A general synthetic approach to para-cyclophanes via ring-closing metathesis

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A new methodology for the synthesis para-cyclophanes and longithorone C frameworks has been demonstrated via alkylation, ceric ammonium nitrate (CAN) oxidation and ring-closing metathesis as key steps.

Keywords: Cyclophane, alkylation, CAN oxidation, ring-closing metathesis, longithorone C

In 1999, Schmitz and coworkers isolated and characterized the longithorone family of natural products from marine sources such as Aplodium longithrax1-3. These natural products consisting of [12]para-cyclophane core unit containing cis-trans-cis double bonds at ansa chain attached to quinone moiety. Due this unique structural feature longithorones exhibit restricted rotation of quinone moiety and display atropism (Figure 1). There are no reports regarding the biological activity of longithorone C, however, longithorone J show some cytotoxic activity toward the human cell line4.

Strategy
Cyclophanes play an important role in host-guest chemistry and supramolecular science5-7 and due to this attractive feature, several methods have been developed to synthesize cyclophane derivatives8,9. As a part of a major program aimed toward design of new methodologies towards various cyclophane derivatives10-18, herein is reported full details of the preliminary results19 dealing with the synthesis of macrocyclic framework of longithorone C via ring-closing metathesis (RCM)20. Retrosynthetic route for the synthesis of longithorone C unit starting from malonate ester, ethyl acetoacetate and alkyl bromide is shown in Figure 2.

Results and Discussion
To realize the strategy shown in Figure 2 monoalkene building blocks 6a-d and 8a-d have been assembled starting with commercially available active methylene compounds (AMC) such as malonate ester, ethyl acetoacetate and various electrophiles, such as bromo-alkenes. In this regard, malonate ester 3 was alkylation with various bromoalkene derivatives 5a-d in the presence of a strong base such as NaH to deliver the monoalkyl derivative 6 as well as dialkyl derivative 7 in 6:1 ratio21,23. Later, to avoid the formation of dialkylation product, ethyl acetoacetate was treated with mild base K2CO3, instead of strong base such as NaH. We also attempted other conditions to obtain the monoalkylated product exclusively. In this regard, we have tried high dilution conditions and variation in sequence addition of AMC/bromoalkene24,25. Unfortunately, we were unable to avoid the dialkylation products (9a-d) under various reaction condition (Scheme I).

Having prepared the monoalkylated derivatives, the next task was to synthesize the RCM precursor by using xylene dibromide 2 (Ref 26) and compound 6. In this sequence, the monoalkylated malonate esters (6a-d) were reacted with dibromo compound 1 and 2 in the presence of NaH to deliver the bis-alkene derivatives 10a,b and 11a-d in good yields (Scheme II).

To expand this methodology, monoalkylated ethyl acetoacetate derivatives were reacted with dibromo compound 1. To this end, monoalkyl ethyl acetoacetate derivative 8a was reacted with dibromo compound 1 in the presence of NaH and we found an unexpected deacetylation product 13a. Perusal of literature indicates that NaH exhibits unusual character in the presence of aprotic solvent such THF to deliver an unexpected product27. To understand the scope of this reaction we subjected other monoalkylated ethyl acetoacetate derivatives 8b-d to alkylation sequence under similar reaction conditions and unexpected
deacetylation products 13b-d were formed. The presence of deacetylated product was further confirmed by NMR data and mass spectral analysis. However, when ethyl acetoactate monoalkylate derivatives 8a-d was reacted under mild base condition such as K₂CO₃ with dibromo derivative 1 gave the expected products 12a-d in good yield (Scheme III).

With RCM precursors 12a-d and 13a-d, two diastereoisomeric mixtures are possible due to the presence of chiral centre next to benzylic position including those where the acetyl group has been lost 13a-d. Unfortunately, it was not possible to separate diastereoismeric mixture by column chromatography because both diastereoisomers have the same Rₚ value (Scheme III).
Here, we have included a possible mechanism for deacylation step during the alkylation sequence. It is assumed that in the presence of an excess amount of NaH in the reaction mixture, hydride may attack the acetyl group and the resulting charge polarization gives the keto-enol tautomerization product which leads to the deacetylated enolate. In this connection, it was planned to trap the enolate intermediate and therefore benzoyl chloride or tosyl chloride was added during the course of the reaction. However, we are unable to trap the reactive intermediate (i.e., enolate) to establish the possible intermediate (Figure 3).

Having prepared the RCM precursor, our next objective was to cyclize the diolefin by using Grubbs catalyst. In this regard, compounds 10a-b, 11c-d, 12c-d and 13c-d were subjected to RCM with Grubbs second generation catalyst in toluene at reflux conditions. Under these conditions the desired para-cyclophane products 14a-b, 15c-d, 16c-d and 17c-d were formed in good yields (Scheme V).

In most of these cases, cyclophane derivatives are formed as a mixture of diastereoisomers which could not be separated by column chromatography because of the same Rf values of individual isomers. For cyclophane derivative containing malonate ester group, there is no chiral center next to the benzylic position. Based on the 13C NMR spectral data it appears like a single isomer, but it was not possible to assign the geometry of the double bond, whether cis or trans isomer. However, the cyclophane derivatives containing ethyl acetoacetate due to presence of chiral centre next to benzylic position including the one where the acetyl group was lost gave the diastereomeric mixture as a cis or trans isomer (Figure 4).

To enhance the scope of this methodology for the synthesis of longithorone C framework, we chose bis-alkenylated product 13c where the acetyl group is present at the benzylic position. Based on the above observations, we concluded that the chain length is crucial for the success of cyclization and the formation of cyclized products 15b, 16b and 17b was not feasible due to the strain involved in the final molecule and moreover, metathesis protocol is under equilibrium conditions (Scheme IV).
lost. The compound 13c had undergone oxidation smoothly in the presence of the silica gel supported ceric ammonium nitrate (CAN)\textsuperscript{10} to deliver the oxidized product 18 in good yield. Later, the quinone derivative 18 was subjected to RCM protocol in the presence of G-II catalyst under toluene reflux conditions to deliver the quinone containing cyclophane 19 as a mixture of cis and trans isomers. \textsuperscript{13}C NMR spectrum clearly indicated that 19 is a mixture of compounds. It may be due to the possibility of cis and trans isomerism or presence of diastereoisomers. Unfortunately, we were unable to separate these two isomers by column chromatography (Scheme VI).

**Experimental Section**

**General procedure for the synthesis of alkene derivatives of malonate ester**

To a suspension of NaH (3 equiv) in THF was added malonate ester 3 (1 equiv) slowly at 0°C and for 1 hr. Later, alkene bromide 5a-d (1.1 equiv) was added and stirred at RT for 12 hr. The progress of reaction was monitored by TLC; the reaction mixture was quenched with H\textsubscript{2}O and extracted with diethyl ether. The organic layer was washed with brine, dried with anhyd. Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified by column
chromatography (silica gel; EtOAc–petroleum ether, 4%) to afford 6a–d (67%) as a liquid.

6a: By adopting the general procedure mention above, malonate ester 3 on 500 mg (0.03 mmol, 1 equiv) scale was treated with allyl bromide (1.1 equiv) in the presence of NaH (3 equiv) at RT to obtain 6a (425 mg, 68%).

IR (neat): 2927, 2856, 1744, 1645, 1461, 1363, 1186 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.26 (t, \(J = 7.3\) Hz, 6H), 2.61–2.66 (m, 2H), 3.42 (t, \(J = 7.6\) Hz, 1H), 4.17–4.25 (m, 4H), 5.03–5.14 (m, 2H) 5.73–5.83 (m, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 14.10, 32.77, 51.56, 61.29, 117.40, 134.07, 168.81; HRMS (Q-Tof): \(m/z\) Calcd 223.0945 for C\(_{10}\)H\(_{16}\)O\(_3\)Na [M + Na]\(^+\). Found 223.0946.

6b: By adopting a general procedure mention above, malonate ester 3 on 500 mg (0.03 mmol, 1 equiv) scale was treated with 4-bromo butane (1.1 equiv) in the presence of NaH (3 equiv) at RT to obtain 6b (441 mg, 66%).

IR (neat): 2930, 2859, 1738, 1645, 1466, 1366, 1181 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.27 (t, \(J = 7.0\) Hz, 6H), 1.98 (q, \(J = 7.3\) Hz, 2H), 2.09 (t, \(J = 7.1\) Hz, 2H), 3.35 (t, \(J = 7.3\) Hz, 1H), 4.19 (q, \(J = 7.0\) Hz, 4H), 5.02 (t, \(J = 9.4\) Hz, 2H) 5.72–5.82 (m, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)): \(\delta\) 14.17, 27.93, 31.40, 51.29, 61.42, 116.05, 136.99, 169.53; HRMS (Q-Tof): \(m/z\) Calcd 237.1094 for C\(_{11}\)H\(_{18}\)O\(_4\)Na [M + Na]\(^+\). Found 237.1103.

6c: By adopting a general procedure mention above, malonate ester 3 on 500 mg (0.03 mmol, 1 equiv) scale was treated with 5-bromo pentene (1.1 equiv) in the presence of NaH (3 equiv) at RT to obtain 6c (477 mg, 67%).
IR (neat): 2929, 2855, 2934, 1742, 1716, 1641, 1448, 1363, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 14.26 (t, J = 7.1 Hz, 3H), 1.90–2.01 (m, 2H), 2.03–2.18 (m, 2H), 2.23 (s, 3H), 3.45 (t, J = 7.5 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 5.00–5.06 (m, 2H), 5.72–5.80 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.26, 26.89, 28.31, 30.62, 61.48, 63.07, 115.32, 137.67, 172.43, 205.20; HRMS (Q-Tof): m/z Calcd 171.1021 for C₆H₁₀O₃ [M + H]^⁺. Found 171.1022.

8b: By adopting a general procedure mention above, ethyl acetoacetate 4 500 mg (0.038 mmol, 1 equiv) scale was treated with 4-bromobutene (1.1 equiv) in the presence of K₂CO₃ at RT to obtain 8b (460 mg, 65%).

IR (neat): 2992, 2932, 1743, 1711, 1644, 1442, 1363, 1215 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.28 (t, J = 7.1 Hz, 3H), 1.32–1.44 (m, 2H), 1.80–1.92 (m, 2H), 2.00–2.10 (m, 2H), 2.22 (s, 3H), 3.41 (t, J = 7.4 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.94–5.04 (m, 2H), 5.72–5.82 (m, 1H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.16, 26.64, 27.62, 28.82.
33.41, 59.77, 61.37, 115.13, 137.96, 169.88, 203.24; HRMS (Q-Tof): m/z Calcd 199.1334 for C\textsubscript{11}H\textsubscript{18}O\textsubscript{3} [M + H]\textsuperscript{+}. Found 199.1334.

**8d**: By adopting a general procedure mention above, ethyl acetoacetate 4 500 mg (0.038 mmol, 1 equiv) scale was treated with 5-bromohexene (1.1 equiv) in the presence K\textsubscript{2}CO\textsubscript{3} at RT to obtain 8d (526 mg, 69%).

IR (neat): 3045, 2918, 1726, 1696, 1578, 1492, 1374, 1348, 1280, 1211 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textdelta 1.27 (t, J = 7.1 Hz, 3H), 1.28–1.37 (m, 8H), 1.70–1.72 (m, 4H), 2.04 (q, J = 7.1 Hz, 4H), 3.18 (s, 4H), 4.10–4.20 (m, 8H), 4.91–5.00 (m, 4H), 5.71–5.81 (m, 2H), 6.52 (s, 2H).

**General procedure for the synthesis of 10a-d**

To a suspension of NaH (3 equiv) in THF was added alkylated malonate ester 6c,d (1 equiv) in a dropwise manner at 0°C and stirred at RT for 1 hr. Later, dibromide 1 (0.5 equiv) was added and the reaction mixture was stirred at RT for 12 hr. The progress of reaction was monitored by TLC, the reaction was quenched with H\textsubscript{2}O and extracted with diethyl ether. The organic layer was washed with brine, dried with anhyd. Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 8%) to afford bis-alkene malonate derivative 10c,d (65%) as a white solid material.

**10a**: By adopting a general procedure mention above, alkylated malonate ester 6e 100 mg (0.4 mmol, 1 equiv) scale was treated with dibromide 1 (0.2 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 10a (176 mg, 65%). m.p. 60–65°C.

IR (neat): 3054, 2989, 1729, 1641, 1422, 1266 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textdelta 1.34–1.41 (m, 4H), 1.70–1.74 (m, 4H), 1.99 (q, J = 7.1 Hz, 4H), 3.24 (s, 4H), 3.65 (s, 6H), 4.09–4.23 (m, 8H), 4.91–5.00 (m, 4H), 5.71–5.81 (m, 2H), 6.52 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textdelta 14.21, 23.87, 31.73, 31.97, 34.18, 55.68, 58.72, 61.13, 114.04, 114.76, 124.20, 138.52, 151.87, 171.76; HRMS (Q-Tof): m/z Calcd 619.3482 for C\textsubscript{36}H\textsubscript{51}O\textsubscript{10} [M + H]\textsuperscript{+}. Found 619.3499.

**10b**: By adopting a general procedure mention above, alkylated malonate ester 6d 100 mg (0.4 mmol, 1 equiv) scale was treated with dibromide 1 (0.2 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 10b (162 mg, 61%). m.p. 60–65°C.

IR (neat): 3054, 2989, 1729, 1641, 1422, 1266 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textdelta 1.23 (t, J = 7.1 Hz, 12H), 1.28–1.37 (m, 8H), 1.70–1.72 (m, 4H), 2.04 (q, J = 7.1 Hz, 4H), 3.24 (s, 4H), 3.64 (s, 6H), 4.08–4.23 (m, 8H), 4.90–5.00 (m, 4H), 5.72–5.82 (m, 2H), 6.53 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \textdelta 14.24, 23.99, 29.45, 31.93, 31.98, 33.81, 55.75, 58.75, 61.13, 114.12, 114.63, 124.28, 138.91, 151.90, 171.85; HRMS (Q-Tof): m/z Calcd 647.3795 for C\textsubscript{36}H\textsubscript{55}O\textsubscript{10} [M + H]\textsuperscript{+}. Found 647.3807.

**General procedure for the synthesis of 11a-d**

To a suspension of NaH (3 equiv) in THF was added alkylated malonate ester 6a-d (1 equiv) in a dropwise manner at 0°C and stirred at RT for 1 hr. Later, p-xylene dibromide 2 (0.5 equiv) was added and stirred at RT for 12 hr. The progress of reaction was monitored by TLC, the reaction was quenched with H\textsubscript{2}O and extracted with diethyl ether. The organic layer was washed with brine, dried with anhyd. Na\textsubscript{2}SO\textsubscript{4}, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 8%) to afford bis-alkene malonate ester derivative 11a-d (62%) as a white solid material.

**11a**: By adopting a general procedure mentioned above, alkylated malonate ester 6a 100 mg (0.5 mmol, 1 equiv) scale was treated with dibromide 2 (0.25 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 11a (168 mg, 67%). m.p. 60–65°C.

IR (neat): 2979, 2911, 1739, 1717, 1531, 1212 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textdelta 1.23 (t, J = 7.1 Hz, 12H), 2.55 (t, J = 7.1 Hz, 4H), 3.18 (s, 4H), 4.10–4.20 (m, 8H), 5.03 (m, 4H), 5.70–5.71 (m, 2H), 7.00 (s, 4H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): \textdelta 14.22, 36.68, 58.94, 61.42, 119.37, 130.08, 132.81, 134.87, 170.93; HRMS (Q-Tof): m/z Calcd 503.2645 for C\textsubscript{36}H\textsubscript{55}O\textsubscript{10} [M + H]\textsuperscript{+}. Found 503.2668.

**11b**: By adopting a general procedure mention above, alkylated malonate ester 6b 100 mg (0.46 mmol, 1 equiv) scale was treated with dibromide 2 (0.23 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 11b (150 mg, 61%). m.p. 60–65°C.
General procedure for the synthesis of 11a-d

To a mixture of alkylated ethyl acetoacetate 8a-d (1 equiv) and K₂CO₃ (4 equiv) in acetonitrile, was stirred at RT for 1 hr. Later, dibromo compound 1 (0.5 equiv) was added and stirred at RT for 12 hr. The progress of reaction was monitored by TLC, the crude mixture was filtered through a celite pad and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 6%) to afford the alkylated ethyl acetoacetate derivative 12a-d (72%) as a solid. m.p. 60–65°C.

12a: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8a 100 mg (0.58 mmol, 1 equiv) scale was treated with dibromide 1 (0.29 mmol, 0.5 equiv) in the presence K₂CO₃ (4 equiv) at RT for 12 hr to obtain 12a (221 mg, 75%), m.p. 60-65°C.

IR (neat): 2980, 2914, 1733, 1716, 1533, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.25–1.26 (m, 6H), 2.12 (s, 6H), 2.41–2.50 (m, 4H), 3.62–3.79 (m, 4H), 4.09–5.01 (m, 4H), 5.69–5.79 (m, 2H), 6.50 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.21, 27.39, 27.42, 32.09, 32.13, 36.41, 36.47, 55.48, 55.53, 61.43, 64.37, 114.67, 114.69, 118.72, 133.43, 133.46, 151.60, 151.58, 172.12, 172.16, 204.37, 204.41; HRMS (Q-Tof): m/z Calcd 503.2640 for C₂₅H₃₅O₈ [M + H]^+; Found 503.2645.

12b: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8b 100 mg (0.54 mmol, 1 equiv) scale was treated with dibromide 1 (0.27 mmol, 0.5 equiv) in the presence K₂CO₃ (4 equiv) at RT for 12 hr to obtain 12b (207 mg, 72%), m.p. 60-65°C.

IR (neat): 2973, 2909, 1732, 1712, 1533, 1204 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.25–1.26 (m, 6H), 1.74–1.90 (m, 4H), 1.92–2.09 (m, 4H), 2.12 (s, 6H), 3.08–3.31 (m, 4H), 3.62 (s, 6H), 4.09–4.25 (m, 4H), 4.93–5.01 (m, 4H), 5.69–5.79 (m, 2H), 6.50 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.18, 27.17, 27.20, 28.57, 30.56, 30.62, 31.49, 31.52, 55.58, 55.62, 61.36, 64.08, 114.31, 114.34, 114.98, 124.15, 124.18, 137.88, 151.65, 151.67, 172.43, 172.47, 204.94, 205.90; HRMS (Q-Tof): m/z Calcd 531.2958 for C₂₅H₃₅O₈ [M + H]^+; Found 531.2967.

12c: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8c 100 mg (0.55 mmol, 1 equiv) scale was treated with dibromide 1 (0.25 mmol, 0.5 equiv) in the presence K₂CO₃ (4 equiv) at RT for 12 hr to obtain 12c (200 mg, 71%), m.p. 60-65°C.

IR (neat): 2979, 2911, 1739, 1717, 1531, 1212 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.23–1.25 (m, 6H), 1.29–1.37 (m, 4H), 1.64–1.76 (m, 4H), 2.03 (q, J = 7.0 Hz, 4H), 2.11 (s, 6H), 3.06–3.31 (m, 4H), 3.62 (s, 6H), 4.09–4.26 (m, 4H), 4.91–5.01 (m, 4H), 5.69–5.79 (m, 2H), 6.50 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.18, 27.17, 27.20, 28.57, 30.56, 30.62, 31.49, 31.52, 55.58, 55.62, 61.36, 64.08, 114.31, 114.34, 114.98, 124.15, 124.18, 137.88, 151.65, 151.67, 172.43, 172.47, 204.94, 205.90; HRMS (Q-Tof): m/z Calcd 531.2958 for C₂₅H₃₅O₈ [M + H]^+; Found 531.2967.
12d: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8d 100 mg (0.47 mmol, 1 equiv) scale was treated with dibromide 1 (0.5 equiv) in the presence K₂CO₃ (0.23 mmol, 4 equiv) at RT for 12 hr to obtain 12d (193 mg, 70%). m.p. 60–65°C.

IR (neat): 2976, 2922, 1739, 1712, 1541, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃):  δ 1.66–1.23 (m, 4H), 1.23–1.25 (m, 6H), 1.29–1.37 (m, 4H), 1.64–1.76 (m, 4H), 2.03 (q, J = 7.0 Hz, 4H), 2.11 (s, 6H), 3.06–3.31 (m, 4H), 3.62 (s, 6H), 4.09–4.26 (m, 4H), 4.91–5.01 (m, 4H), 5.69–5.80 (m, 2H), 6.50 (s, 2H);
¹³C NMR (100 MHz, CDCl₃): δ 14.19, 29.80, 27.12, 27.14, 29.48, 31.47, 31.54, 33.73, 55.50, 55.55, 61.30, 64.32, 114.27, 114.30, 114.79, 124.29, 124.32, 138.73, 151.66, 172.63, 172.66, 205.14, 205.20; HRMS (Q-Tof): m/z Calcd 587.3584 for C₃₂H₄₀O₈Na [M + Na⁺]. Found 587.3602.

**General procedure for the synthesis of 11a-d**

To a mixture of alkylated ethyl acetoacetate 8a-d (1 equiv) and K₂CO₃ (4 equiv) in acetonitrile was stirred at RT for 1 hr. Later, dibromide compound 1 (0.5 equiv) was added and stirred at RT for 12 hr. The progress of reaction was monitored by TLC, the crude mixture was filtered through a celite plate and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 6%) to afford the alkylated ethyl acetoacetate derivative 12a-d (72%) as a solid. m.p. 60–65°C.

13a: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8a 100 mg (0.58 mmol, 1 equiv) scale was treated with dibromide 1 (0.29 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 13a (172 mg, 70%). m.p. 60–65°C.

IR (neat): 2931, 2860, 1726, 1506, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.12–1.14 (m, 6H), 1.33–1.45 (m, 4H), 1.45–1.54 (m, 2H), 1.59–1.70 (m, 2H), 2.00–2.07 (m, 4H), 2.65–2.75 (m, 2H), 2.75–2.85 (m, 4H), 3.74 (s, 6H), 4.00–4.08 (m, 4H), 4.90–5.00 (m, 4H), 5.71–5.82 (m, 2H), 6.59 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.42, 33.01, 36.53, 45.49, 45.52, 56.07, 60.24, 113.71, 116.84, 126.37, 135.67, 151.36, 175.49; HRMS (Q-Tof): m/z Calcd 419.2430 for C₃₂H₃₀O₅Na [M + H⁺]. Found 419.2431.

13b: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8b 100 mg (0.54 mmol, 1 equiv) scale was treated with dibromide 1 (0.27 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 13b (152 mg, 63%). m.p. 60–65°C.

IR (neat): 2932, 2865, 1721, 1506, 1217 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.13–1.15 (m, 6H), 1.52–1.60 (m, 2H), 1.69–1.79 (m, 2H), 1.98–2.14 (m, 4H), 2.67–2.76 (m, 2H), 2.73–2.85 (m, 4H), 3.74 (s, 6H), 4.00–4.08 (m, 4H), 4.92–5.03 (m, 4H), 5.70–5.82 (m, 2H), 6.59 (s, 2H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.43, 31.62, 31.67, 33.41, 33.44, 45.40, 45.44, 56.12, 60.20, 113.65, 115.07, 126.50, 138.19, 151.38, 176.11; HRMS (Q-Tof): m/z Calcd 447.2745 for C₃₃H₃₂O₅Na [M + H⁺]. Found 447.2747.

13c: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8c 100 mg (0.55 mmol, 1 equiv) scale was treated with dibromide 1 (0.25 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 13c (158 mg, 66%). m.p. 60–65°C.

IR (neat): 2931, 2860, 1726, 1506, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.12–1.14 (m, 6H), 1.33–1.45 (m, 4H), 1.45–1.54 (m, 2H), 1.59–1.70 (m, 2H), 2.00–2.07 (m, 4H), 2.65–2.75 (m, 2H), 2.75–2.85 (m, 4H), 3.74 (s, 6H), 4.00–4.08 (m, 4H), 4.90–5.00 (m, 4H), 5.71–5.82 (m, 2H), 6.59 (s, 2H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.43, 26.71, 32.01, 33.48, 33.75, 45.83, 56.11, 60.15, 113.64, 114.74, 126.60, 138.70, 151.36, 176.23; HRMS (Q-Tof): m/z Calcd 475.3060 for C₃₃H₃₂O₅Na [M + H⁺]. Found 475.3060.

13d: By adopting a general procedure mention above, alkylated ethyl acetoacetate 8d 100 mg (0.47 mmol, 1 equiv) scale was treated with dibromide 1 (0.23 mmol, 0.5 equiv) in the presence NaH (3 equiv) at RT for 12 hr to obtain 13d (158 mg, 67%). m.p. 60–65°C.

IR (neat): 2933, 2862, 1746, 1516, 1211 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.12–1.14 (m, 6H), 1.23–1.42 (m, 8H), 1.42–1.53 (m, 2H), 1.58–1.68 (m, 2H), 1.98–2.05 (m, 4H), 2.63–2.71 (m, 2H), 2.73–2.84 (m, 4H), 3.73 (s, 6H), 3.98–4.08 (m, 4H), 4.90–5.00 (m, 4H), 5.73–5.83 (m, 2H), 6.59 (s, 2H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.43, 26.92, 28.91, 31.62, 31.67, 33.41, 33.44, 45.40, 45.44, 56.12, 60.20, 113.65, 115.07, 126.50, 138.19, 151.38, 176.11; HRMS (Q-Tof): m/z Calcd 447.2745 for C₃₃H₃₂O₅Na [M + H⁺]. Found 447.2747.
14c: By adopting a general procedure mention above, the bis-alkylated derivative 11c on 50 mg (0.089 mmol) scale in toluene was added G-II 4 mg (5 mol %) and reaction mixture was reflux for overnight to obtain 15c (39 mg, 82%).

IR (neat): 2980, 2936, 1728, 1444, 1269 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.95–1.12 (m, 4H), 1.22–1.33 (m, 12H), 1.46–1.48 (m, 4H), 1.83–1.88 (m, 4H), 3.30 (s, 4H), 4.16–4.28 (m, 8H), 5.07–5.09 (m, 2H), 7.01 (s, 4H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.27, 23.49, 31.53, 32.49, 39.06, 58.15, 61.50, 129.75, 130.53, 135.36, 172.06; HRMS (Q-Tof): m/z Calcd 531.2958 for C₃₀H₴₅O₈ [M + H]⁺. Found 531.2957.

15d: By adopting a general procedure mention above, the bis-alkylated derivative 11d on 50 mg (0.085 mmol) scale in toluene was added G-II 4 mg (5 mol %) and reaction mixture was reflux for overnight to obtain 15d (38 mg, 80%).

IR (neat): 2982, 2940, 1732, 1446, 1266 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.26 (m, 4H), 1.27 (m, 12H), 1.29–1.30 (m, 4H), 1.63–1.67 (m, 4H), 1.68–1.69 (m, 4H), 3.31 (s, 4H), 4.22–4.23 (m, 8H), 5.26–5.29 (m, 2H), 6.98 (s, 2H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.24, 14.26, 23.50, 31.27, 32.43, 33.26, 55.78, 57.64, 61.13, 61.32, 114.37, 124.44, 130.34, 151.71, 172.16, 172.40; HRMS (Q-Tof): m/z Calcd 559.3960 for C₃₂H₳₅O₈ [M + H]⁺. Found 559.3960.

16c: By adopting a general procedure mention above, the bis-alkylated derivative 12c on 50 mg (0.089 mmol) scale in toluene was added G-II 4 mg (5 mol %) and reaction mixture was reflux for overnight to obtain 16c (39 mg, 83%).

IR (neat): 2980, 2907, 1739, 1717, 1533, 1219 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.85–1.14 (m, 4H), 1.29 (t, J = 7.1 Hz, 6H), 1.30–1.42 (m, 2H), 1.52–1.63 (m, 2H), 1.74–1.81 (m, 2H), 1.88–1.96 (m, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 3.09–3.19 (m, 2H), 3.49–3.53 (m, 2H), 3.61–3.68 (m, 6H), 4.16–4.31 (m, 4H), 4.93–5.11 (m, 2H), 6.58–6.65 (m, 2H); ¹³C NMR (100.6 MHz, CDCl₃): δ 14.22, 14.27, 23.14, 23.32, 23.44, 23.62, 26.25, 26.29, 26.84, 26.86, 30.69, 30.72, 30.87, 32.06, 32.11, 32.23, 32.45, 32.49, 32.67, 32.71, 55.25, 55.31, 55.80, 61.32, 61.51, 63.57, 63.95, 64.04, 114.51, 114.62, 114.72, 114.81, 124.36, 124.49, 124.63, 124.80, 129.97, 130.03, 130.90, 130.42, 151.49, 151.54, 151.74, 172.38, 173.02, 173.10, 204.54, 204.16, 205.60; HRMS (Q-Tof): m/z Calcd 531.2950 for C₃₀H₴₅O₈ [M + H]⁺. Found 531.2951.
16d: By adopting a general procedure mention above, the bis-alkylated derivative 12d on 50 mg (0.085 mmol) scale in toluene was added G-II 3.6 mg (5 mol%) and reaction mixture was reflux for overnight to obtain 16d (38 mg, 81%).

IR (neat): 2983, 2912, 1714, 1715, 1536, 1220 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.10–1.14 (m, 4H), 1.23–1.28 (m, 6H), 1.55–1.62 (m, 4H), 1.62–1.85 (m, 4H), 1.85–1.95 (m, 4H), 2.15–2.20 (m, 6H), 2.97–3.15 (m, 4H), 3.62–3.65 (m, 6H), 4.17–4.23 (m, 4H), 1.85–1.95 (m, 4H), 2.15–2.20 (m, 6H), 2.80–2.91 (m, 2H), 3.16–3.33 (m, 2H), 3.74–3.79 (m, 2H), 4.15–4.21 (m, 2H), 2.97–3.15 (m, 4H), 3.62–3.65 (m, 6H), 4.17–4.23 (m, 4H), 1.85–1.95 (m, 4H), 2.15–2.20 (m, 6H), 2.80–2.91 (m, 2H), 3.16–3.33 (m, 2H), 3.74–3.80 (m, 6H), 4.15–4.21 (m, 4H), 4.84–4.99 (m, 2H), 6.59–6.69 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.53, 26.59, 28.15, 31.25, 34.83, 42.54, 56.12, 60.38, 115.18, 126.52, 130.63, 151.39, 176.91; HRMS (Q-Tof): m/z Calcld 475.3055 for C₂₈H₄₃O₆ [M + H]^+. Found 475.3060.

19: By adopting a general procedure mention above, the bis-alkylated derivative 18 on 50 mg (0.11 mmol) scale in toluene was added G-II 5 mg (5 mol%) and reaction mixture was reflux overnight to obtain 19 (33 mg, 71%).

IR (neat): 2942, 2865, 1733, 1469, 1270 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.09–1.17 (m, 2H), 1.18–1.41 (m, 12H), 1.79–1.98 (m, 4H), 2.25–2.50 (m, 2H), 2.68–2.75 (m, 2H), 3.10–3.16 (m, 2H), 4.14–4.20 (m, 4H), 5.09–5.19 (m, 2H), 6.59–6.63 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.29, 25.97, 28.87, 31.62, 33.11, 41.89, 60.70, 131.05, 134.73, 147.04, 175.04, 187.14; HRMS (Q-Tof): m/z Calcld 417.2274 for C₂₅H₃₅O₅ [M + H]^+. Found 417.2277.

General procedure for the synthesis of 18

To a mixture of (5 mol%) CAN and charged flash chromatograph-grade silica gel (6 g) in water (2.5 mL) that give the free-flowing yellow solid. Dichloromethane (25 mL) was added and the bis-alkylated derivative 13c (200 mg) was filtered through a Celite pad (washed with dichloromethane). Dichloromethane (25 mL) was added and the bis-alkylated derivative 13c (200 mg) was dissolved in dichloromethane (2 mL) was added in a dropwise manner and stirred for 5 min. The crude mixture was filtered through a Celite pad (washed with dichloromethane) and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 5%) to give the bis-alkylated quinone derivative 18 (125 mg, 67%) as a liquid.

IR (neat): 2931, 2858, 1728, 1464, 1266 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.19–1.22 (m, 6H), 1.37–1.45 (m, 4H), 1.49–1.56 (m, 2H), 1.63–1.70 (m, 2H), 2.00–2.12 (m, 4H), 2.59–2.65 (m, 6H), 4.07–4.12 (m, 4H), 4.94–5.02 (m, 4H), 5.71–5.81 (m, 2H), 6.54 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 14.42, 26.40, 31.75, 32.22, 33.52, 44.24, 60.67, 115.10, 133.89, 138.24, 146.68, 174.78, 187.40; HRMS (Q-Tof): m/z Calcld 445.2601. Found 445.2601.

Conclusion

In conclusion, a simple synthetic route has been developed toward various macrocyclic cyclophanes (14c,d, 15c,d, 16c,d and 17c,d) and also quinone containing cyclophane derivative 19 which is related to the longithorone C framework via RCM as a key step. Here, readily available starting materials have been employed, such as maleic ester, hydroquinone, unsaturated bromides and more importantly no
involvement of protecting groups. Moreover, the methodology reported here is armed with several diversity points and is capable of producing a library of cyclophane derivatives.

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