Sulfoximine Version of Double Elimination Protocol for Synthesis of Chiral Acetylenic Cyclophanes

Akihiro Orita, De Lie An, Takehiko Nakano, Jayamma Yaruva, Nianchun Ma, and Junzo Otera*[a]

Abstract: A new strategy for constructing enantiopure acetylenic cyclophanes is described on the basis of one-pot double elimination reaction starting from dialdehydes and bis(sulfoximine)s. In this case, the conventional sulfone protocol affords poorer yields of the desired cyclophanes. Thus, arylene – ethynylene moieties with terminal sulfoximine or formyl functions are linked to binaphthyl cores and these building blocks are then subjected to double elimination reaction. The desired macrocycles are obtained in up to 35% yield. The corresponding Sonogashira coupling fails to afford cyclophanes indicative of effectiveness of the double elimination methodology.

Keywords: alkynes · arenes · chiral auxiliaries · elimination · synthetic method

Introduction

Cyclophanes with an arylene–ethynylene motif have attracted extensive attention in view of both synthetic and physical organic chemistries.[1] In addition, these macrocycles are of particular promise in terms of applications to new materials in electronics[2] and precursors for novel carbon materials.[3] From the synthetic standpoint, incorporation of acetylene units in the ring system is a key technology to this end. Since the linear disposition is strongly directed with sp carbon, the coupling between terminal acetylenes and aryl halides, which is the most commonly employed technology for generating aryl–acetylene bond,[4] often suffers low yield in cyclization.

Another subject that remains unexplored is the synthesis of chiral derivatives, for which useful optical properties are expected. In addition, these compounds may serve as unique chiral host molecules. Several chiral acetylenic cyclophanes were reported, but, unfortunately, most of them were obtained as racemates.[3b, 5] According to our literature survey, the studies on non-racemic compounds are rather limited.[6] All of these procedures made recourse to the terminal acetylene coupling technology.

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In the preceding paper, we disclosed that the double elimination methodology is effective for constructing cyclic acetylenes because, in this protocol, the carbon–carbon bond is initially formed between sp^3 carbons and the successive eliminations follow giving rise to sp^2 and finally sp carbons in a stepwise manner.[7] As a result, involvement of bent sp^3 or sp^2 carbons should allow this protocol to build arylene–ethynylene cyclophane skeletons more easily than the terminal acetylene coupling modes. We present here a double elimination strategy for the rational design of this class of compounds by use of binaphthyl group as a stereogenic arylene moiety. Furthermore, it is demonstrated that sulfoximines serve as better substrates than sulfones for cyclization.

Results and Discussion

First, we attempted application of the conventional double elimination reaction involving coupling between disulfone and dialdehyde units as shown in Scheme 1. A binaphthyl group with *R* conformer was employed as a stereogenic core,[8] to which arylene–ethynylene moieties with terminal sulfone or formyl functions are linked.

These building blocks, **1** and **2**, were readily prepared according to the procedures shown in Schemes 2 and 3.[9] Unfortunately, however, the double elimination reaction between these partners led to poor yields of the desired macrocycles **3** (Scheme 1).

Then, we turned our attention to employ sulfoximines **13** instead of **1**. The synthesis of **13** is shown in Scheme 4, where the requisite sulfoximine was conveniently synthesized by

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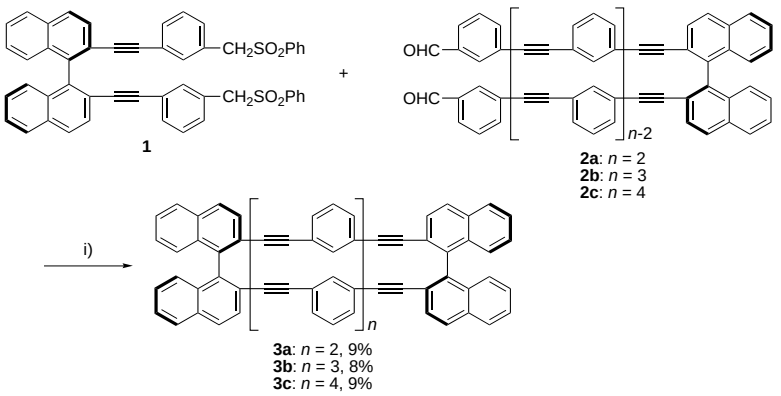
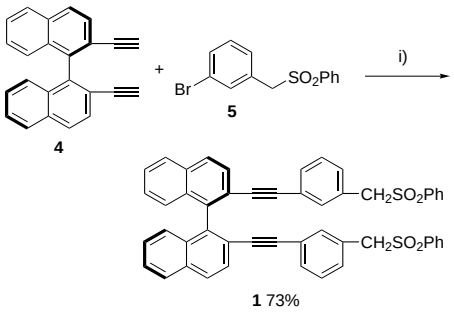


Scheme 1. i) BuLi, THF; $ClP(O)(OEt)_2$; *t*BuOK.



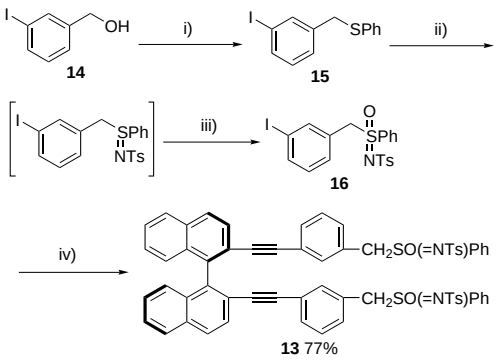
Scheme 2. i) $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 75 °C, 12 h.

one-pot conversion of sulfide through successive action of Chloramine-T[10] and $RuO_2/NaIO_4$.[11]

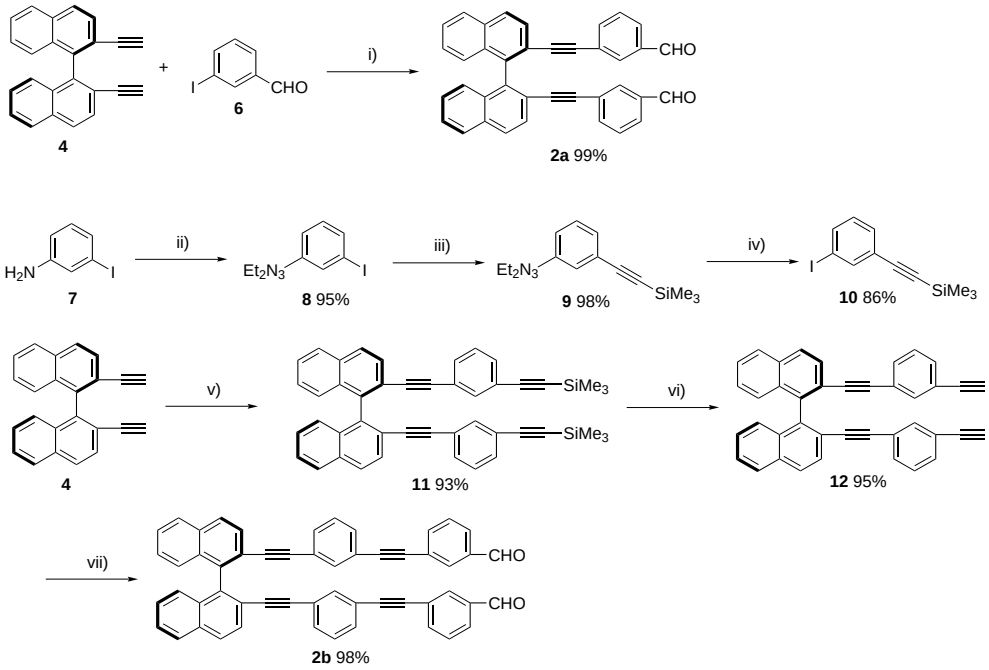
Treatment of **13** with **2** under double elimination conditions led to a good deal of improvement for the yield of **3** (Scheme 5).

The same methodology was applied to pyridine-containing cyclophane **18** (Scheme 6). The yield was better than the sulfone protocol.

Another type of sulfoximine **19** was also successfully employed to provide **3c** (Scheme 7). It should be noted that the Sonogashira-coupling failed to afford the desired macrocycle (Scheme 8). Only a trace amount of **3a** was detected on TLC upon treatment of diacetylene **12** and diiodide **20**, indicative of the effectiveness of the double elimination protocol. As a consequence, the convergent double elimination methodology has been achieved to afford a variety of non-racemic acetylenic cyclophanes. These results suggest the



Scheme 4. i) $(PhS)_2$, Bu_3P; ii) Chloramine-T; iii) RuO_2, $NaIO_4$; iv) **4**, $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 75 °C, 12 h.



Scheme 3. i) $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 75 °C, 12 h; ii) $NaNO_2$, HCl; then Et_2NH, K_2CO_3; iii) trimethylsilylacetylene, $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 50 °C, 3 h; iv) MeI, 130 °C, 12 h; v) **10**, $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 75 °C, 15 h; vi) K_2CO_3, THF, MeOH; vii) **6**, $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene, 75 °C, 12 h.

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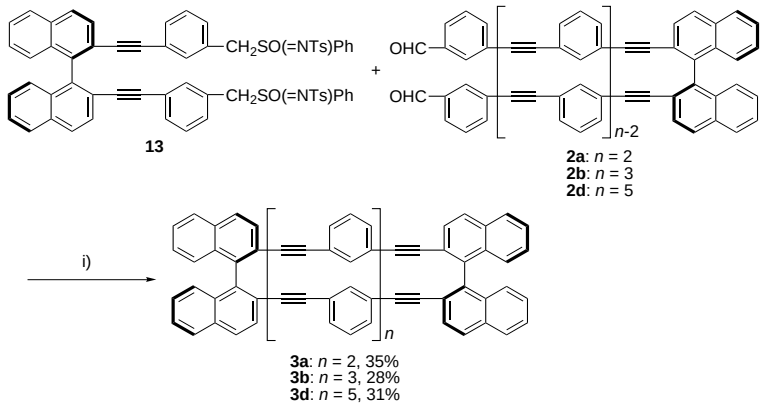
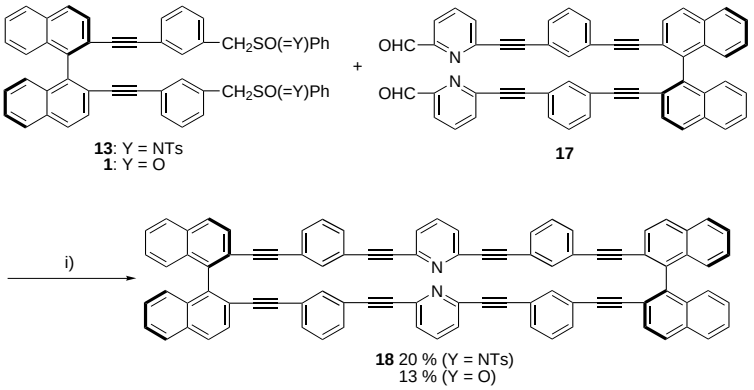
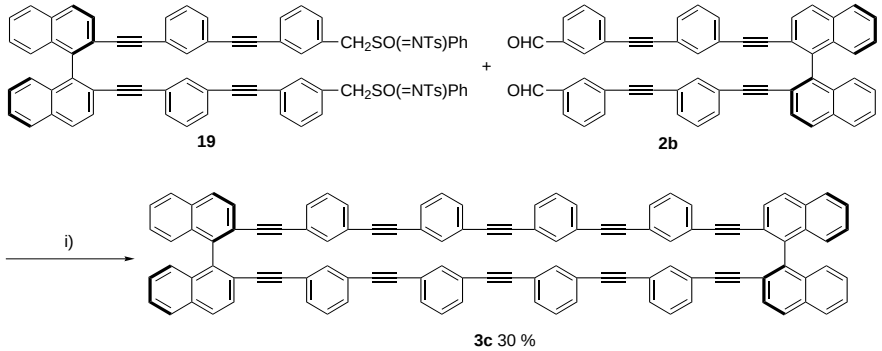


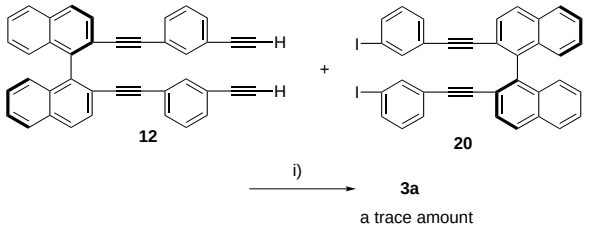
Scheme 5. i) BuLi, THF; $ClP(O)(OEt)_2$; *t*BuOK.



Scheme 6. i) BuLi, THF; $ClP(O)(OEt)_2$; *t*BuOK.



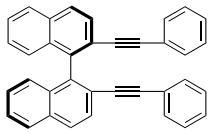
Scheme 7. i) BuLi, THF; $ClP(O)(OEt)_2$; *t*BuOK.



Scheme 8. i) $[Pd(Ph_3P)_4]$, CuI, iPr_2NH, toluene.

synthetic potential of sulfoximine chemistry although rather little attention has been paid on this field so far.

CD spectra of the acetylenic cyclophanes thus obtained are shown in Figure 1 together with that of the smallest one (*R*,*P*)-**3e** ($n=1$). This compound was prepared separately by iterative Sonogashira reactions and found to possess a twisted double helical structure on the basis of X-ray analysis.[12] A characteristic CD spectral profile of this compound is apparent by comparison with an acyclic compound (*R*)-**21**.[13]



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The rigid double helical structure of **3e** is reflected on disappearance of the strong Cotton effect with zero-point at 320 nm observed for (*R*)-**21** concurrent with loss of a negative peak at 340 nm. On the other hand, the higher homologues **3a–d** give rise to different patterns. The revival of the Cotton effect in these compounds implies that the arylene–acetylene rings are so flexible that the double helical structure could not be fixed. Notably, the strength of the negative peak at 340 nm increases with increasing ring size. Apparently, the relatively smaller compounds such as **3a–c** are partially twisted while virtually no double helicity remains on the largest ring of **3d**. In other words, the CD spectroscopy serves for diagnosis of the helicity of acetylenic cyclophanes.

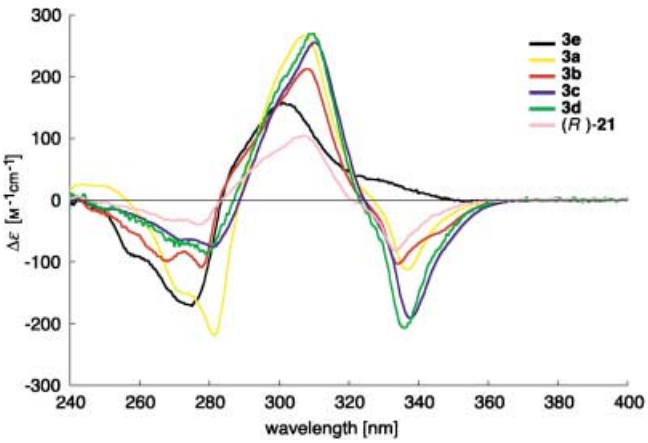

Figure 1. CD spectra of acetylenic cyclophanes.

In summary, the double elimination protocol has proved to be effective for the synthesis of acetylenic cyclophanes. The difficulty encountered in the cyclization involving sp carbon can be overcome by bond formation between sp^3 or sp^2 carbons prior to generation of sp carbons. In case where sulfones are not effective, sulfoximines may serve better. The sulfoximine protocol thus achieved is not necessarily excellent with respect to yield, yet acceptable if the difficulties in this sort of cyclization technology is taken into account. The conciseness of the process and successful synthesis of otherwise difficult-to-obtain molecules will find a wide range of applications.

Experimental Section

General: All reactions were carried out under an atmosphere of nitrogen with freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Other solvents such as toluene and diisopropylamine were distilled from CaH_2. A hexane solution of BuLi was purchased from Aldrich and titrated before use by Gilman method.[14] $[Pd(PPh_3)_4]$ was prepared according to the reported method.[15] Silica gel (Daiso gel IR-60) was used for column chromatography. NMR spectra were recorded at 25 °C on Varian Gemini-300, JEOL Lambda 300 and JEOL Lambda 500 instruments and calibrated with tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on JEOL MStation JMS-700, Shimadzu/Kratos MALDI 4 and Platform II single quadrupole (Micromass, Altrinchan, UK) mass spectrometers. Elemental analyses were performed by the Perkin–Elmer PE 2400. Optical rotation was measured on a JASCO DIP-1000 polarimeter. UV/Vis and circular dichroism were measured on HITACHI U-3000 and JASCO J-820 spectrometers, respectively.

Synthesis of 3 with disulfone 1 (representative) (Scheme 1): BuLi (1.39 M in hexane, 1.99 mL, 2.76 mmol) was added to a THF solution (25 mL) of disulphone **1** (1.05 g, 1.38 mmol) at −78 °C, and the mixture was stirred for 1 h. Dialdehyde **2a** (705 mg, 1.38 mmol) in THF (50 mL) was added dropwise over 30 min at this temperature. After an additional 1 h, $ClP(O)(OEt)_2$ (0.44 mL, 3.04 mmol) was added at −78 °C and the mixture was stirred at room temperature for 1 h. After addition of *t*BuOK (3.81 g, 27.6 mmol) at −78 °C, the mixture was stirred at this temperature for 10 min and, then, at room temperature for 3 h. After usual work-up with aqueous NH_4Cl solution and AcOEt, the organic layer was evaporated. The crude mixture was subjected to column chromatography (hexane/CH_2Cl_2 2:1) to give **3a** (114 mg, 9 %) as a pale yellow foam. The similar treatment of **1a** (1.05 g, 1.38 mmol) with **2b** (981 mg, 1.38 mmol) or **2c** (1.26 g, 1.38 mmol) furnished **3b** (127 mg, 8 %) or **3c** (168 mg, 9 %), respectively. Characterization data of these compounds are given later.

Preparation of 1 (Scheme 2): A 100 mL flask was charged with **4** (913 mg, 3.02 mmol), **5** (2.35 g, 7.55 mmol), $[Pd(Ph_3P)_4]$ (174 mg, 0.15 mmol), CuI (29 mg, 0.15 mmol), diisopropylamine (10 mL) and toluene (50 mL). After being stirred at 75 °C for 12 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was purified by chromatography (CH_2Cl_2/AcOEt 50:1) to give **1** (1.68 g, 73 %) as a yellow foam. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.10$ (s, 4 H), 6.49 (s, 2 H), 6.64 (d, $J = 7.6$ Hz, 2 H), 6.82 (d, $J = 7.6$ Hz, 2 H), 6.96 (t, $J = 7.8$ Hz, 2 H), 7.28–7.36 (m, 8 H), 7.47–7.50 (m, 4 H), 7.53 (d, $J = 8.3$ Hz, 4 H), 7.72 (d, $J = 8.6$ Hz, 2 H), 7.95 (d, $J = 7.0$ Hz, 2 H), 7.97 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 62.35$ (2 CH_2), 90.03 (2 C≡), 92.65 (2 C≡), 121.28 (2 C), 123.54 (2 C), 126.54 (2 CH), 126.56 (2 CH), 126.77 (2 CH), 127.97 (2 CH), 127.98 (2 CH), 128.04 (2 CH), 128.07 (2 C), 128.13 (2 CH), 128.40 (4 CH), 128.81 (4 CH), 130.05 (2 CH), 131.35 (2 CH), 132.49 (2 C), 132.97(2 C), 133.40 (2 CH), 133.69 (2 CH), 137.53 (2 C), 140.31 (2 C); ESI-MS: calcd for 762.19; found 762.01 $[M]^+$.

Preparation of 2a (Scheme 3): A 100 mL flask was charged with **4** (493 mg, 1.63 mmol), **6** (873 mg, 3.76 mmol), $[Pd(Ph_3P)_4]$ (92 mg, 0.08 mmol), CuI (15 mg, 0.08 mmol), diisopropylamine (5 mL) and toluene (25 mL). After being stirred at 75 °C for 15 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was prified by chromatography (hexane/CH_2Cl_2 1:3) to give **2a** (824 mg, 99 %) as a yellow foam. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.99$ (d, $J = 7.7$ Hz, 2 H), 7.12 (s, 2 H), 7.26 (t, $J = 7.7$ Hz, 2 H), 7.35–7.42 (m, 4 H), 7.53 (t, $J = 7.3$ Hz, 2 H), 7.64 (d, $J = 7.7$ Hz, 2 H), 7.79 (d, $J = 8.5$ Hz, 2 H), 8.00 (d, $J = 8.3$ Hz, 2 H), 8.03 (d, $J = 8.5$ Hz, 2 H), 9.81 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 90.86$ (2 C≡), 92.14 (2 C≡), 121.06 (2 C), 124.16 (2 C), 126.56 (2 CH), 126.83 (2 CH), 126.95 (2 CH), 127.93 (2 CH), 128.08 (2 CH), 128.17 (2 CH), 128.20 (2 CH), 128.64 (2 CH), 132.53 (2 C), 132.91 (2 CH), 133.13 (2 C), 136.11 (2 C), 136.43 (2 CH), 140.66 (2 C), 191.28 (2 CHO); ESI-MS: calcd for 510.16; found 510.21 $[M]^+$.

Preparation of 2b (Scheme 3): A 100 mL flask was charged with **12** (1.57 g, 3.12 mmol), **6** (1.67 g, 7.18 mmol), $[Pd(Ph_3P)_4]$ (180 mg, 0.16 mmol), CuI (30 mg, 0.16 mmol), diisopropylamine (10 mL) and toluene (50 mL). After being stirred at 75 °C for 12 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was purified by chromatography (hexane/CH_2Cl_2 1:3) to give **2b** (2.18 g, 98 %) as a pale yellow foam. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 6.71$ (d, $J = 7.7$ Hz, 2 H), 6.94 (s, 2 H), 7.10 (t, $J = 7.8$ Hz, 2 H), 7.30 (d, $J = 8.0$ Hz, 2 H), 7.34–7.40 (m, 4 H), 7.51–7.55 (m, 4 H), 7.75 (d, $J = 7.7$ Hz, 2 H), 7.79 (d, $J = 8.6$ Hz, 2 H), 7.85 (d, $J = 7.7$ Hz, 2 H), 7.99 (d, $J = 8.0$ Hz, 2 H), 8.01 (s, 2 H), 8.02 (d, $J = 8.0$ Hz, 2 H), 10.03 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 88.11$ (2 C≡), 90.01 (2 C≡), 90.18 (2 C≡), 92.60 (2 C≡), 121.31 (2 C), 122.51 (2 C), 123.52 (2 C), 124.20 (2 C), 126.56 (2 CH), 126.67 (2 CH), 126.86 (2 CH), 128.03 (2 CH), 128.08 (2 CH), 128.10 (2 CH), 128.13 (2 CH), 129.04 (2 CH), 129.06 (2 CH), 130.87 (2 CH), 131.29 (2 CH), 132.55 (2 C), 132.73 (2 CH), 133.05 (2 C), 134.25 (2 CH), 136.41 (2 C), 136.95 (2 CH), 140.44 (2 C), 191.39 (2 CHO); ESI-MS: calcd for 710.2; found 710.0 $[M]^+$.

Preparation of 15 (Scheme 4): A 100 mL flask was charged with **14** (9.2 g, 39.3 mmol), diphenyl disulfide (9.4 g, 43.1 mmol) and THF (40 mL). Tributylphosphine (8.7 g, 43.1 mmol) was added dropwise slowly at room temperature with stirring, and then the resulting solution was stirred for 6 h. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with NaOH (aq. 10 %) followed by brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was purified by chromatography (hexane/AcOEt 50:1) to give **15** (12.2 g, 95 %) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.01$ (s, 2 H), 6.99 (t, $J = 7.8$ Hz, 1 H), 7.21 (t, $J = 6.6$ Hz, 2 H), 7.24–7.29 (m, 4 H), 7.55 (d, $J = 7.9$ Hz, 1 H), 7.61 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 38.53 (CH_2), 94.23 (C), 126.70 (CH), 127.96 (CH), 128.87 (2 CH), 130.06 (CH), 130.28 (2 CH), 135.53 (C), 136.13 (CH), 137.67(CH), 139.91 (C).

Preparation of 16 (Scheme 4): Solid Chloramine-T trihydrate (7.8 g, 27.7 mmol) was added slowly with stirring at room temperature to a solution of sulfide **15** (7.02 g, 21.5 mmol) and tributyl hexadecylphosphonium bromide (639 mg, 1.26 mmol) in CH_2Cl_2 (70 mL). The mixture was stirred at 35 °C for 3 h. After addition of CH_2Cl_2 (20 mL), RuO_2(167 mg, 1.25 mmol) and $NaIO_4$ (10.8 g, 50.5 mmol) in H_2O (60 mL) were added. After being stirred for overnight, the reaction mixture was extracted with CH_2Cl_2. Isopropanol (12 mL) was added to organic layer and the mixture was stirred for 10 min to reduce residual ruthenium tetroxide to the insoluble ruthenium dioxide. The mixture was then dried over $MgSO_4$ and filtered. The solvent was evaporated in vacuo, and the residue was purified by chromatography (CH_2Cl_2/AcOEt 30:1) to give **16** (10.7 g, 97 %) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3 H), 4.71, 4.79 (AB, $J_{AB} = 13.8$ Hz, 2 H), 6.98 (t, $J = 7.7$ Hz, 1 H), 7.09 (d, $J = 7.7$ Hz, 1 H), 7.18 (s, 1 H), 7.26 (d, $J = 7.9$ Hz, 2 H), 7.49 (t, $J = 7.9$ Hz, 2 H), 7.63–7.68 (m, 4 H), 7.87 (d, $J = 8.3$ Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.35$ (Me), 63.56 (CH_2), 93.62 (C), 126.37 (2 CH), 128.54 (2 CH), 128.65 (C), 129.04 (2 CH), 129.09 (2 CH), 130.03 (CH), 130.48 (CH), 134.26 (C), 134.44 (CH), 138.11 (CH), 139.80 (CH), 140.54 (C), 142.66 (C).

Preparation of 13 (Scheme 4): A 100 mL flask was charged with **4** (1.0 g, 3.3 mmol), **16** (3.8 g, 7.45 mmol), $[Pd(Ph_3P)_4]$ (191 mg, 0.17 mmol), CuI (32 mg, 0.17 mmol), diisopropylamine (10 mL) and toluene (50 mL). After being stirred at 75 °C for 12 h, the reaction mixture was cooled to room

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temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was purified by chromatography (CH_2Cl_2/AcOEt 25:1) to give **13** (2.73 g, 77%) as a yellow foam (a mixture of diastereomers). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.37$ (s, 6H), 4.50–4.54 (m, 2H), 4.68–4.74 (m, 2H), 6.27–6.34 (m, 2H), 6.63–6.65 (m, 2H), 6.79 (d, $J = 6.7$ Hz, 2H), 6.94 (t, $J = 7.6$ Hz, 2H), 7.24 (d, $J = 7.4$ Hz, 4H), 7.29–7.34 (m, 8H), 7.45–7.52 (m, 8H), 7.71 (dd, $J = 8.6$, 2.5 Hz, 2H), 7.86 (d, $J = 7.0$ Hz, 2H), 7.87 (d, $J = 7.4$ Hz, 2H), 7.95 (d, $J = 8.9$ Hz, 2H), 7.97 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.21$ (Me), 63.77 (CH_2), 90.03 (C≡), 90.04 (C≡), 90.06 (C≡), 90.08 (C≡), 92.22 (C≡), 92.24 (C≡), 92.25 (C≡), 120.88 (C), 120.95 (C), 123.25 (C), 126.23 (CH), 126.27 (CH), 126.34 (C), 126.46 (CH), 126.54 (CH), 126.62 (CH), 126.67 (CH), 127.69 (CH), 127.75 (CH), 127.87 (CH), 127.94 (CH), 128.01 (CH), 128.26 (CH), 128.81 (CH), 128.97 (CH), 130.43 (CH), 131.59 (CH), 131.62 (CH), 132.21 (C), 132.75 (C), 132.78 (C), 133.70 (CH), 133.75 (CH), 134.12 (CH), 134.26 (C), 140.07 (C),140.10 (C),140.12 (C), 140.14 (C), 140.60 (C), 140.63 (C), 142.50 (C); ESI-MS: calcd for 940.32; found 940.66 $[M]^+$.

Synthesis of 3 with bis(sufoximine) (representative procedure) (Scheme 5): BuLi (1.39 M in hexane, 0.81 mL, 1.13 mmol) was added at −78 °C to a THF solution (50 mL) of bis(sulfoximine) **13** (547 mg, 0.51 mmol), and the mixture was stirred for 5 min. Dialdehyde **2a** (286 mg, 0.56 mmol) in THF (25 mL) was added dropwise over 20 min at this temperature. After an additional 1 h, $ClP(O)(OEt)_2$ (0.21 mL, 1.41 mmol) was added at −78 °C and the mixture was stirred at room temperature for 1 h. After addition of *t*BuOK (1.14 g, 10.2 mmol) at −78 °C, the mixture was stirred at this temperature for 10 min and, then, at room temperature for 3 h. After usual work-up with aqueous NH_4Cl solution and ethyl acetate, the organic layer was evaporated. The crude mixture was subjected to column chromatography (hexane/CH_2Cl_2 2:1) to give **3a** (170 mg, 35%) as a pale yellow foam. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.73$ (d, $J = 7.7$ Hz, 4H), 7.05 (t, $J = 7.7$ Hz, 4H), 7.25 (d, $J = 8.0$ Hz, 4H), 7.27 (d, $J = 7.7$ Hz, 4H), 7.31 (t, $J = 7.7$ Hz, 4H), 7.47 (t, $J = 8.0$ Hz, 4H), 7.49 (s, 4H), 7.83 (d, $J = 8.6$ Hz, 4H), 7.92 (d, $J = 8.0$ Hz, 4H), 7.96 (d, $J = 8.6$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 89.14$ (4C≡), 89.74 (4C≡), 92.07 (4C≡), 121.45 (4C), 122.96 (4C), 123.58 (4C), 126.42 (4CH), 126.49 (4CH), 126.74 (4CH), 128.04 (4CH), 128.07 (4CH), 128.13 (4CH), 128.39 (4CH), 130.56 (4CH), 130.89 (4CH), 132.49 (4C), 132.96 (4C), 134.86 (4CH), 139.95 (4C); MALDI-MS: calcd for 952.3; found 952.8 $[M]^+$; $[\alpha]_D^{29.2} = +81.2$ ($c = 0.995$, $CHCl_3$); $[M]_D = +773.9$; UV/Vis ($CHCl_3$, 4.5×10^{-6} M): λ_{max} (ε_{max}) = 239 (1.0×10^5), 281 (1.7×10^5), 305 (1.1×10^4), 331 (5.0×10^4); CD ($c = 7.9 \times 10^{-5}$ M in $CHCl_3$, 0.1 cm cell): $\theta = -57.3$, $\Delta\varepsilon = -218.7$ (at 282 nm); $\theta = 69.8$, $\Delta\varepsilon = 266.3$ (at 308 nm); $\theta = -29.5$, $\Delta\varepsilon = -112.5$ (at 337 nm).

The similar treatment of **13** (547 mg, 0.51 mmol) with **2b** (398 mg, 0.56 mmol) or **2d** (622 mg, 0.56 mmol) furnished **3b** (165 mg, 28%) or **3d** (246 mg, 31%), respectively. **3b**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.65$ (d, $J = 7.6$ Hz, 4H), 7.04 (t, $J = 7.8$ Hz, 4H), 7.12 (s, 4H), 7.26–7.35 (m, 14H), 7.43 (d, $J = 8.3$ Hz, 4H), 7.46 (t, $J = 7.5$ Hz, 4H), 7.70 (s, 2H), 7.84 (d, $J = 8.3$ Hz, 4H), 7.94 (d, $J = 8.0$ Hz, 4H), 8.01 (d, $J = 8.6$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 88.78$ (4C≡), 89.19 (4C≡), 90.12 (4C≡), 92.68 (4C≡), 121.45 (4C), 122.85 (4C), 123.38 (4C), 123.50 (4C), 126.47 (4CH), 126.62 (4CH), 126.84 (4CH), 128.05 (4CH), 128.09 (8CH), 128.13 (4CH), 128.46 (2CH), 130.80 (4CH), 131.08 (4CH), 131.25 (4CH), 132.58 (4C), 132.98 (4C), 134.42 (4CH), 134.68 (2CH), 140.41 (4C); MALDI-MS: calcd for 1152.4; found 1151.2 $[M]^+$; $[\alpha]_D^{28.1} = +9.2$ ($c = 1.000$, $CHCl_3$); $[M]_D = +106.1$; UV/Vis ($CHCl_3$, 4.5×10^{-6} M): λ_{max} (ε_{max}) = 245 (1.1×10^5), 281 (2.6×10^5), 305 (1.6×10^5), 332 (8.7×10^4); CD ($c = 9.19 \times 10^{-6}$ M in $CHCl_3$, 1.0 cm cell): $\theta = -47.7$, $\Delta\varepsilon = -157.3$ (at 280 nm); $\theta = 82.4$, $\Delta\varepsilon = 271.5$ (at 310 nm); $\theta = -42.9$, $\Delta\varepsilon = -141.8$ (at 336 nm); **3d**: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.67$ (d, $J = 7.8$ Hz, 4H), 7.02 (s, 4H), 7.06 (t, $J = 7.8$ Hz, 4H), 7.28 (d, $J = 8.0$ Hz, 4H), 7.31–7.37 (m, 14H), 7.45–7.52 (m, 16H), 7.70 (s, 4H), 7.74 (s, 2H), 7.80 (d, $J = 8.6$ Hz, 4H), 7.98 (d, $J = 8.0$ Hz, 4H), 8.01 (d, $J = 8.6$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 88.76$ (4C≡), 89.14 (4C≡), 89.17 (4C≡), 89.24 (4C≡), 90.07 (4C≡), 92.64 (4C≡), 121.42 (4C), 122.85 (4C), 123.32 (4C), 123.36 (4C), 123.43 (4C), 123.50 (4C), 126.57 (4CH), 126.64 (4CH), 126.85 (4CH), 128.06 (4CH), 128.10 (8CH), 128.14 (4CH), 128.52 (4CH), 128.55 (2CH), 130.81 (4CH), 131.07 (4CH), 131.36 (8CH), 131.45 (4CH), 132.56 (4C), 133.03 (4C), 134.40 (4CH), 134.70 (4CH), 134.74 (2CH), 140.38 (4C); MS (MALDI): calcd for 1552.5; found 1553.0 $[M]^+$; $[\alpha]_D^{29.8} = -69.22$ ($c = 0.795$, $CHCl_3$); $[M]_D = -1075.56$; UV/Vis ($CHCl_3$, 8.95×10^{-6} M): λ_{max} (ε_{max}) = 240 (1.3×10^5), 282 (3.4×10^5), 305 (2.5×10^5), 332 (8.3×10^4); CD ($c = 4.47 \times 10^{-6}$ M in $CHCl_3$, 1.0 cm cell): $\theta = -13.7$, $\Delta\varepsilon = -93.3$ (at 279 nm); $\theta = 39.6$, $\Delta\varepsilon = 268.3$ (at 309 nm); $\theta = -30.6$, $\Delta\varepsilon = -207.8$ (at 336 nm).

Preparation of 18 (Scheme 6): BuLi (1.39 M in hexane, 0.23 mL, 0.32 mmol) was added at −78 °C to a THF solution (30 mL) of **13** (141.2 mg, 0.15 mmol), and the mixture was stirred for 10 min. A THF solution (8 mL) of **17** (118 mg, 0.17 mmol) was added dropwise over 30 min. After 15 min, $ClP(O)(OEt)_2$ (0.06 mL, 0.40 mmol) was added at −78 °C, and the reaction mixture was stirred at room temperature for 1.5 h. *t*BuOK (337 mg, 3.0 mmol) was added at −78 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After usual work-up with aqueous NH_4Cl solution and AcOEt, the organic layer was evaporated. The crude mixture was subjected to column chromatography (hexane/CH_2Cl_2 1:2) to give **18** (34.7 mg, 20%) as a yellow foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.70$ (dd, $J = 1.1$, 7.7 Hz, 4H), 7.04 (t, $J = 7.7$ Hz, 4H), 7.27–7.38 (m, 18H), 7.46 (m, 4H), 7.54 (t, $J = 7.8$ Hz, 4H), 7.88 (d, $J = 8.4$ Hz, 4H) , 7.94 (d, $J = 8.1$ Hz, 4H), 8.03(d, $J = 8.4$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 88.47$, 88.61, 90.11, 92.36, 121.43, 122.03, 123.64, 126.21, 126.45, 126.61, 126.73, 128.03, 128.06, 128.18, 128.41, 131.18, 131.80, 132.52, 132.97, 134.70, 136.31, 140.18, 143.35; ESI-MS: calcd for 1155.4; found 1155.4 $[M+H]^+$; $[\alpha]_D^{29.3} = -58.80$ ($c = 1.000$, $CHCl_3$); $[M]_D = -679.3$; UV/Vis ($CHCl_3$, 8.74×10^{-5} M): λ_{max} (ε_{max}) = 245 (1.1×10^5), 281 (2.4×10^5), 313 (1.5×10^5); CD ($c = 8.74 \times 10^{-5}$ M in $CHCl_3$, 0.1 cm cell): $\theta = -29.0$, $\Delta\varepsilon = -100.4$ (at 281 nm); $\theta = 59.2$, $\Delta\varepsilon = 205.4$ (at 310 nm); $\theta = -34.5$, $\Delta\varepsilon = -119.5$ (at 337 nm).

Preparation of 19: A 100 mL flask was charged with **12** (1.66 g, 3.30 mmol), **16** (3.53 g, 6.93 mmol), $[Pd(Ph_3P)_4]$ (191 mg, 0.17 mmol), CuI (32 mg, 0.17 mmol), diisopropylamine (10 mL) and toluene (50 mL). After being stirred at 70 °C for 2 h, the reaction mixture was cooled to room temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$, and filtered. The solvent was evaporated in vacuo, and the residue was chromatographed (CH_2Cl_2/AcOEt 25:1) to give **19** (2.56 g, 68%) as a yellow foam (a mixture of inseparable diastereomers). ^{1}H NMR (500 MHz, $CDCl_3$):[16] $\delta = 2.36$ (s, 6H), 4.74, 4.88 ($J_{AB} = 13.9$ Hz, 4H), 6.65–8.05 (m, 46H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 21.35$, 63.99, 88.39, 89.29, 90.05, 92.53, 121.18, 122.56, 123.33, 123.42, 126.45, 126.61, 126.79, 126.90, 128.00, 128.01, 128.06, 128.54, 128.60, 129.07, 129.14, 130.75, 131.05, 131.10, 132.22, 132.42, 132.95, 134.03, 134.19, 134.36, 134.50, 140.33, 140.66, 142.70; ESI-MS: calcd for 713.2; found 713.9 $[M+H]^+$.

Preparation of 3c with sulfoximine 19 (Scheme 7): BuLi (1.39 M in hexane, 0.43 mL, 0.60 mmol) was added at −78 °C to a THF solution (50 mL) of **19** (285 mg, 0.25 mmol), and the mixture was stirred for 15 min. Dialdehyde **2b** (196 mg, 0.28 mmol) in THF (20 mL) was added dropwise over 40 min at this temperature with stirring. After 15 min, $ClP(O)(OEt)_2$ (0.10 mL, 0.69 mmol) was added at −78 °C and the mixture was stirred at room temperature for 2.5 h. To this mixture was added *t*BuOK (337 mg, 3.0 mmol) at −78 °C and the mixture was stirred at room temperature for overnight. After usual work-up with aqueous NH_4Cl solution and AcOEt, the organic layer was evaporated. The crude mixture was subjected to column chromatography (hexane/CH_2Cl_2 2:1) to give **3c** (103 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.68$ (d, $J = 7.8$ Hz, 4H), 7.00 (s, 4H), 7.07 (t, $J = 7.8$ Hz, 4H), 7.28 (d, $J = 7.7$ Hz, 4H), 7.30–7.36 (m, 12H), 7.46 (d, $J = 7.7$ Hz, 4H), 7.49–7.52 (m, 8H), 7.71 (s, 4H), 7.78 (d, $J = 8.6$ Hz, 4H), 7.98 (d, $J = 8.6$ Hz, 4H), 8.00 (d, $J = 8.6$ Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 88.77$ (4C≡), 89.15 (4C≡), 89.28 (4C≡), 90.09 (4C≡), 92.64 (4C≡), 121.44 (4C), 122.87 (4C), 123.36 (4C), 123.49 (4C), 123.54 (4C), 126.60 (4CH), 126.63 (4CH), 126.85 (4CH), 128.05 (4CH), 128.09 (8CH), 128.15 (4CH), 128.53 (4CH), 130.79 (4CH), 131.05 (4CH), 131.37 (8CH), 132.58 (4C), 133.06 (4C), 134.47 (4CH), 134.71 (4CH), 140.40 (4C); MALDI-MS: calcd for 1352.4; found 1351.0 $[M]^+$: $[\alpha]_D^{29.2} = -70.47$ ($c = 0.990$, $CHCl_3$); $[M]_D = -953.9$; UV/Vis ($CHCl_3$, 7.83×10^{-5} M): λ_{max} (ε_{max}) = 246 (1.3×10^4), 282 (3.1×10^5), 305 (2.2×10^5), 332 (8.8×10^4); CD ($c = 7.8 \times 10^{-5}$ M in $CHCl_3$, 0.1 cm cell): $\theta = -19.6$, $\Delta\varepsilon = -76.7$ (at 281 nm); $\theta = 65.5$, $\Delta\varepsilon = 255.6$ (at 310 nm); $\theta = -48.9$, $\Delta\varepsilon = -191.0$ (at 338 nm).

Reaction between 12 and 20 (Scheme 8): A two-necked flask was charged with $[Pd(Ph_3P)_4]$ (40 mg, 35 μmol), CuI (7 mg, 35 μmol), diisopropylamine (2 mL), and toluene (10 mL). Then, to the above suspension was added a solution of **12** (174 mg, 0.35 mmol) and **20** (245 mg, 0.35 mmol) in diisopropylamine (10 mL) and toluene (50 mL) at 75 °C by a syringe pump

(2.5 mL h^{-1}). The reaction mixture was cooled to room temperature and filtered. The filtrate was poured into aqueous NH_4Cl, and extracted with ethyl acetate. The extract was then washed with brine, dried over $MgSO_4$ and filtered. The solvents were evaporated in vacuo, and the crude mixture was subjected to column chromatography (1:1.5 hexane/CH_2Cl_2) to give a trace amount of **3a** (<2.7%, not pure).

The preparation of **2c**, **2d**, **4**, **5**, **6**, **8**–**12**, and **17** is described in the Supporting Information.

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