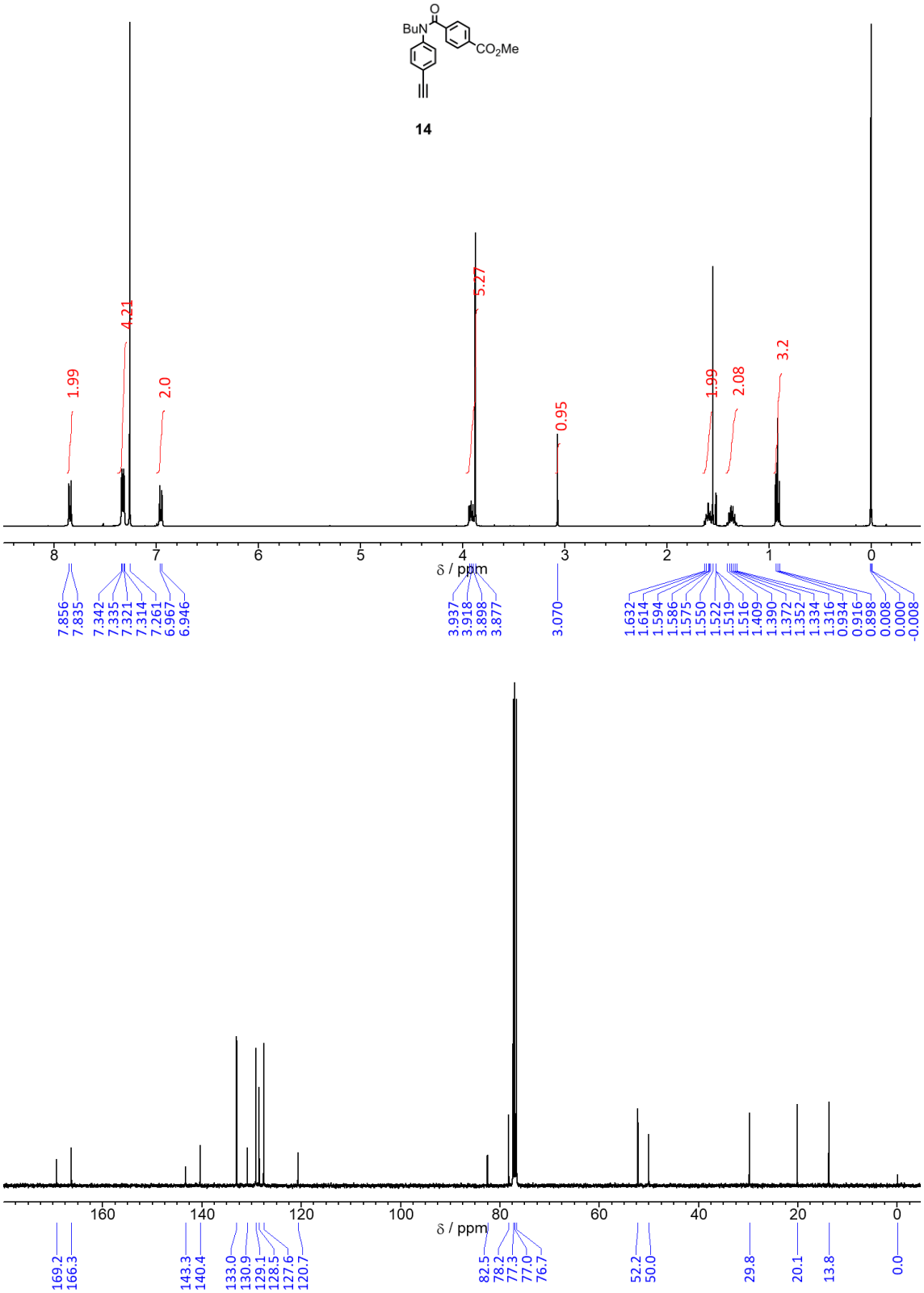
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of (*R*,*R*,*R*)-**1b**, measured in chloroform-*d* at room temperature.



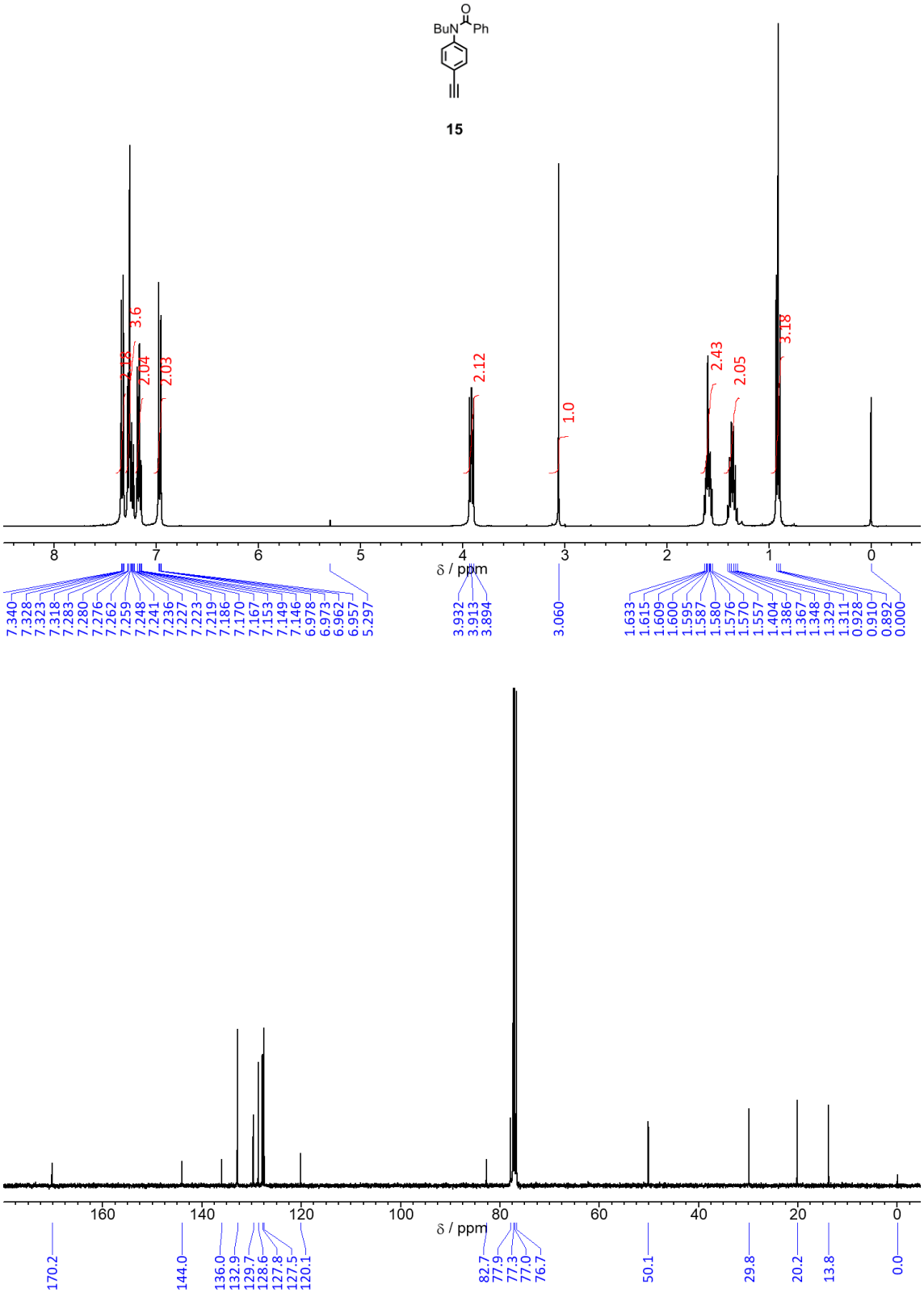
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **12**, measured in chloroform-*d* at room temperature.



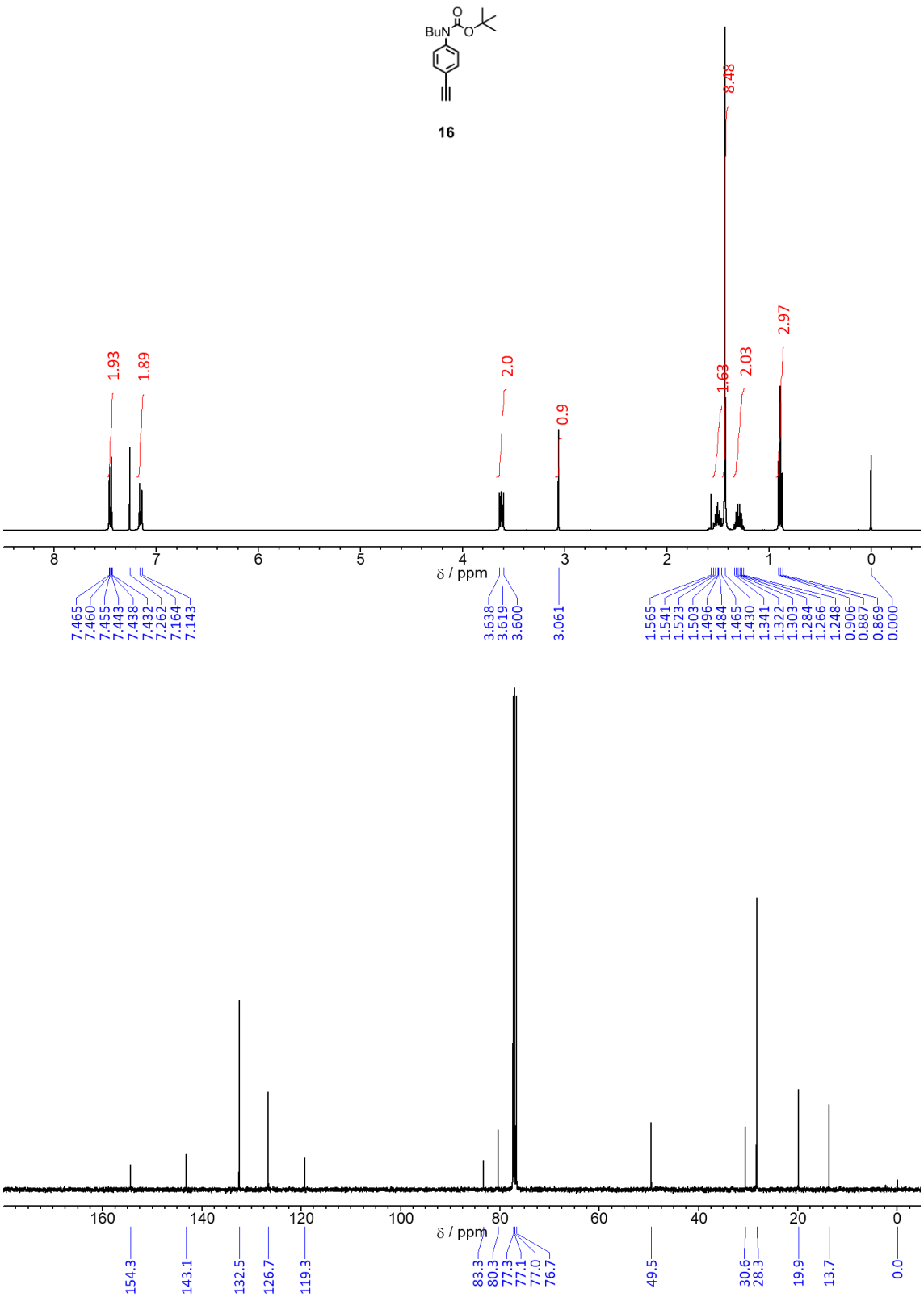
^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **2**, measured in chloroform-*d* at room temperature.



^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **14**, measured in chloroform-*d* at room temperature.



^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **15**, measured in chloroform-*d* at room temperature.



^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of **16**, measured in chloroform-*d* at room temperature.

References

1 Y. Tobe, N. Nakagawa, J. Kishi, M. Sonoda, K. Naemura, T. Wakabayashi, T. Shida and Y. Achiba, *Tetrahedron*, 2001, **57**, 3629−3636.

2 R. Katoono, K. Fujiwara and T. Suzuki, *Chem*. *Commun*., 2014, **50**, 5438−5440.

3 R. Katoono, H. Kawai, M. Ohkita, K. Fujiwara and T. Suzuki, *Chem*. *Commun*., 2013, **49**, 10352−10354.

4 P. Ehlers, A. Neubauer, S. Lochbrunner, A. Villinger and P. Langer, *Org*. *Lett*., 2011, **13**, 1618−1621.

5 (a) J. J. Wolff, F. Gredel, T. Oeser, H. Irngartinger and H. Pritzkow, *Chem*. *Eur*. *J*., 1999, **5**, 29−38; (b) M. Sonoda, A. Inaba, K. Itahashi and Y. Tobe, *Org*. *Lett*., 2001, **3**, 2419−2421.