JOC The Journal of Organic Chemistry

Article

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Diversity-Oriented Approach to Cyclophanes via Fischer Indolization and Ring-Closing Metathesis: Substrate-Controlled Stereochemical Outcome in RCM

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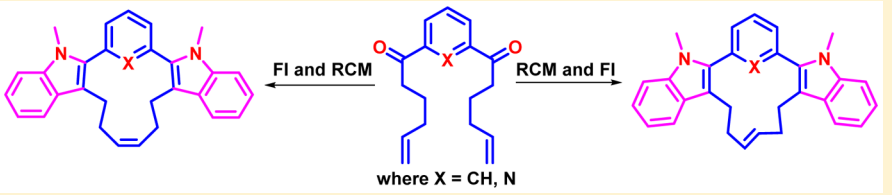
Supporting Information



ABSTRACT: Here, we report a new and diversity-oriented approach to macrocyclic cyclophanes by a Grignard reaction, followed by Fischer indolization and ring-closing metathesis (RCM) as key steps. The configuration of the double bond formed during the RCM depends upon the order of synthetic sequence used. Fischer indolization followed by RCM delivers the cis isomer, whereas RCM followed by Fischer indolization gives the trans isomer.

INTRODUCTION

Ring-closing metathesis (RCM) is a useful tool for assembling various macrocycles which are commonly found in many natural products, pharmaceuticals, and supramolecular chemistry.[1] Among several available methods for the synthesis of cyclophane derivatives,[2] RCM allows a late-stage ring closure with substrates containing polar functional groups.[3] However, it is difficult to control the stereochemistry of the olefin during the macrocyclic formation involving RCM, and generally it gives a mixture of cis and trans isomers. Few methods are available to control the stereochemical outcome of the RCM process, and a limited number of catalysts are accessible for this purpose.[4] However, there have been no reports of substrate-based selectivity during the RCM process. Here, we have designed and developed a new strategy for diversity-oriented synthesis[5] of cyclophane derivatives via RCM.[6] In this context, the indole moiety present in the RCM precursor acts as a conformational control element (CCE)[7] to deliver the cyclophane derivative with predetermined olefinic configuration. When the indole moiety is present in the cyclophane precursor, the cis isomer was produced. Interestingly, the trans isomer was formed in the absence of such an inbuilt CCE.

STRATEGY

As part of a major program aimed at the development of new strategies to various macrocycles,[8] here we have designed a new synthetic approach to indole-based cyclophane derivatives via RCM. The retrosynthetic analysis conceived here involves nucleophilic addition of a Grignard reagent such as alkenylmagnesium bromide with 2,6-pyridinedicarbonitrile (or isophthalonitrile), Fischer indolization, and RCM (Figure 1) as key steps.

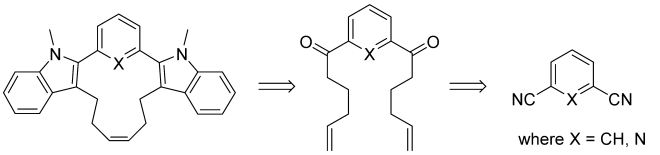


Figure 1. Retrosynthetic route to indole-based cyclophane derivatives.

RESULTS AND DISCUSSION

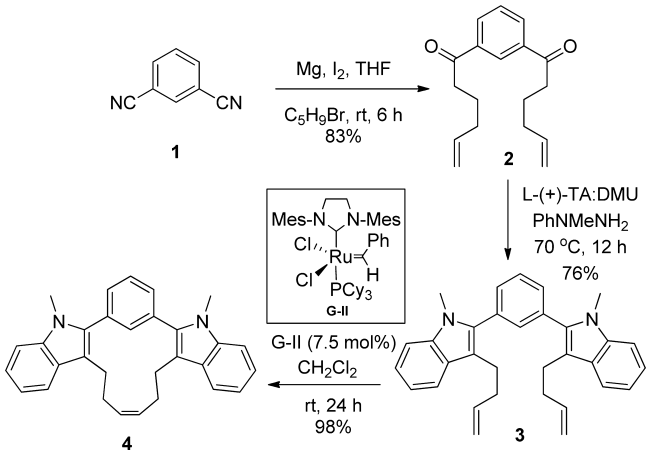
Our journey toward the synthesis of cyclophanes begin with commercially available starting materials. In this regard, isophthalonitrile **1** was reacted with a Grignard reagent such as 5-hexenylmagnesium bromide to generate the dione **2** (83%),[8b] which was then subjected to Fischer indolization in the presence of 1-methyl-1-phenylhydrazine by using low-melting mixture conditions[9] to give the bis-indole derivative **3**. To this end, the conventional Fischer indolization conditions (AcOH/HCl) are not useful. Next, the bis-indole derivative **3** was subjected to the RCM protocol in the presence of Grubbs second-generation (G-II) catalyst to deliver the cyclized product **4** as a single isomer (Scheme 1). Later, it was identified by ^{1}H and ^{13}C NMR data. The structure of the cyclophane **4** was confirmed by single-crystal X-ray diffraction studies and the configuration of the double bond was found to be cis.[10] Formation of the cyclophane with a trans double bond generates a strained system when it contains bulky indole rings on both sides of the olefinic precursor.

We were interested in exploring the possibility of controlling the configuration of the double bond by changing the reaction

Received: July 2, 2015

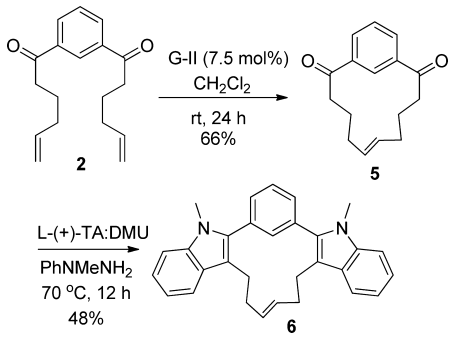
DOI: 10.1021/acs.joc.5b01433
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of Cyclophane Derivative 4



sequence. When the dione **2** was subjected to the RCM protocol, the configuration of the double bond present in the cyclophane **5** on the basis of the NMR data was not conclusive. However, the number of ^{13}C NMR signals of **5** indicated that it is a single compound.[8b] The cyclized product **5** was further subjected to Fischer indolization to give the bis-indole-based cyclophane derivative **6** (Scheme 2). Later, its structure was

Scheme 2. Synthesis of Cyclophane Derivative 6



identified by ^{1}H and ^{13}C NMR data, but the spectral data did not match those of the compound **4** obtained by an earlier route, which involved Fischer indolization followed by RCM. The single-crystal X-ray diffraction studies clearly indicated that the double bond present in **6** is in a trans configuration.[10] Thus, compound **2** without any substituents gave the trans isomer. However, an indole-appended substrate such as **3** gave the cis isomer on cyclization. We do not anticipate the change in configuration of the double bond present in **5** during the Fischer indolization sequence.

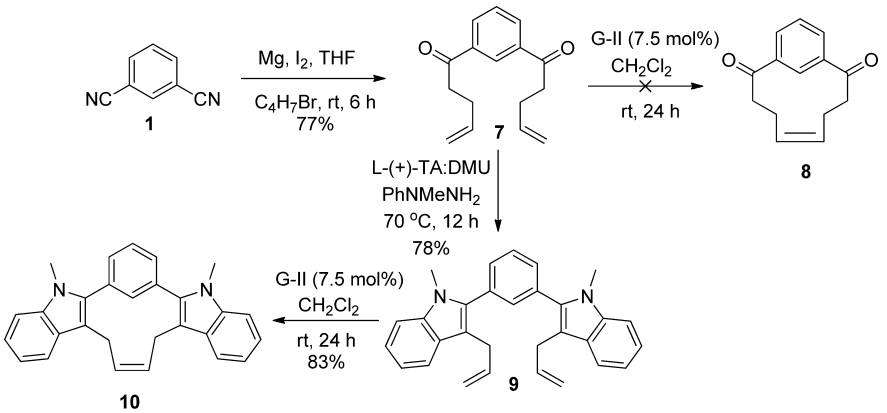
To understand the scope of the above methodology, the cyclophane derivative **10** was synthesized along similar lines. In this regard, isophthalonitrile **1** was treated with the Grignard reagent derived from 4-bromo-1-butene to deliver the dione **7** (75%), which was then subjected to an RCM sequence. Unfortunately, the expected ring-closure product **8** was not formed. Then, the dione **7** was subjected to Fischer indolization to generate the bis-indole derivative **9**, and later this derivative was reacted with G-II catalyst to give the RCM product **10** as a cis isomer (Scheme 3); we found that the indole units are helping the RCM process and the configuration of **10** was confirmed by single-crystal X-ray diffraction studies.[10] Here, in compound **7** the alkenyl chains are not disposed in a suitable conformation to facilitate the metathesis process. We anticipated that by introducing the two indole moieties on the alkenyl chains (e.g., compound **9**), they would be steered into a suitable conformation which facilitates the RCM protocol.

To expand the scope this strategy, 2,6-pyridinedicarbonitrile **11** was reacted with a Grignard reagent such as 5-hexenylmagnesium bromide to generate the Grignard addition product **12** (96%).[8b] Later, the dione **12** was subjected to Fischer indolization in the presence of 1-methyl-1-phenylhydrazine under low-melting mixture conditions to afford the bis-indole derivative **13**, which was subjected to the RCM protocol in the presence of G-II to deliver the cyclized product **14**; its structure was supported by NMR data (Scheme 4). Finally, the structure of the cyclophane **14** was confirmed by single-crystal X-ray diffraction studies and the configuration of the double bond was found to be cis.[10]

To generalize our strategy, the dione **12** was subjected to RCM to generate the cyclophane derivative **15**[8b] as a single isomer, and then it was subjected to Fischer indolization to deliver the bis-indole derivative **16** (Scheme 5).

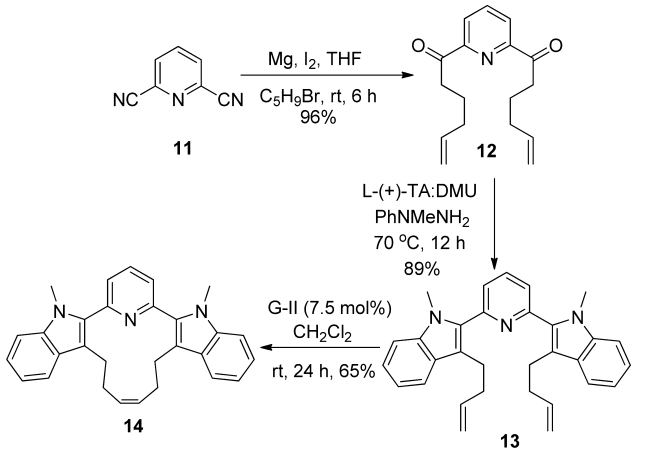
Along similar lines, cyclophane derivative **19** synthesis was conceived. To this end, 2,6-pyridinedicarbonitrile **11** was treated with the Grignard reagent derived from 4-bromo-1-butene to deliver the dione **17** (74%). Next, the dione **17** was subjected to an RCM sequence and the expected ring-closure product was not formed. Then, the dione **17** was subjected to

Scheme 3. Synthesis of Cyclophane Derivative 10

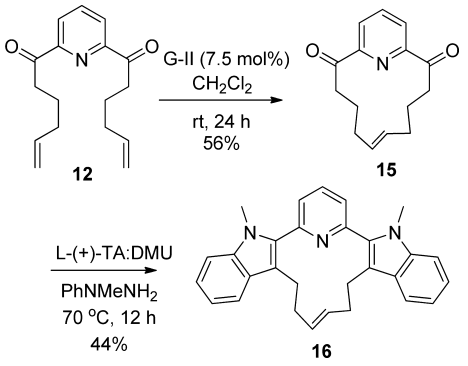


DOI: 10.1021/acs.joc.5b01433
J. Org. Chem. XXXX, XXX, XXX−XXX

Scheme 4. Synthesis of Cyclophane Derivative 14



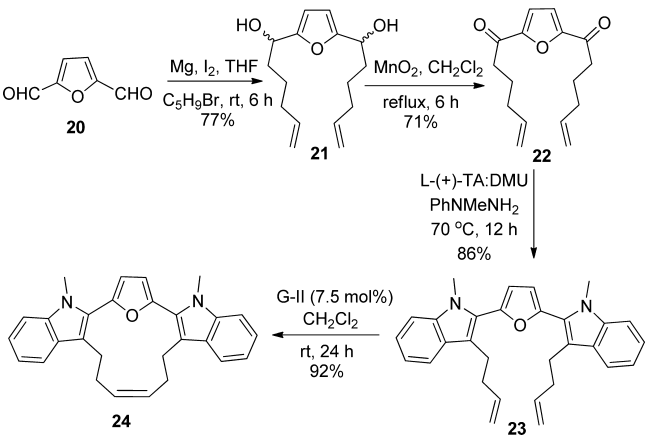
Scheme 5. Synthesis of Cyclophane Derivative 16



Fischer indolization to generate the bis-indole derivative **18**, and later it was subjected to RCM to generate the cyclized product **19** (Scheme 6) as a cis isomer. The structure of the cyclophane derivative **19** was confirmed by single-crystal X-ray diffraction studies.[10]

To expand the scope of this methodology, we have also assembled a furan-based cyclophane derivative such as **24**. Since furan derivatives can undergo Diels–Alder chemistry, these cyclophanes are interesting substrates for further synthetic manipulation.[11] To this end, the 2,5-furandicarboxaldehyde **20**,[12] prepared by a known method, was treated with a Grignard reagent such as 5-hexenylmagnesium bromide to generate the diol **21** (77%). Later, the diol **21** was subjected to MnO_2 oxidation in CH_2Cl_2 to deliver the dione **22** (71%). Next, dione **22** was subjected to a Fischer indolization sequence with 1-methyl-1-phenylhydrazine to give the bis-indole product **23** (86%). Then, the bis-indole derivative **23** was treated with G-II catalyst to deliver the cyclized product **24** in good yield (92%, Scheme 7).

Scheme 7. Synthesis of Cyclophane Derivative 24



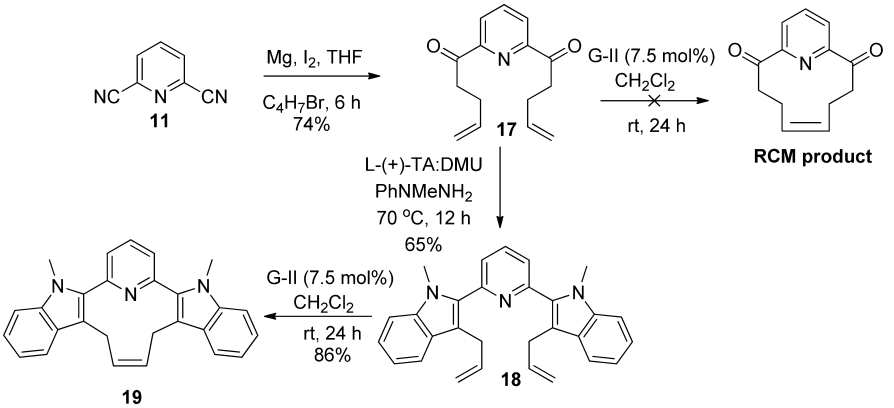
CONCLUSION

We have developed a simple synthetic strategy to indole-based cyclophane derivatives via RCM utilizing G-II catalyst. The presence of an inbuilt indole moiety next to the aromatic ring gave the cis isomer during the RCM sequence. However, without such an inbuilt indole ring, the trans isomer was obtained during the RCM process. The structures of the five macrocycles synthesized were confirmed by single-crystal X-ray diffraction data and clearly indicated that the macrocycle **4** was endowed with a cis double bond, whereas the macrocycle **6** contains a trans double bond.

EXPERIMENTAL SECTION

All reactions were performed under an argon or nitrogen atmosphere using a well-dried reaction flask. All commercial products were used as received without further purification. All of the solvents used as reaction media were dried over molecular sieves (4 Å) predried in a microwave oven, Column chromatography was performed with silica gel (100–200 mesh) using a mixture of petroleum ether and EtOAc as eluent. ^{1}H and ^{13}C NMR spectral data were recorded on 400 and 100 MHz or 500 and 126 MHz spectrometers using tetramethylsilane

Scheme 6. Synthesis of Cyclophane Derivative 19



DOI: 10.1021/acs.joc.5b01433
J. Org. Chem. XXXX, XXX, XXX–XXX

(TMS) as an internal standard and chloroform-*d* as solvent. Mass spectral data were recorded on a Q-TOF micromass spectrometer. High-resolution mass spectroscopy (HRMS) was performed with a TOF mass spectrometer in positive ESI mode. X-ray diffraction data for compounds **4**, **6**, **10**, **14**, and **19** were collected on a diffractometer equipped with graphite-monochromated Mo Kα radiation. The structure was solved by direct methods using shelxs-97 and refined by full-matrix least squares against F^2 using shelxl-97 software. The melting points recorded are uncorrected.

General Procedure for Grignard Addition Reaction. Mg turnings and iodine in THF were heated to reflux until the brown color disappeared. Then, 5-bromo-1-pentene (273 mg, 1.92 mmol) was added and the mixture was stirred for 30 min. Next, isophthalonitrile **1** (100 mg, 0.77 mmol) was added and the resulting mixture was stirred and heated to reflux for 3 h. At the conclusion of the reaction (TLC monitoring), 2 N HCl was added and the reaction mixture was stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and H_2O (10 mL), and the reaction mixture was stirred well and extracted with EtOAc. The organic layer was washed with brine and dried with Na_2SO_4. EtOAc was removed under reduced pressure, and the crude product obtained was purified by column chromatography to give the dione.

*1,1′-(1,3-Phenylene)bis(pent-4-en-1-one) (**7**):* semisolid, 77% (436 mg, starting with 300 mg of isophthalonitrile **1** + 4-pentenymagnesium bromide); R_f = 0.70 (petroleum ether/EtOAc 80/20); IR (neat) $\tilde{\nu}_{max}$ 3634, 3463, 2986, 2086, 1890, 1742, 1447, 1374, 1242, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47−2.53 (m, 4H), 3.10 (t, J = 4.60 Hz, 4H), 4.99−5.11 (m, 4H), 5.84−5.94 (m, 2H), 7.56 (t, J = 7.76 Hz 1H), 8.14 (dd, J_1 = 1.76 Hz, J_2 = 7.76 Hz 2H), 8.51 (t, J = 1.51 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.1, 38.0, 115.7, 127.6, 129.2, 132.3, 137.1, 137.4, 198.8; HRMS (Q-Tof) m/z calcd 243.1380 for $C_{16}H_{19}O_2$ [M + H]$^+$, found 243.1370.

*1,1′-(Pyridine-2,6-diyl)bis(pent-4-en-1-one) (**17**):* pale yellow oil, 74% (242 mg, starting with 200 mg of 2,6-pyridinedicarbonitrile **11** + 4-pentenymagnesium bromide); R_f = 0.70 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3684, 3619, 3019, 2976, 2927, 2400, 1729, 1688, 1601, 1519, 1423, 1221, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (q, J = 7.24 Hz, 4H), 3.37 (t, J = 7.29 Hz, 4H), 5.00−5.12 (m, 4H), 5.87−5.97 (m, 2H), 7.98 (t, J = 7.92 Hz, 1H), 8.19 (d, J = 7.80 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.2, 37.0, 115.4, 125.9, 137.5, 138.2, 152.6, 200.7; HRMS (Q-Tof) m/z calcd 266.1151 for $C_{15}H_{17}NNaO_2$ [M + Na]$^+$, found 266.1157.

*1,1′-(Furan-2,5-diyl)bis(hex-5-en-1-ol) (**21**):* pale yellow oil, 77% (300 mg, starting with 200 mg of 2,5-furandicarboxaldehyde **20** + 5-hexenylmagnesium bromide); R_f = 0.60 (petroleum ether/EtOAc 80/20); IR (neat) $\tilde{\nu}_{max}$ 3524, 3022, 2946, 2835, 1638, 1463, 1365, 1286, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31−1.39 (m, 2H), 1.40−1.57 (m, 2H) 1.76−1.86 (m, 4H), 2.02−2.10 (m, 4H), 2.84 (bs, 2H), 4.58 (t, J = 6.56 Hz, 2H) 4.92−5.01 (m, 4H), 5.72−5.82 (m, 2H), 6.10 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.9, 33.5, 34.8, 34.8, 67.6, 106.4, 106.4, 114.9, 138.6, 156.1, 156.2; HRMS (Q-Tof) m/z calcd 287.1618 for $C_{16}H_{24}NaO_3$ [M + Na]$^+$, found 287.1618.

General Procedure for the Preparation of Oxidation. To a solution of dialcohol derivative **21** (50 mg) in CH_2Cl_2 (10 mL) was added MnO_2 (4 equiv) oxidizing agent at room temperature, and the reaction mixture was heated at reflux overnight. At the conclusion of the reaction (TLC monitoring), the crude reaction mixture was filtered through a Celite pad (washed with CH_2Cl_2) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc/petroleum ether, 10%) to diketone derivative **22**.

*1,1′-(Furan-2,5-diyl)bis(hex-5-en-1-one) (**22**):* pale yellow oil, 71% (140 mg, starting with 200 mg of furan diol **21**); R_f = 0.50 (petroleum ether/EtOAc 80/20); IR (neat) $\tilde{\nu}_{max}$ 3162, 3021, 2943, 2627, 2410, 2293, 2254, 1637, 1376, 1230, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.80−1.87 (m, 4H), 2.14 (q, J = 7.16 Hz, 4H) 2.90 (t, J = 7.40 Hz, 4H), 4.97−5.06 (m, 4H), 5.74−5.84 (m, 2H), 7.18 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.0, 33.2, 38.0, 115.7, 117.1, 137.9, 153.6, 190.3; HRMS (Q-Tof) m/z calcd 283.1305 for $C_{16}H_{20}NaO_3$ [M + Na]$^+$, found 283.1304.

General Procedure for the Preparation of Bis-Indole Derivatives. In a typical experiment, 1.5 g of an L-(+)-tartaric acid/*N*,*N*′-dimethylurea (30/70) mixture was heated to 70 °C to obtain a clear melt. To this melt were added 2 mmol of *N*-methyl-*N*-phenylhydrazine and 1 mmol of diketone at 70 °C. At the conclusion of the reaction (TLC monitoring by mini workup), the reaction mixture was quenched with water while it was still hot. The reaction mixture was cooled to room temperature, and the solid was filtered through a sintered-glass funnel and washed with water (2 × 5 mL). The crude product was dried under vacuum, and then it was purified by silica gel column chromatography.

*1,3-Bis(3-(but-3-en-1-yl)-1-methyl-1H-indol-2-yl)benzene (**3**):* pale yellow oil, 76% (150 mg, starting with 120 mg of 1,1′-(1,3-phenylene)bis(hex-5-en-1-one) (**2**)); R_f = 0.60 (petroleum ether/EtOAc 95/5); IR (neat) $\tilde{\nu}_{max}$ 3774, 2919, 2850, 1734, 1641, 1467, 1363, 1244, 1047 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50−2.51 (m, 4H), 2.98−2.99 (m, 4H), 3.73 (s, 6H), 5.00−5.11 (m, 4H), 5.92−5.95 (m, 2H), 7.27−7.29 (m, 2H), 7.36−7.39 (m, 2H), 7.45−7.46 (m, 2H), 7.55−7.57 (m, 3H), 7.69−7.78 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.5, 31.0, 35.4, 109.6, 113.4, 114.7, 119.3, 119.4, 122.0, 127.7, 128.6, 130.4, 132.5, 132.7, 137.4, 138.8; HRMS (Q-Tof) m/z calcd 445.2638 for $C_{32}H_{33}N_2$ [M + H]$^+$, found 445.2638.

*(E)-5,11-Dimethyl-5,11,16,17,20,21-hexahydro-6,10-(metheno)-cyclotrideca[1,2-b:8,7-b′]diindole (**6**):* white solid, 48% (24 mg, starting with 30 mg of dione **5**); mp 269−270 °C; R_f = 0.80 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 2923, 2853, 1656, 1601, 1468, 1363, 1220, 1020 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (q, J = 5.92 Hz, 4H), 2.88 (t, J = 6.00 Hz, 4H), 3.72 (s, 6H), 5.47 (t, J = 4.08 Hz, 2H), 7.15−7.19 (m, 2H), 7.28−7.32 (m, 2H), 7.35−7.44 (m, 4H), 7.57 (t, J = 7.60 Hz, 2H), 7.66 (d, J = 7.84 Hz, 2H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 25.3, 31.5, 32.8, 109.6, 113.4, 119.3, 119.4, 122.0, 127.9, 128.9, 131.6, 131.9, 134.6, 137.4, 137.8; HRMS (Q-Tof) m/z calcd 417.2325 for $C_{30}H_{29}N_2$ [M + H]$^+$, found 417.2325.

*1,3-Bis(3-allyl-1-methyl-1H-indol-2-yl)benzene (**9**):* pale yellow oil, 78% (80 mg, starting with 60 mg of 1,1′-(1,3-phenylene)bis(pent-4-en-1-one) (**7**)); R_f = 0.70 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 2920, 1712, 1467, 1427, 1365, 1223, 1092 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.52−3.53 (m, 4H), 3.69 (s, 6H), 5.00−5.06 (m, 4H), 6.00−6.07 (m, 2H), 7.15−7.19 (m, 2H), 7.27−7.31 (m, 2H), 7.38 (d, J = 8.16 Hz, 2H), 7.45−7.49 (m, 3H), 7.62 (t, J = 7.61 Hz, 1H), 7.66 (d, J = 7.90 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.4, 31.2, 109.6, 111.1, 114.9, 119.5, 122.1, 127.9, 128.6, 130.3, 132.2, 132.5, 137.6, 137.7, 137.9; HRMS (Q-Tof) m/z calcd 417.2325 for $C_{30}H_{29}N_2$ [M + H]$^+$, found 417.2323.

*2,6-Bis(3-(but-3-en-1-yl)-1-methyl-1H-indol-2-yl)pyridine (**13**):* pale yellow oil, 89% (101 mg, starting with 70 mg of 1,1′-(pyridine-2,6-diyl)bis(hex-5-en-1-one) (**12**)); R_f = 0.70 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 2984, 2941, 2878, 1522, 1424, 1216, 1046 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (q, J = 7.55 Hz, 4H), 3.03 (t, J = 7.75 Hz, 4H), 3.82 (s, 6H), 4.96−5.08 (m, 4H), 5.87−5.95 (m, 2H), 7.21 (t, J = 7.05 Hz, 2H), 7.32−7.35 (m, 2H), 7.41 (d, J = 8.25 Hz, 2H), 7.54 (d, J = 7.75 Hz, 2H), 7.74 (d, J = 7.89 Hz, 2H), 7.94 (t, J = 7.80 Hz, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 24.6, 31.5, 35.4, 109.7, 114.7, 115.1, 119.4, 119.6, 122.7, 124.0, 127.6, 136.0, 136.6, 137.9, 138.7, 151.9; HRMS (Q-Tof) m/z calcd 468.2410 for $C_{31}H_{31}N_3Na$ [M + Na]$^+$, found 468.2414.

*(E)-5,11-Dimethyl-5,11,16,17,20,21-hexahydro-6,10-(azeno)-cyclotrideca[1,2-b:8,7-b′]diindole (**16**):* white solid, 44% (59 mg, starting with 80 mg of dione **15**); mp 248−250 °C; R_f = 0.40 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3004, 2969, 2924, 1714, 1422, 1364, 1223, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26−2.29 (m, 4H), 3.02−3.09 (m, 4H), 3.84 (s, 6H), 5.15 (s, 2H), 7.14−7.21 (m, 2H), 7.29−7.36 (m, 2H), 7.38−7.48 (m, 4H), 7.68−7.71 (m, 2H), 7.87−7.95 (m, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 24.2, 31.8, 32.9, 109.7, 116.6, 119.4, 119.6, 122.6, 122.9, 127.9, 130.7, 135.8, 136.6, 138.0, 151.9; HRMS (Q-Tof) m/z calcd 418.2278 for $C_{29}H_{28}N_3$ [M + H]$^+$, found 418.2275.

*2,6-Bis(3-allyl-1-methyl-1H-indol-2-yl)pyridine (**18**):* pale yellow oil, 65% (103 mg, starting with 80 mg of 1,1′-(pyridine-2,6-diyl)bis(pent-4-en-1-one) (**17**)); R_f = 0.70 (petroleum ether/EtOAc

DOI: 10.1021/acs.joc.5b01433
J. Org. Chem. XXXX, XXX, XXX−XXX

90/10); IR (neat) $\tilde{\nu}_{max}$ 3854, 2949, 2844, 2349, 2261, 1651, 1459, 1022 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64−3.65 (m, 4H), 3.85 (s, 6H), 5.07−5.12 (m, 4H), 6.07−6.17 (m, 2H), 7.14−7.18 (m, 2H), 7.28−7.33 (m, 2H), 7.39 (d, J = 8.20 Hz, 2H), 7.53 (d, J = 7.81 Hz, 2H), 7.67 (d, J = 7.88 Hz, 2H), 7.90 (t, J = 5.32 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 29.5, 31.7, 109.7, 112.6, 115.2, 119.5, 119.8, 122.8, 123.9, 127.7, 136.3, 136.6, 137.7, 137.9, 151.5; HRMS (Q-Tof) m/z calcd 440.2097 for $C_{29}H_{27}N_3Na$ $[M + Na]^+$, found 440.2095.

2,5-Bis(3-(but-3-en-1-yl)-1-methyl-1H-indol-2-yl)furan (**23**): pale yellow oil, 86% (143 mg, starting with 100 mg of 1,1′-(furan-2,5-diyl)bis(hex-5-en-1-one) (**22**)); R_f = 0.70 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3054, 2928, 2854, 2291, 2253, 1639, 1467, 1368, 1238, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48−2.52 (m, 4H), 3.04−3.07 (m, 4H), 3.87 (s, 6H), 4.99−5.13 (m, 4H), 5.92−6.00 (m, 2H), 6.75 (d, J = 6.65 Hz, 2H), 7.20 (t, J = 7.10 Hz, 2H), 7.33 (t, J = 8.00 Hz, 2H), 7.38 (t, J = 6.21 Hz, 2H), 7.69 (t, J = 7.76 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.7, 31.6, 35.4, 109.6, 112.2, 114.9, 115.9, 119.5, 119.6, 122.8, 127.4, 127.6, 137.8, 138.7, 146.6; HRMS (Q-Tof) m/z calcd 435.2431 for $C_{30}H_{31}N_2O$ $[M + H]^+$, found 435.2438.

General Procedure for RCM Reaction. A solution of the bis-indole-alkene derivative **3** (0.36 mmol) in dry CH_2Cl_2 (50 mL) was degassed with nitrogen for 15 min. Then, G-II catalyst (7.5 mol %) was added and the reaction mixture was stirred at room temperature for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc/petroleum ether) to give the RCM compound **4** as a colorless solid.

(Z)-5,11-Dimethyl-5,11,16,17,20,21-hexahydro-6,10-(metheno)-cyclotrideca[1,2-b:8,7-b′]diindole (**4**): white solid, 98% (55 mg, starting with 60 mg of 1,3-bis(3-(but-3-en-1-yl)-1-methyl-1*H*-indol-2-yl)benzene (**3**)); mp 263−265 °C; R_f = 0.60 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3621, 3018, 2926, 2853, 1733, 1602, 1466, 1216, 1046 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.63 (s, 4H), 3.05 (bs, 4H), 3.77 (s, 6H), 5.89 (bs, 2H), 7.18−7.22 (m, 2H), 7.28−7.32 (m, 2H), 7.39−7.42 (m, 4H), 7.62 (t, J = 7.68 Hz, 1H), 7.72 (d, J = 7.89 Hz, 2H), 7.80 (t, J = 1.31 Hz, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 27.7, 30.5, 31.4, 109.7, 114.3, 119.3, 119.5, 122.2, 127.7, 128.3, 129.6, 130.7, 132.2, 132.7, 137.3, 137.8; HRMS (Q-Tof) m/z calcd 417.2325 for $C_{30}H_{29}N_2$ $[M + H]^+$, found 417.2329.

(Z)-5,11-Dimethyl-5,11,16,19-tetrahydro-6,10-(metheno)-cyclotrideca[1,2-b:8,7-b′]diindole (**10**): white solid, 83% (13 mg, starting with 17 mg of 1,3-bis(3-allyl-1-methyl-1*H*-indol-2-yl)benzene (**9**)); mp 268−271 °C; R_f = 0.60 (petroleum ether/EtOAc 85/15); IR (neat) $\tilde{\nu}_{max}$ 2984, 2935, 1697, 1652, 1422, 1371, 1239, 1023 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.40 (d, J = 14.55 Hz, 2H), 3.77−3.82 (m, 2H), 3.90 (s, 6H), 5.82 (s, 2H), 7.20 (t, J = 7.70 Hz, 2H), 7.30 (t, J = 7.40 Hz, 2H), 7.40 (d, J = 8.15 Hz, 2H), 7.47 (dd, J_1 = 1.45 Hz, J_2 = 7.60 Hz, 2H), 7.62 (t, J = 7.61 Hz, 1H), 7.73 (d, J = 7.85 Hz, 2H), 8.14 (s, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 23.5, 31.3, 109.7, 113.6, 118.6, 119.7, 122.2, 127.3, 128.3, 128.7, 131.8, 137.1, 137.3, 138.9; HRMS (Q-Tof) m/z calcd 389.2018 for $C_{28}H_{25}N_2$ $[M + H]^+$, found 389.2009.

(Z)-5,11-Dimethyl-5,11,16,17,20,21-hexahydro-6,10-(azeno)-cyclotrideca[1,2-b:8,7-b′]diindole (**14**): white solid, 65% (46 mg, starting with 80 mg of 2,6-bis(3-(but-3-en-1-yl)-1-methyl-1*H*-indol-2-yl)pyridine (**13**)); mp 265−267 °C; R_f = 0.50 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3612, 3013, 2938, 2860, 1736, 1561, 1466, 1445, 1355, 1264, 1012 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.71−2.73 (m, 4H), 2.94−2.98 (m, 4H), 3.76 (s, 6H), 5.98 (s, 2H), 7.23−7.25 (m, 2H), 7.34−7.43 (m, 6H), 7.81 (d, J = 7.90 Hz, 2H), 7.92 (t, J = 7.75 Hz, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 27.4, 30.0, 31.7, 109.8, 116.8, 119.6, 119.8, 122.7, 124.4, 127.7, 131.1, 135.7, 136.1, 138.3, 152.2; HRMS (Q-Tof) m/z calcd 440.2097 for $C_{29}H_{27}N_3Na$ $[M + Na]^+$, found 440.2096.

(Z)-5,11-Dimethyl-5,11,16,19-tetrahydro-6,10-(azeno)-cyclotrideca[1,2-b:8,7-b′]diindole (**19**): white solid, 86% (32 mg, starting with 40 mg of 2,6-bis(3-allyl-1-methyl-1*H*-indol-2-yl)pyridine (**18**)); mp 265−267 °C; R_f = 0.60 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 2962, 2928, 2857, 1647, 1466, 1261, 1095, 1019 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.39 (d, J = 13.80 Hz, 2H), 3.83 (s, 6H), 3.99 (t, J = 11.51 Hz, 2H), 5.74 (dd, J_1 = 4.75 Hz, J_2 = 6.15 Hz, 2H), 7.18−7.21 (m, 2H), 7.28−7.33 (m, 2H), 7.36 (d, J = 8.20 Hz, 2H), 7.43 (d, J = 7.85 Hz, 2H), 7.77 (d, J = 7.91 Hz, 2H); 7.93, (t, J = 7.81 Hz, 1H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 23.4, 31.9, 109.9, 116.6, 119.3, 119.8, 121.7, 122.9, 127.0, 128.3, 136.2, 137.1, 138.3, 151.3; HRMS (Q-Tof) m/z calcd 390.1970 for $C_{27}H_{24}N_3$ $[M + H]^+$, found 390.1980.

(Z)-5,10-Dimethyl-5,10,15,16,19,20-hexahydro-6,9-epoxycyclododeca[1,2-b:8,7-b′]diindole (**24**): white solid, 92% (43 mg, starting with 50 mg of 2,5-bis(3-(but-3-en-1-yl)-1-methyl-1*H*-indol-2-yl)furan (**23**)); mp 268−271 °C; R_f = 0.30 (petroleum ether/EtOAc 90/10); IR (neat) $\tilde{\nu}_{max}$ 3054, 2935, 2861, 2345, 1650, 1464, 1265 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.56−2.61 (m, 4H), 3.00−3.04 (m, 4H), 3.85 (s, 6H), 5.87−5.93 (m, 2H), 6.67 (s, 2H), 7.17−7.20 (m, 2H), 7.28−7.32 (m, 2H), 7.35 (d, J = 8.20 Hz, 2H), 7.71 (d, J = 7.90 Hz, 2H); ^{13}C NMR (125.6 MHz, $CDCl_3$) δ 27.5 30.1, 31.5, 109.7, 111.7, 116.2, 119.3, 119.7, 122.8, 127.4, 127.5, 131.1, 138.2, 147.3; HRMS (Q-Tof) m/z calcd 407.2123 for $C_{28}H_{27}N_2O$ $[M + H]^+$, found 407.2141.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01433.

^1H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data and refinement parameters for **4**, **6**, **10**, **14**, and **19** (PDF)

X-ray crystallographic data for **4**, **6**, **10**, **14**, and **19** (ZIP)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Department of Science and Technology (DST), New Delhi, India, for financial support and the Sophisticated Analytical Instrument Facility (SAIF), IIT-Bombay, for recording spectral data. S.K. thanks the Department of Science and Technology for the award of a J. C. Bose fellowship. A.K.C. thanks the University Grants Commission, New Delhi, India, for the award of a research fellowship. M.E.S. thanks the IIT-Bombay for the award of a research fellowship.

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J. Org. Chem. XXXX, XXX, XXX−XXX