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Diversity-Oriented Approach to Normuscopyridine and Its Analogues through Ring-Closing Metathesis[‡]

Sambasivarao Kotha,*[a][‡‡] Gopalkrushna T. Waghule,[a][‡‡] and Mukesh E. Shirbhate[a][‡‡]

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Ring-closing metathesis (RCM) is a useful protocol for assembling macrocycles. To synthesize normuscopyridine, and its analogues we used RCM as a key step in our strategy. Our approach to the synthesis of pyridine macrocycles involves two routes. The first approach starts with alkenylation of 2,6-bis[(phenylsulfonyl)methyl]pyridine and involves five steps with 10 % overall yield. The second route begins with Grignard addition to pyridine-2,6-dicarbo nitrile, followed by RCM and one-pot removal of the carbonyl group and hydrogenation of the double bond in 28 % overall yield. This approach has only three steps. Neither route involves the use of protecting groups. Various points of diversification are embedded in our strategy and eight different cyclophanes were assembled by adopting a general approach to these macrocyclics.

Introduction

Musk is an important component of the perfumery industry. It is obtained from musk deer (*Moschus moschiferus*). Muscone and muscopyridine are the major products whereas musk xylene, musk ambrette, musk ketone, diphenhydramine, and imipramine are minor products of musk.[1] Although, several efforts have been directed toward the preparation of these products synthetically, only a few reports are available for the synthesis of normuscopyridine and its analogues.[2,3] In view of our interest in devising new strategies for assembling cyclophanes[4] and different macrocycles,[5] it was considered useful to synthesize various analogues of muscopyridine by using a general strategy. Moreover, some of the earlier studies on normuscopyridine synthesis are not general in nature and result in low yields. Introducing a stereodirecting sulfone group at the α-position of the aryl ring or changing the hybridization of the carbon atom from sp^3 to sp^2 at this position may facilitate the ring-closing metathesis (RCM) protocol by steering the alkenyl chain into a favorable conformation. This approach also provides an opportunity to introduce alkenyl moieties of variable chain length in a stepwise manner. If required the additional functionality available here can be used as a handle for further synthetic manipulation. Consequently, symmetrical and unsymmetrical alkenylated aryl derivatives suitable for RCM can be assembled.

Results and Discussion

Our diversity-oriented approach to *meta*-pyridinophanes and their analogues starts with arylsulfonylmethyl aromatics such as **2** that are derived from *meta*-substituted benzylic halides **1**.[6]

These sulfones may be alkenylated either in a stepwise manner to generate mono alkenyl compounds **3** or, alternatively by dialkenylation leading to symmetrically functionalized bis-sulfone **4**, from which the RCM protocol may generate cyclized product **5**. Further, desulfonylation followed by hydrogenation can provide an entry to *meta*-cyclophane derivatives, such as **6** (Figure 1). Alternatively, alkylation of monoalkenyl derivative **3** with a different alkenyl halide can generate unsymmetrically functionalized RCM precursors **7**. Analogues of normuscopyridines, such as **9,** can be assembled by attaching an alkenyl chain of a suitable length on one arm of compound **3** followed by RCM[7] and removal of functional groups.

Our journey to normuscopyridine starts with treatment of readily available 2,6-lutidine dibromide (**1a**) with sodium benzenesulfinate to give 2,6-bis[(phenylsulfonyl)methyl]pyridine (**2a**) in quantitative yield.[8] Later, pentenylation of bis sulfone **2a** with 5-bromo-1-pentene in the presence of NaH gave an inseparable mixture of the *cis* and *trans* isomers **10** and **11**. Because our target is devoid of stereogenic centers, the configuration of the sulfonyl groups is of no consequence, and, therefore, we have carried out the RCM with the diastereoisomeric mixture in the presence of Grubbs first-generation (G-I) catalyst to generate cyclophane **12** (51% yield) and dimeric cyclophane **13** (20% yield; Scheme 1). The dimeric nature of **13** was confirmed by HRMS data. No detailed characterization was carried out, and compound **13** was directly used in the desulfonation and hydrogenation sequence. To improve the monomer/di-

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[a] Department of Chemistry, Indian Institute of Technology, Bombay, Powai, Mumbai
E-mail: srk@chem.iitb.ac.in
http://www.chem.iitb.ac.in/~srk/

[‡‡]G. T. W. and M. E. S. made an equal contribution to the paper.

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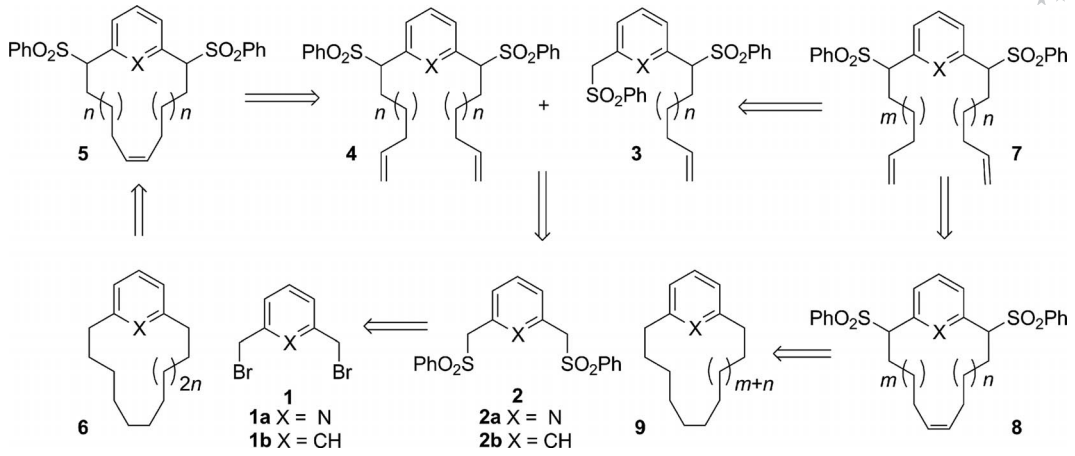
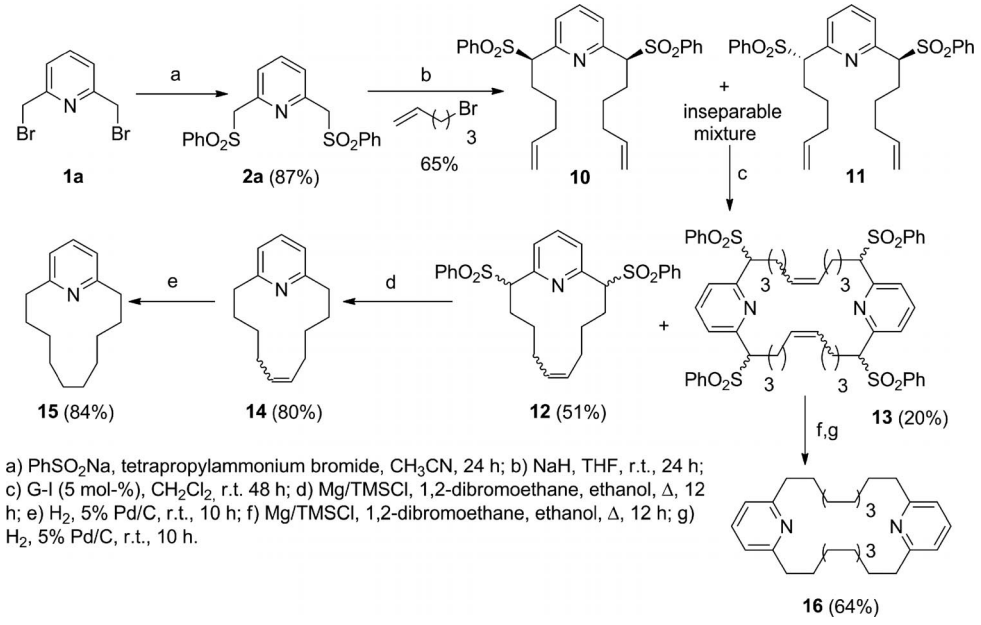


Figure 1. Diversity-oriented approach to normuscopyridine and its analogues.



Scheme 1. Preparation of *meta*-pyridinophane derivatives **15** and **16**.

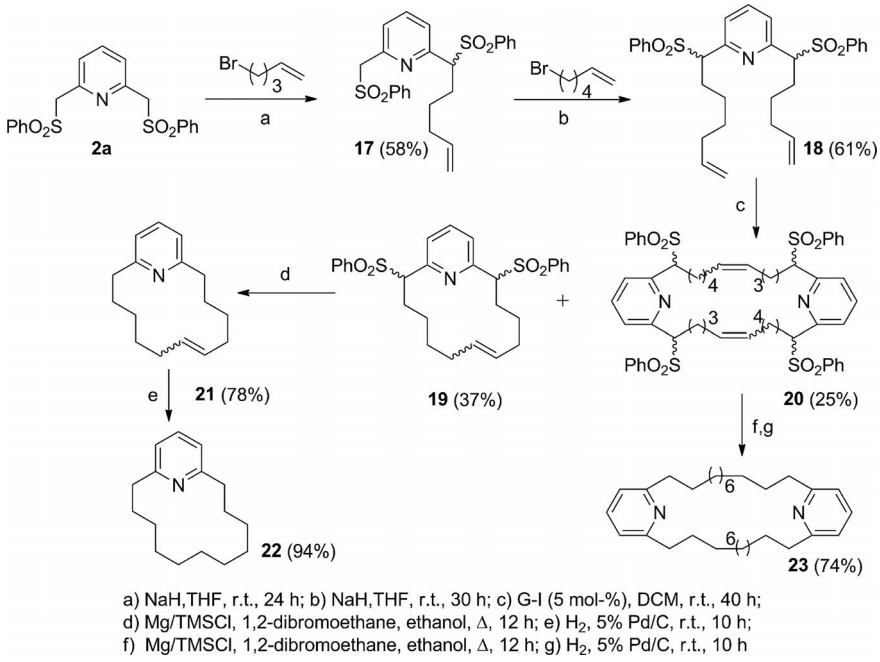
mer selectivity, the RCM was tested in different solvents such as $CHCl_3$ and CCl_4. In addition, the RCM was performed with Grubbs second-generation catalyst (G-II). However, G-I appears to be a better option for this purpose. After a considerable amount of experimentation on the desulfonylation protocol,[9] bisulfone **12** was subjected to reduction in Mg/ethanol, aided by 1,2-dibromoethane in the presence of trimethylsilyl chloride (TMSCl) to generate cyclophane derivative **14** (80% yield). Further, hydrogenation of the double bond in cyclophane **14** with 5% Pd/C under a H_2 atmosphere gave normuscopyridine **15** (84% yield).

Under similar reaction conditions, dimeric product **13**, consisting of diastereoisomers was directly subjected to a desulfonation and hydrogenation sequence to deliver macrocyclic pyridinophane **16** in 64% yield (Scheme 1).

To prepare an analogue of normuscopyridine, bisulfone **2a** was treated with 5-bromo-1-pentene to give monoalkylated product **17**, which on further alkylation with 6-bromo-1-hexene in presence of NaH gave unsymmetrically functionalized pyridine derivative **18** in 61% yield. The diastereoisomeric mixture of **18** was not separable through column chromatography. Further, RCM of **18** with G-I gave monomeric cyclophane **19** (37% yield) and dimeric cyclophane **20** (25% yield; Scheme 2). Macrocyclic bis sulfone **19** was desulfonylated by employing similar reaction conditions developed earlier to deliver **21** (78% yield). Subsequent, hydrogenation of **21** gave (2,6)-pyridinacyclododecaphane **22** (94% yield). Along similar lines, dimeric product **20** consisting of diastereoisomers was subjected to the desulfonation and hydrogenation sequence to generate pyridinophane **23** in 74% yield.

To expand this strategy to other cyclophane derivatives, we chose commercially available bis benzylic bromide **1b** as a starting material.

Thus, 1,3-bis(bromomethyl)benzene **1b** was treated with sodium benzenesulfinate in acetonitrile in the presence of



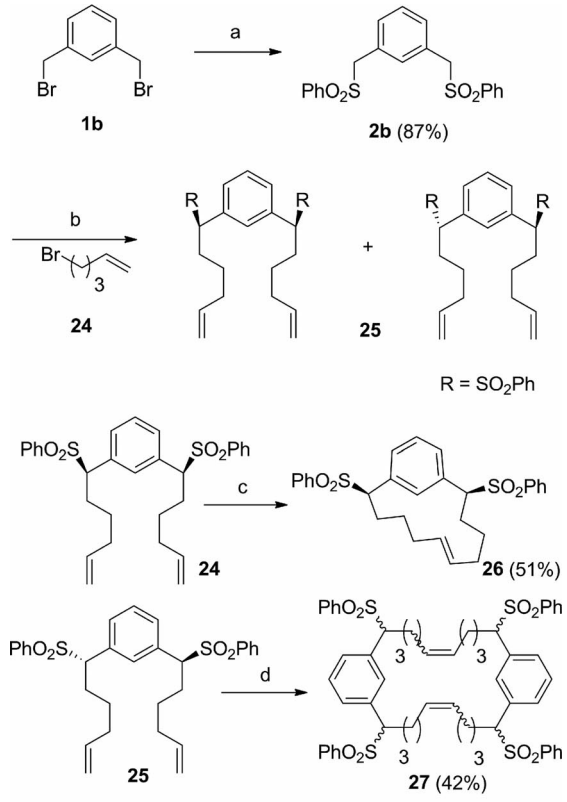
Scheme 2. Synthesis of *meta*-pyridinophanes **22** and **23**.

tetrapropylammonium bromide as a phase-transfer catalyst to deliver 1,3-bis[(phenylsulfonyl)methyl]benzene **2b** in 87% yield. Bis sulfone **2b** was alkylated with 5-bromo-1-pentene in the presence of NaH to give both a monopentenylated and a dipentenylated product depending on the number of equivalents of the electrophile employed. Thus, two diastereoisomeric dipentenylated products **24** and **25** were prepared from **2b**, and these two diastereoisomers were separated by column chromatography. *syn*-Isomer **24** was subjected to the RCM protocol to deliver monomeric ring-closing product **26** in 51% yield. In contrast, *anti*-isomer **25** gave dimeric product **27** in 42% yield. The structure of the dimer was supported by HRMS data (Scheme 3).

The *syn* relationship of the phenyl sulfonyl groups present in cyclophane **26** was confirmed by single-crystal X-ray data that clearly established that the two phenyl sulfonyl groups are situated on the same side of the benzylic carbons and that the double bond has a *trans* arrangement (Figure 2).[10]

Cyclophane **26** derived from **24** was subjected to desulfonylation and hydrogenation to deliver saturated cyclophane **29** in 92% yield. Dimeric cyclophane **27**, consisting of a mixture of diastereoisomers was also subjected to desulfonation followed by hydrogenation to give macrocyclic cyclophane **30** in 78% yield (Scheme 4).

Previously, in our laboratory we prepared the RCM precursor **33** through diallyl Grignard addition to aldehyde **31** followed by oxidation. However, RCM of dione **33** failed to give the cyclized product.[11] During these studies it occurred to us that generation of a carbonyl derivative, such as **33**, directly without involvement of an oxidation step would be a better choice (Scheme 5). To this end, dicyano precursors **34a**–**34b** seemed a better option because Grignard addition can deliver the dicarbonyl derivative directly and avoid double-bond-isomerized product **33a**, which was



Scheme 3. Synthesis of *meta*-cyclophanes **26** and **27**.

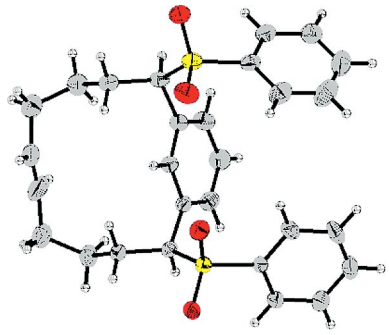
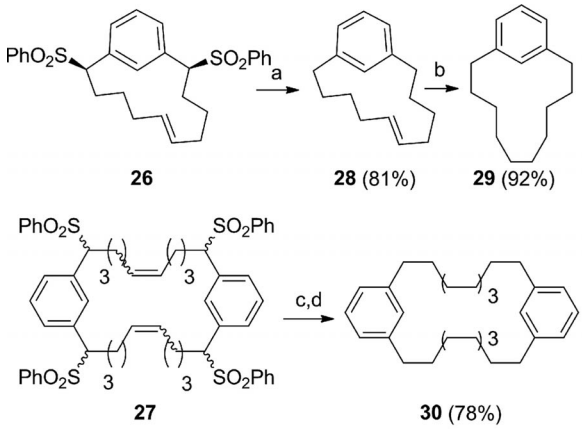


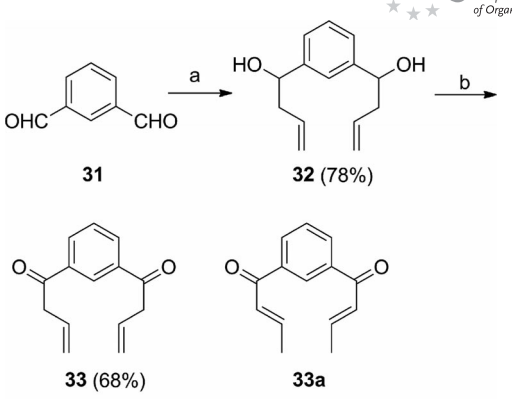
Figure 2. The molecular crystal structure of **26** with 50% probability.



a) Mg/TMSCl, 1,2-dibromoethane, ethanol, Δ, 12 h; b) H_2, 5% Pd/C, r.t., 10 h; c) Mg/TMSCl, 1,2-dibromoethane, ethanol, Δ, 12 h; d) H_2, 5% Pd/C, r.t., 10 h.

Scheme 4. Synthesis of *meta*-cyclophanes **29** and **30**.

observed during oxidation of diol **32** to dione **33**. Later, addition of $CaCO_3$ during pyridinium chlorochromate (PCC) oxidation avoided isomerization of the double bond. We also found that the RCM precursor containing a three- or four-carbon alkenyl chain is not suitable for the RCM protocol (Figure 3).



a) indium/ Mg, allyl bromide, DMF/Et_2O, r.t.; b) PCC, $CaCO_3$, DCM, r.t.

Scheme 5. Synthesis of diketo precursor **33**. Dimethyl formamide (DMF).

To realize the strategy shown in Figure 3, commercially available pyridine-2,6-dicarbonitrile **34a** was treated with 5-bromo-1-pentene in presence of Mg/tetrahydrofuran (THF) to give dicarbonyl compound **37** in 96% yield. RCM of **37** in the presence of G-II in toluene under reflux conditions gave cyclized product **39** as a mixture of *cis-trans* isomers (56% yield). Further, reduction of ring-closed compound **39** with 5% Pd/C gave a partially reduced, racemic alcohol. Reduction of the carbonyl group as well as the double bond present in cyclophane **39** was successfully carried out in one-pot under Wolff–Kishner reduction conditions in ethylene glycol (EG) to generate normuscopyridine **15** in 53% yield.

Along similar lines, the Grignard reagent derived from 6-bromo-1-hexene was treated with dinitrile **34a**, followed by RCM and a Wolff–Kishner reduction sequence gave cyclophane **41**, bis-homologue of normuscopyridine in 51% yield (Scheme 6).

To expand the strategy to other macrocyclic cyclophane derivatives containing a simple benzene moiety, commer-

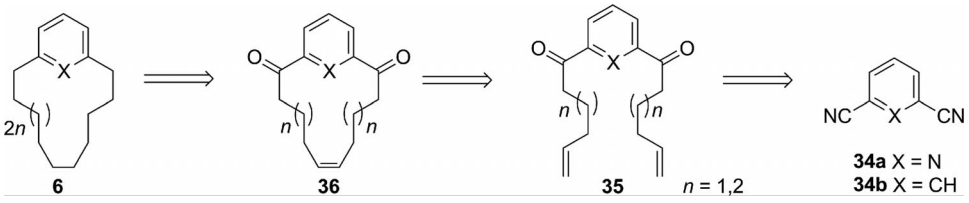
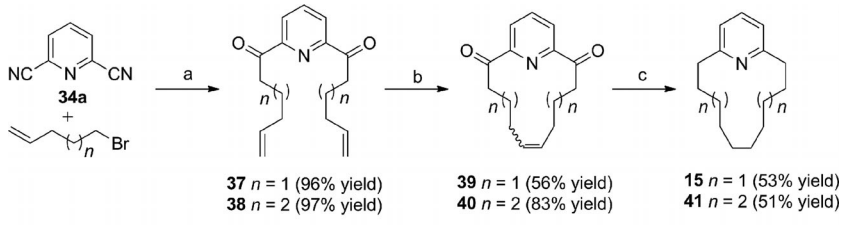
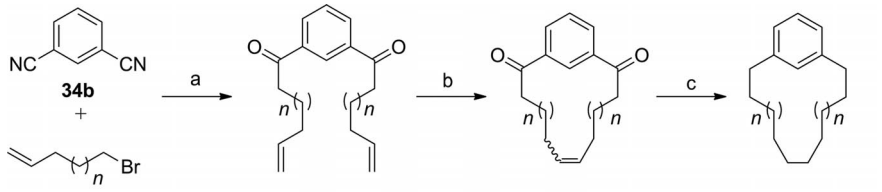


Figure 3. Retrosynthetic approach to a cyclophane through dicyano compound **34a**–**34b**.



a) Mg, THF, H_2O/H^+, 3.5 h; b) G-II (5 mol-%), toluene, Δ, 16 h; c) N_2H_4, K_2CO_3, EG, 180 °C, 19 h

Scheme 6. Synthesis of normuscopyridine **15** and analogue **41**.



Scheme 7. Synthesis of benzene analogues of normuscopyridine **29** and **46**.

cially available isophthalonitrile **34b** was treated with 5-bromo-1-pentene in the presence of Mg/THF to give dicarbonyl compound **42** in 83% yield. RCM of diolefin **42** was carried out in toluene with G-II to give ring-closing product **44** in 66% yield. Subsequent Wolff–Kishner reduction gave saturated cyclophane **29** in 59% yield.

Along similar lines, the Grignard reagent derived from 6-bromo-1-hexene, was treated with dinitrile **34b**, and subsequent RCM and Wolff–Kishner reduction gave normuscopyridine analogues **46** in 53% yield (Scheme 7).

Conclusions

In summary, we have demonstrated a new and general synthetic strategy for the synthesis of normuscopyridine and related compounds. Normuscopyridine and its analogues prepared here did not possess any perfumery smell. Single crystal X-ray data of **26** clearly indicate that the stereochemical orientation of the phenyl sulfonyl groups is *syn* and that the geometry of the double bond is *trans*. The presence of *cis* substituents at the α-carbon atom of the aryl system restricts the freedom of the alkyl chain and thus facilitates a conformation suitable for RCM to deliver the macrocyclic cyclophane. The *trans* disposition of the sulfonyl groups facilitates dimer formation under the same RCM conditions. These two new and simple protocols are capable of producing a variety of macrocyclic cyclophanes of varying chain length.

Experimental Section

General: Analytical TLC was performed on (10 × 5 cm) glass plate coated with silica gel G or GF 254 (containing 13% $CaSO_4$ as a binder). Visualization of the spots on the TLC plate was achieved either by exposure to I_2 vapor or UV light. Column chromatography was performed with silica gel (100–200 mesh) and the column was usually eluted with an ethyl acetate and petroleum ether (b.p. 60–80 °C) mixture. ^{1}H NMR and ^{13}C NMR spectroscopic data were recorded with Bruker 400 spectrometers with tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as a solvent. The coupling constants (J) are given in Hertz (Hz). Chemical shifts are expressed in parts per million (ppm) downfield from the internal reference, TMS. The standard abbreviations, s, br. s, d, t, q, m, dd and td, refer to singlet, broad singlet, doublet, triplet, quartet, multiplet, doublet of doublets, and triplet of doublets, respectively. Mass spectroscopic data were recorded with a Q-ToF micromass spectrometer. Anhydrous THF, was prepared by passing it through a column of activated alumina, then by heating to reflux over and distillation from P_2O_5, and then heated to reflux with Na/benzophenone and distilled, and stored over sodium wire. Anhydrous toluene was obtained by distillation from P_2O_5 and stored over sodium wire. Other reagents and solvents were purchased from commercial suppliers and used without further purification.

Monopentenylation of 2a: To a suspension of NaH (37 mg, 1.55 mmol; 55% in oil) in THF was added 2,6-bis[(phenylsulfonyl)-methyl]pyridine (**2a**; 200 mg, 0.51 mmol) dissolved in dry THF (20 mL) dropwise over a period of 30 min. Then, the reaction mixture was stirred at room temp. for 30 min. Later, 5-bromo-1-pentene (115 mg, 0.77 mmol) dissolved in dry THF (20 mL) was added dropwise over a period of 30 min. Further, the reaction mixture was stirred at room temp. for 20 h under a nitrogen atmosphere. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) to afford **17** (136 mg, 58% yield) and trace quantity of **10** and **11** as an inseparable mixture.

17: (136 mg, 58% yield), m.p. 165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93–1.14 (m, 2 H), 1.75–1.99 (m, 2 H), 2.00–2.10 (m, 1 H), 2.14–2.34 (m, 1 H), 4.15 (dd, J_1 = 4, J_2 = 13 Hz, 1 H), 4.31 (S, 2 H), 4.90–4.96 (m, 2 H), 5.59–5.69 (m, 1 H), 7.36–7.69 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 26.0, 26.8, 27.0, 33.3, 33.3, 72.6, 115.5, 115.6, 123.7, 124.9, 128.8, 129.1, 133.6, 133.7, 137.1, 137.4, 137.5, 137.6, 137.8, 152.6, 152.9 ppm. HRMS (Q-ToF): calcd. for $C_{24}H_{26}NS_2O_4$ $[M + H]^+$ 456.1303; found 456.1291. IR (neat): $\tilde{\nu}_{max}$ = = 757, 1216, 1659, 3018 cm^{-1}.

Dipentenylation of 2a: To a suspension of NaH (49 mg, 2.06 mmol; 55% in oil) in THF was added 2,5-bis(phenylsulfonylmethyl)pyridine (**2a**; 200 mg, 0.52 mmol) dissolved in dry THF (50 mL) dropwise over a period of 30 min. Then, the reaction mixture was stirred at room temp. for 30 min. Then, 5-bromo-1-pentene (293 mg, 2.06 mmol) in THF was added dropwise over a period of 30 min. Further, the reaction mixture was stirred at room temp. for 20 h under a nitrogen atmosphere. At the conclusion of the reaction (TLC monitoring), reaction was diluted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) to afford an inseparable mixture of diastereoisomers **10** and **11** (1:1 ratio; 236 mg, 65% yield).

Dipentenylation of 2b: To a suspension of NaH (49 mg, 2.07 mmol; 55% in oil) in THF was added dropwise solution of 1,3-bis(phenylsulfonylmethyl)benzene (**2b**; 200 mg, 0.51 mmol) dissolved in dry THF (20 mL). Then, the reaction mixture was stirred at room

temp. for 30 min. Later, 5-bromo-1-pentene (306 mg, 2.05 mmol) dissolved in THF (20 mL) was added dropwise over a period of 30 min, further, the reaction mixture was stirred at room temp. for 20 h. under a nitrogen atmosphere. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) to afford **24** (77 mg, 29% yield) and **25** (79 mg, 30% yield).

24: Colorless solid (77 mg, 29% yield), m.p. 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.27 (m, 4 H), 1.91–2.08 (m, 6 H), 2.32–2.41 (m, 2 H), 3.98 (dd, J_1 = 3.7, J_2 = 11.6 Hz, 2 H), 4.95–5.01 (m, 4 H), 5.64–5.74 (m, 2 H), 6.91–7.11 (m, 4 H), 7.32–7.40 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 26.9, 33.2, 71.0, 115.6, 128.8, 128.8, 128.9, 129.0, 129.7, 133.0, 133.6, 137.4, 137.5 ppm. HRMS (Q-ToF): calcd. for $C_{30}H_{35}S_2O_4$ [M + H]$^+$ 523.1977; found 523.1976. IR (KBr pellet): $\tilde{\nu}_{max}$ = 738, 1264, 1421, 1606, 2987, 3054 cm^{-1}.

25: Colorless solid (79 mg, 30% yield), m.p. 190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08–1.26 (m, 4 H), 1.91–2.08 (m, 6 H), 2.32–2.41 (m, 2 H), 3.99 (dd, J_1 = 3.7, J_2 = 11.6 Hz, 2 H), 4.93–5.00 (m, 4 H), 5.60–5.71 (m, 2 H), 6.91–7.11 (m, 4 H), 7.32–7.42 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 26.7, 33.1, 33.1, 70.8, 115.4, 128.7, 128.8, 128.89, 129.6, 132.9, 133.5, 137.3, 137.4 ppm. HRMS (Q-ToF): calcd. for $C_{30}H_{35}S_2O_4$ [M + H]$^+$ 523.1977; found 523.1975. IR (KBr pellet): $\tilde{\nu}_{max}$ = 744, 1267, 1655, 2923 cm^{-1}.

Monohexenylation of 17: To a suspension of NaH (19 mg, 0.82 mmol; 55% in oil) in THF was added monopentenyl product **17** (250 mg, 0.55 mmol) dissolved in dry THF (20 mL) dropwise over a period of 30 min. Then, the reaction mixture was stirred at room temp. for 30 min. Later, 6-bromo-1-hexene (134 mg, 0.82 mmol) dissolved in dry THF (20 mL) was added dropwise over a period of 30 min. Further, the reaction mixture was stirred at room temp. for 20 h under nitrogen atmosphere. At the conclusion of the reaction (TLC monitoring), the reaction mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) to afford **18** (179 mg, 61% yield).

18: (179 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80–1.40 (m, 6 H), 1.90–2.31 (m, 8 H), 4.10–4.20 (m, 2 H), 4.90–4.97 (m, 4 H), 5.58–5.77 (m, 2 H), 7.30–7.68 (m, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 26.0, 26.1, 26.3, 26.9, 27.0, 27.2, 27.4, 28.4, 33.2, 33.3, 72.6, 72.7, 114.9, 115.5, 115.6, 123.8, 124.9, 128.9, 128.9, 129.1, 133.6, 133.6, 133.7, 137.1, 137.4, 137.5, 137.6, 137.6, 137.8, 138.4, 152.6, 152.8, 152.9, 153.0 ppm. HRMS (Q-ToF): calcd. for $C_{30}H_{36}NS_2O_4$ [M + H]$^+$ 538.2086; found 538.2064. IR (neat): $\tilde{\nu}_{max}$ = 757, 1016, 1216, 1669, 3020 cm^{-1}.

General Procedure for RCM Reaction: Compound **18** (50 mg. 93 mmol) was dissolved in dry CH_2Cl_2 and degassed with nitrogen for 15 min. G-I (7 mg, 5 "mol-%") catalyst was added and the reaction mixture was stirred at room temp. for 48 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. The crude product was directly subjected to column chromatography (silica gel, 8% ethyl acetate/petroleum ether) gave product **19** (35 mg, 37% yield) and dimeric cyclophane **20** (23 mg, 25% yield).

Similar procedure was adopted on 50 mg scale for RCM of **10** and **11** to obtain **12** and **13**; RCM of **24** gives **26** further RCM of **25** gives **27**.

12: Semi solid (48 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61–0.73 (m, 2 H), 1.60–1.74 (m, 4 H), 1.91–2.07 (m, 4 H), 2.65–2.75 (m, 2 H), 4.15 (dd, J_1 = 2, J_2 = 12.0 Hz, 2 H), 4.99 (m, 2 H), 6.98 (d, J = 8 Hz, 2 H), 7.41 (t, J = 8 Hz, 1 H), 7.50–7.82 (m, 10 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 28.2, 29.7, 73.2, 127.4, 129.1, 129.2, 129.5, 131.0, 133.7, 136.5, 137.8, 151.8 ppm. HRMS (Q-ToF): calcd. for $C_{27}H_{30}NS_2O_4$ [M + H]$^+$ 496.1616; found 496.1610. IR (KBr pellet): $\tilde{\nu}_{max}$ = 734, 896, 1147, 1264, 1422, 1606, 2987, 3055 cm^{-1}.

19: Semi solid (35 mg, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.48–0.57 (m, 1 H), 0.77–1.21 (m, 3 H), 1.33–1.54 (m, 1 H), 1.81–2.02 (m, 4 H), 2.07–2.46 (m, 5 H), 4.12–4.18 (dd, J_1 = 6, J_2 = 4 Hz, 1 H), 4.22–4.30 (dd, J_1 = 4, J_2 = 6 Hz, 1 H), 4.95–5.15 (m, 2 H), 6.99 (d, J_1 = 8, J_2 = 8 Hz, 1 H); 7.10 (d, J = 8 Hz, 1 H); 7.39–7.76 (m, 11 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.8, 26.4, 27.6, 28.3, 30.2, 31.2, 73.2, 73.4, 127.0, 127.4, 129.0, 129.0, 129.2, 129.2, 129.3, 129.5, 129.7, 130.0, 130.7, 130.8 ppm. HRMS (Q-ToF): calcd. for $C_{28}H_{31}NS_2O_4$ [M + H]$^+$ 509.1694; found 509.1699. IR (KBr pellet): $\tilde{\nu}_{max}$ = 739, 840, 1265, 1420, 1616, 2986, 3066 cm^{-1}.

26: Colorless crystalline solid material (48 mg, 51% yield), m.p. 174 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76–0.79 (m, 2 H), 1.64–1.75 (m, 6 H), 1.94–2.11 (m, 3 H), 2.39–2.45 (m, 1 H), 3.92 (dd, J_1 = 2, J_2 = 12.4 Hz, 2 H), 4.99 (t, J = 2.6 Hz, 2 H), 6.70–6.73 (dd, J_1 = 1.6, J_2 = 8.6 Hz, 2 H), 6.89 (t, J = 2.6 Hz, 1 H), 7.43 (t, J = 7.9 Hz, 2 H), 7.57 (t, J = 1.2 Hz, 4 H), 7.67–7.74 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 26.2, 30.0, 71.2, 127.9, 128.1, 129.0, 129.2, 130.7, 132.8, 132.9, 133.6, 133.6, 137.8 ppm. HRMS (Q-ToF): calcd. for $C_{28}H_{31}S_2O_4$ [M + H]$^+$ 495.1663; found 495.1661. IR (KBr pellet): $\tilde{\nu}_{max}$ = 739, 849, 1265, 1421, 1606, 2986, 3054 cm^{-1}.

13, 20, 27: Contain mixtures of isomers that were further used in the desulfonation and hydrogenation sequence.

General Procedure for Desulfonylation Reaction: To Mg turnings (48 mg, 2.02 mmol) activated by TMSCl (cat. amount) and 1,2-dibromoethane (cat. amount), was added dropwise solution of compound **12** (100 mg, 0.20 mmol) in MeOH (8 mL) at 0 °C and kept at same temperature for 1 h. Then, the reaction mixture was heated to reflux overnight. Next, the reaction mixture was cooled to room temp., and diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4 × 10 mL). The combined organic phase was washed with H_2O and dried with Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, 3% ethyl acetate/petroleum ether) to obtain **14** (34 mg, 80% yield) as a pale yellow oil.

A similar procedure was adopted on 100 mg scale for desulfonation of **19** to obtain **21** and **26** to give **28**.

14: (34 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22–1.41 (m, 4 H), 1.65–1.82 (m, 4 H), 1.90–2.10 (m, 4 H), 2.71 (t, J = 6.5 Hz, 4 H), 5.35–5.43 (m, 2 H), 6.97 (d, J = 6.5 Hz, 2 H), 7.52 (t, J = 6.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 28.1, 29.2, 35.6, 119.8, 130.5, 136.8, 161.1 ppm. HRMS (Q-ToF): calcd. for $C_{15}H_{22}N$ [M + H]$^+$ 216.1752; found 216.1764. IR (neat): $\tilde{\nu}_{max}$ = 896, 1265, 1421, 1639, 3986, 3054 cm^{-1}.

21: (35 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.33 (m, 8 H), 1.59–1.96 (m, 6 H), 2.71–2.80 (m, 4 H), 5.04–5.11 (m, 1 H), 5.37–5.45 (m, 1 H), 6.84–6.92 (m, 2 H), 7.41 (t, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.4, 26.7, 27.9, 28.8, 29.2, 31.2, 31.3, 37.4, 37.6, 120.6, 121.2, 130.4, 131.6, 136.3, 161.0, 162.0 ppm. HRMS (Q-ToF): calcd. for $C_{16}H_{24}N$ [M

+ H]$^+$ 230.1908; found 230.1909. IR (neat): $\tilde{\nu}_{max}$ = 896, 1265, 1421, 1639, 3986, 3054 cm^{-1}.

28: (35 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04–1.33 (m, 4 H), 1.30–1.32 (m, 4 H), 1.70–1.72 (m, 4 H), 2.70–2.75 (m, 4 H), 4.98 (t, J = 3 Hz, 2 H), 6.84–6.92 (m, 3 H), 7.41 (t, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 28.0, 30.8, 34.7, 125.6, 128.2, 130.0, 131.4, 142.3 ppm. HRMS (Q-ToF): calcd. for $C_{16}H_{23}$ [M + H]$^+$ 215.1799; found 215.1794. IR (neat): $\tilde{\nu}_{max}$ = 896, 1265, 1421, 1639, 3986, 3054 cm^{-1}.

General Procedure for Desulfonylation Hydrogenation of 13, 20, and 27 Consecutively: To Mg turnings (24 mg, 1.01 mmol) activated by TMSCl (cat. amount) and 1,2-dibromoethane (cat. amount), was added dropwise a solution of compound **13** (100 mg, 0.10 mmol) in MeOH (8 mL) at 0 °C and kept at same temperature for 1 h. Then, the reaction mixture was heated to reflux overnight. Next, the reaction mixture was cooled to room temp., and it was diluted with Et_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (4× 10 mL). The combined organic phases were washed with H_2O and dried with Na_2SO_4, filtered and concentrated. The crude product obtained was dissolved in dry ethyl acetate (10 mL), Pd/C (6 mg, 5%) was added, and the mixture was stirred at room temp. under a hydrogen atmosphere (1 atm) for 12 h. At the conclusion of the reaction (TLC monitoring), the solvent was evaporated under reduced pressure, and the product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) gave hydrogenated product **16** (28 mg, 64% yield).

A similar procedure was adopted on 100 mg scale for desulfonation and hydrogenation of **20** to obtain **23** and **27** to give **30**.

16: (28 mg, 64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.31 (m, 10 H), 1.60–1.64 (m, 12 H), 1.90–1.95 (m, 10 H), 2.73 (m, 8 H), 6.91 (d, J = 8 Hz, 4 H), 7.45 (t, J = 8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.8, 29.4, 29.5, 30.0, 38.1, 120.1, 136.5, 161.8 ppm. HRMS (Q-ToF): calcd. for $C_{30}H_{47}N_2$ [M + H]$^+$ 435.3738; found 435.3739. IR (neat): $\tilde{\nu}_{max}$ = 894, 1245, 1644, 2913, 3154 cm^{-1}.

23: (33 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.22 (br. s, 20 H), 1.58–1.61 (m, 8 H), 2.20 (br. s, 8 H), 2.70 (t, J = 7 Hz, 8 H), 6.96–7.00 (m, 4 H), 7.16 (t, J = 7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 28.9, 29.5, 30.0, 32.1, 38.3, 120.0, 136.4, 161.8 ppm. HRMS (Q-ToF): calcd. for $C_{32}H_{51}N_2$ [M + H]$^+$ 463.4052; found 463.4067. IR (neat): $\tilde{\nu}_{max}$ = 894, 1265, 1645, 2983, 3054 cm^{-1}.

30: (34 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25–1.27 (bd, 22 H), 1.58–1.61 (m, 10 H), 2.57 (t, J = 7 Hz, 8 H), 6.96–7.00 (m, 6 H), 7.16 (t, J = 7 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.6, 29.2, 29.5, 31.3, 35.7, 125.9, 128.2, 128.7, 142.8 ppm. HRMS (Q-ToF): calcd. for $C_{32}H_{49}$ [M + H]$^+$ 433.4834; found 433.3830. IR (neat): $\tilde{\nu}_{max}$ = 890, 1260, 1645, 2973, 3014 cm^{-1}.

Synthesis of Normuscopyridine 15 and Analogues 22 and 29 by Hydrogenation Reaction: To a solution of unsaturated cyclophane **14** (10 mg, 0.46 mmol) in dry ethyl acetate (10 mL), Pd/C (6 mg, 5%) was added, and the mixture was stirred at room temp. under a hydrogen atmosphere (1 atm) for 12 h. At the conclusion of the reaction (TLC monitoring), the solvent was evaporated under reduced pressure, and the product was purified by column chromatography (silica gel, 10% ethyl acetate/petroleum ether) to give hydrogenated product **15** (8.4 mg, 84% yield).

A similar procedure was adopted on 10 mg scale for hydrogenation of **21** to give **22** and **28** to give **29**.

15: (8.4 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.15–1.18 (m, 12 H), 1.77–1.83 (m, 4 H), 2.82–2.85 (m, 4 H), 6.95 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 25.2, 26.2, 26.5, 28.0, 37.0, 120.3, 136.5, 161.7 ppm. HRMS (Q-ToF): calcd. for $C_{15}H_{24}N$ [M + H]$^+$ 218.1908; found 218.1910. IR (neat): $\tilde{\nu}_{max}$ = 740, 1265, 1645 cm^{-1}.

22: (9.4 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.71–0.75 (m, 2 H), 1.01–1.08 (m, 4 H), 1.20–1.32 (m, 8 H), 1.78–1.85 (m, 4 H), 2.81 (t, J = 2.5 Hz, 4 H), 6.92 (d, J = 8 Hz, 2 H), 7.47 (t, J = 8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3, 24.4, 25.9, 26.5, 26.6, 37.1, 121.5, 136.3, 161.4 ppm. HRMS (Q-ToF): calcd. for $C_{16}H_{26}N$ [M + H]$^+$ 232.2065; found 232.2070. IR (neat): $\tilde{\nu}_{max}$ = 894, 1265, 1645, 2983, 3054 cm^{-1}.

29: (9.2 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91–0.97 (m, 4 H), 1.09–1.25 (m, 8 H), 1.65–1.71 (m, 4 H), 2.66 (t, J = 6 Hz, 4 H), 6.99 (d, J = 7 Hz, 2 H), 7.00 (br. s, 1 H), 7.19 (t, J = 7 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 26.3, 27.0, 28.4, 35.4, 126.1, 128.6, 130.4, 142.2 ppm. HRMS (Q-ToF): calcd. for $C_{16}H_{25}$ [M + H]$^+$ 217.1956; found 217.1955. IR (neat): $\tilde{\nu}_{max}$ = 740, 1265, 1645 cm^{-1}.

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 mixture was stirred for 30 min. Consecutively, pyridine-2,6-dicarbonitrile (**34a**; 100 mg, 0.77 mmol) was added and the resulting mixture was stirred and heated to reflux for 3 h. At the conclusion of reaction (TLC monitoring), 2 N HCl was added and 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 obtain **37**.

A similar procedure was adopted on 100 mg scale with **34a** with 6-bromo-1-hexene to obtain **38** (224 mg, 97% yield). Under similar condition and same scale, **34b** with 5-bromo-1-pentene and 6-bromo-1-hexene electrophiles gave **42** and **43**, respectively.

37: (201 mg, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85–1.98 (m, 4 H), 2.20–2.25 (m, 4 H), 3.28 (t, J = 7.3 Hz, 4 H), 4.99–5.09 (m, 4 H), 5.80–5.90 (m, 2 H), 7.98 (t, J = 7.5 Hz, 1 H), 8.20 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.4, 33.5, 37.1, 115.4, 124.9, 138.1, 138.2, 152.6, 201.5 ppm. HRMS (Q-ToF): calcd. for $C_{17}H_{21}NNaO_2$ [M + Na]$^+$ 294.1466; found 294.1464. IR (neat): $\tilde{\nu}_{max}$: 740, 1266, 1698, 2935, 2935, 3077, 3382, 3664, 3934 cm^{-1}.

38: (224 mg, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49–1.57 (m, 4 H), 1.76–1.84 (m, 4 H), 2.10–2.17 (m, 4 H), 3.27 (t, J = 7.6 Hz, 4 H), 4.94–5.06 (m, 4 H), 5.78–5.88 (m, 2 H), 7.98 (t, J = 7.5 Hz, 1 H), 8.21 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.8, 28.8, 33.7, 37.6, 114.8, 124.9, 138.1, 138.7, 152.6, 201.6 ppm. HRMS (Q-ToF): calcd. for $C_{19}H_{25}NNaO_2$ [M + Na]$^+$ 322.1770; found 322.1777. IR (neat): $\tilde{\nu}_{max}$: 745, 1266, 1696, 2935, 2935, 3054, 3377, 3689, 3944 cm^{-1}.

42: (192 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.87 (m, 4 H), 2.12 (q, J = 7.1 Hz, 4 H), 2.98 (t, J = 7.4 Hz, 2 H), 2.99 (t, J = 7.1 Hz, 2 H), 4.95–5.04 (m, 4 H), 5.73–5.84 (m, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 8.10 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 2 H), 8.47 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.1, 33.0, 37.8, 115.4, 127.4, 128.9, 132.1, 137.3, 137.8, 199.4 ppm. HRMS (Q-ToF): calcd. for $C_{18}H_{23}O_2$ [M + H]$^+$ 271.1692; found 271.1693. IR (neat): $\tilde{\nu}_{max}$ = 738, 1267, 1687, 2934, 3055, 3357, 3690, 3945 cm^{-1}.

43: (201 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.54 (m, 4 H), 1.74–1.81 (m, 4 H), 2.11 (q, J = 7.1 Hz, 4 H), 3.02 (t, J = 7.4 Hz, 4 H), 4.95–5.05 (m, 4 H), 5.76–5.87 (m, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 8.13 (dd, J_1 = 7.8, J_2 = 1.5 Hz, 2 H), 8.51 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.7, 28.6, 33.6, 38.6, 114.8, 127.6, 129.1, 132.2, 137.4, 138.5, 199.6 ppm. HRMS (Q-ToF): calcd. for $C_{20}H_{26}NaO_2$ $[M + Na]^+$ 321.1822; found 321.1825. IR (neat): $\tilde{\nu}_{max}$ = 741, 1266, 1686, 2935, 2984, 3356, 3687, 3943 cm^{-1}.

General Procedure for RCM Reaction: A solution of bis-alkene derivative **37** (100 mg, 0.36 mmol) in dry toluene (50 mL) was degassed with nitrogen for 15 min. Then, Grubbs second-generation catalyst (14 mg, 5 "mol-%") was added and reaction mixture was heated to reflux overnight. At the conclusion of reaction (TLC monitoring), the crude 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, 5% EtOAc-petroleum ether) to afford cyclophane derivative **39** (50 mg, 56% yield).

A similar procedure was adopted on 100 mg scale with substrate **38**, **42**, and **43** individually to obtain cyclophane derivatives **40**, **44** and **45**, respectively.

39: (50 mg, 56% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65–1.72 (m, 4 H), 1.99–2.03 (m, 4 H), 3.15 (t, J = 8.0 Hz, 4 H), 5.43–5.45 (m, 2 H), 7.88 (t, J = 7.5 Hz, 1 H), 8.06 (d, J = 12.0 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$):δ = 26.1, 31.0, 34.4, 124.9, 131.6, 138.3, 152.0, 202.6 ppm. HRMS (Q-ToF): calcd. for $C_{15}H_{17}NNaO_2$ $[M + Na]^+$ 266.1154; found 266.1151. IR (neat): $\tilde{\nu}_{max}$ = 741, 1266, 1965, 2928, 3054, 3681, 3939 cm^{-1}.

40: (74 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62–1.66 (m, 4 H), 1.76–1.83 (m, 4 H), 2.10–2.14 (m, 4 H), 3.26 (t, J = 7.8 Hz, 4 H), 5.54–5.56 (m, 2 H), 7.98 (t, J = 7.5 Hz, 1 H), 8.15 (d, J = 7.7 Hz, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.8, 26.1, 31.1, 34.5, 125.0, 131.7, 138.4, 152.0, 202.7 ppm. HRMS (Q-ToF): calcd. for $C_{17}H_{21}NNaO_2$ $[M + Na]^+$ 294.1464; found 294.1464. IR (neat): $\tilde{\nu}_{max}$ = 752, 1270, 1995, 2931, 3062, 3693, 3940 cm^{-1}.

44: (54 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75–1.82 (m, 4 H), 2.11 (q, J = 5.4 Hz, 4 H), 2.93 (t, J = 7.6 Hz, 4 H), 5.35–5.45 (m, 2 H), 7.41–7.45 (m, 1 H), 8.04 (dd, J_1 = 1.6, J_2 = 7.5 Hz, 2 H), 8.44 (d, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.6, 31.9, 37.4, 127.6, 129.1, 130.1, 131.0, 132.10, 137.3, 199.6 ppm. HRMS (Q-ToF): calcd. for $C_{16}H_{18}NaO_2$ $[M + Na]^+$ 265.1195; found 265.1199. IR (neat): $\tilde{\nu}_{max}$ = 741, 1266, 1695, 2986, 3054, 3686, 3945 cm^{-1}.

45: (63 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.61–1.67 (m, 4 H), 1.76–1.85 (m, 4 H), 2.21–2.27 (m, 4 H), 2.90–2.96 (m, 4 H), 5.49 (t, J = 3.5 Hz, 2 H), 7.59 (t, J = 7.7 Hz, 1 H), 8.20 (dd, J_1 = 6.3, J_2 = 1.6 Hz, 2 H), 8.27 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.7, 28.3, 29.9, 40.3, 129.7, 130.0, 131.2, 132.6, 136.15, 200.9 ppm. HRMS (Q-ToF): calcd. for $C_{18}H_{22}NaO_2$ $[M + Na]^+$ 293.1517; found 293.1512. IR (neat): $\tilde{\nu}_{max}$ = 750, 1275, 1667, 2990, 3061, 3689, 3950 cm^{-1}.

One-Pot Decarbonylation and Hydrogenation Procedure: To a solution of diketone cyclophane derivative **39** (50 mg, 0.20 mmol) dissolved in ethylene glycol (4 mL) was added hydrazine hydrate (52 mg, 1.64 mmol) followed by solid K_2CO_3 (228 mg, 1.65 mmol). The reaction mixture was heated to 120 °C for 3 h and further heated to 180 °C for 16 h. At the conclusion of reaction (TLC monitoring), reaction was diluted with EtOAc (10 mL) and H_2O (10 mL). The reaction mixture was well stirred for 15 min. and extracted with EtOAc. The organic layer was washed with brine solution and dried with Na_2SO_4. Organic solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 3% EtOAc/petroleum ether) to obtain **15** (23 mg, 53% yield).

A similar procedure was adopted on 50 mg scale to obtain cyclophane derivatives **40, 44** and **45** from **41, 29** and **46**, respectively.

Normuscopyridine 15: ^{1}H and ^{13}C NMR spectroscopic data obtained here is the same as that derived from the hydrogenation route.

41: (23 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 1.12–1.12 (m, 4 H), 1.15–1.28 (m, 10 H), 1.69–1.76 (m, 6 H), 2.79–2.85 (m, 4 H), 6.95 (d, J = 7.5 Hz, 2 H), 7.48 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.9, 26.1, 26.8, 27.1, 29.1, 37.7, 120.5, 136.3, 161.9 ppm. HRMS (Q-ToF): calcd. for: $C_{17}H_{27}NK$ $[M + K]^+$ 284.1780; found 284.1782. IR (neat): $\tilde{\nu}_{max}$ = 740, 1265, 2929, 3154, 3686, 3935 cm^{-1}.

29: ^{1}H and ^{13}C NMR spectroscopic data obtained here is the same as that derived from the hydrogenation route.

46: (23 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$):δ = 0.71–0.75 (m, 4 H), 1.00–1.12 (m, 4 H), 1.25–1.35 (m, 8 H), 1.65–1.71 (m, 4 H), 2.66 (t, J = 6.2 Hz, 4 H), 6.98 (dd, J_1 = 1.4, J_2 = 4 Hz, 2 H), 7.13 (s, 1 H), 7.18 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.8, 24.5, 25.9, 26.5, 26.6, 37.2, 126.1, 128.6, 131.4, 142.2 ppm. HRMS (Q-ToF): calcd. for $C_{18}H_{28}K$ $[M + K]^+$ 283.1823; found 283.1823. IR (neat): $\tilde{\nu}_{max}$: 740, 1265, 2929, 3054, 3686, 3945 cm^{-1}.

Supporting Information (see footnote on the first page of this article): NMR spectroscopic data for all compounds and X-ray crystallographic data for **26** are provided.

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