Diversity-Oriented Approach to Macrocyclic Cyclophane Derivatives via Ring-Closing Metathesis[1]

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Dedicated to Professor Mariappan Periasamy on the occasion of his 60th birthday.

Abstract: A short synthetic approach to the macrocyclic framework of longithorone C is described via ring-closing metathesis using the Grubbs 2nd generation catalyst.

Keywords: paracyclophane, macrocycles, ring-closing metathesis, oxidation, alkylation

Longithorone is a unique prenylated [12]paracyclophane derivative containing a quinone moiety. The macrocycle, which resembles a *cis*-farnesol unit around the quinone moiety, exhibits restricted rotation, which is responsible for the asymmetric nature of the paracyclophane unit.[2a] Schmitz and co-workers isolated the longithorone family of natural products (Figure 1) from the marine tunicate *Alpodium longithorax*.[2b–e]

Kato and co-workers have reported the synthesis of longithorone B,[3] and Shair and co-workers have prepared a dimeric member of the longithorone family, longithorone A.[4] On another occasion, Collins and co-workers have reported the macrocyclic portion of longithorone C.[5]

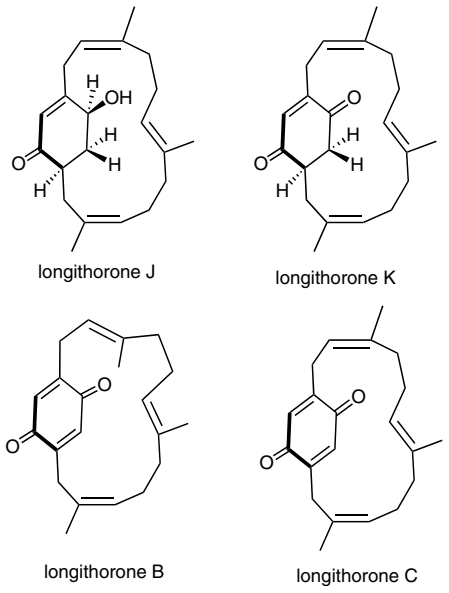

Figure 1 Longithorone family of natural products

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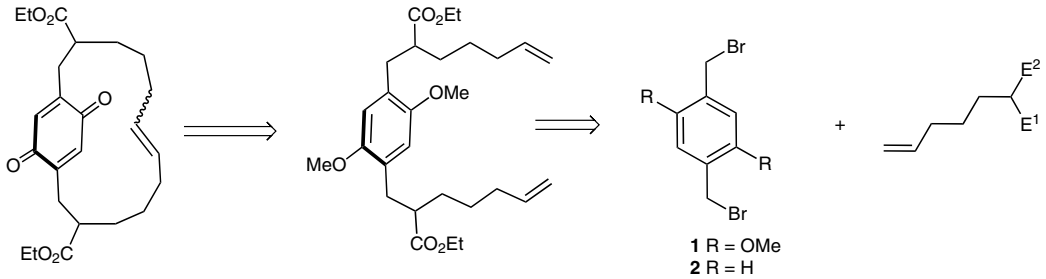
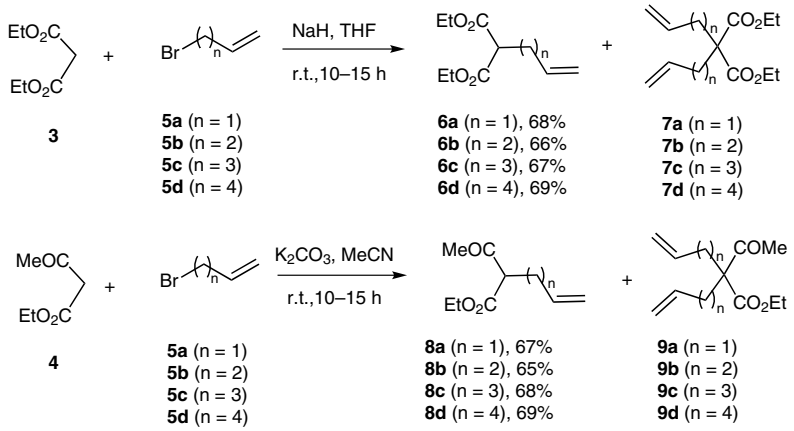
Ring-closing metathesis (RCM)[6] has become one of the most efficient ways to assemble macrocycles.[7] Several macromolecules are known to play an important role in bioorganic and medicinal chemistry, they possess unique chemical properties and play a pivotal role in host–guest[8] and supramolecular chemistry.[9] Synthesis of cyclophane derivatives is a challenging task because of the entropy factors and ring strain involved with these systems. These aspects may account for the lengthy synthetic sequence and low yield of cyclophane derivatives.[10] As part of a major program focused on the design of simple methodologies that can be used to access cyclophanes,[11] herein, we report a short and simple synthetic approach to the macrocyclic framework of longithorone C via RCM.

The ability to perform RCM in the presence of diverse functional groups provides greater flexibility in retrosynthetic planning. The retrosynthetic analysis of the longithorone C framework involving RCM as a key step is shown Scheme 1. Here, the carbon framework of longithorone C is derived by alkylation of an active methylene compound (AMC) containing an unsaturated alkene moiety, cerium(IV) ammonium nitrate (CAN) mediated oxidation, followed by RCM. The macrocyclic precursor could be obtained by coupling of the dibromide (e.g., **1** or **2**) with an alkene derivative. Dibromide **1** is prepared according to a known procedure[12] and the parent dibromide **2** is commercially available.

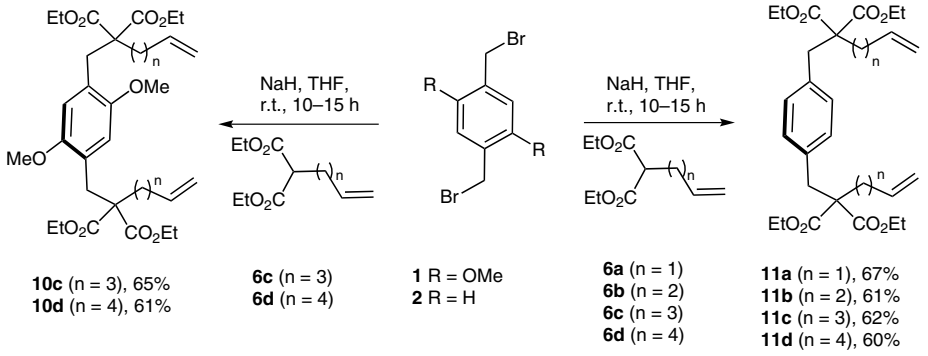
The unsaturated side chain fragments were assembled by adapting the previously reported procedure.[13a] Specifically, alkylation of AMC **3** or **4** was achieved with NaH or K_2CO_3 (Scheme 2). Various alkylated compounds **6a–d**, **8a**, **8b** and **8d** are known in the literature and have been synthesized under different reaction conditions.[13b–e] To the best of our knowledge, compound **8c** has not previously been reported. The *para*-disubstituted substrates suitable for RCM (**10c**, **10d**, **11a–d**, **12a–d** and **13a–d**) were prepared by coupling two equivalents of mono-alkene derivatives **6a–d**, **8a–d** with one equivalent of dibromo compound **1** or **2** in the presence of a base such as NaH or K_2CO_3 (Scheme 3 and Scheme 4). However, we found the formation of unexpected deacetylated products **13a–d** when the coupling of ethyl acetoacetate derivatives **8a–d** was performed with dibromide **1** and a suspension of NaH in aprotic solvent such as tetrahydrofuran (THF). The identity of the deacetylated products obtained were confirmed by ^1H, ^{13}C NMR spectral data and further supported by HRMS data (Scheme 4). The formation of retro-



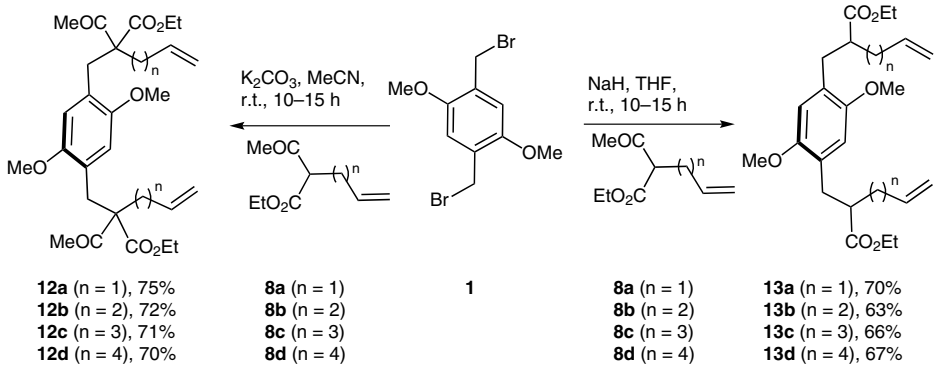
Scheme 1 Retrosynthetic analysis of a paracyclophane derivative



Scheme 2 Alkylation of active methylene compounds



Scheme 3 Synthesis of RCM precursor involving malonic ester

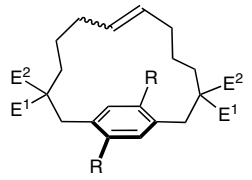


Scheme 4 Synthesis of RCM precursor involving ethyl acetoacetate

Claisen products **13a–d** is in line with the earlier observation.[14]

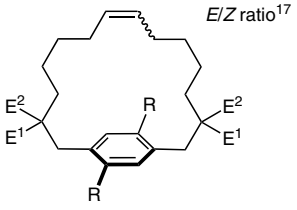
Having prepared various *para*-disubstituted derivatives (**10c–d**, **11a–d**, **12a–d** and **13a–d**) they were subjected to the metathesis protocol with Grubbs 2nd generation catalyst to deliver the RCM products. Molecular modeling revealed that in instances where the carbon tether is short (n = 1 or 2), formation of the RCM product may be difficult due to the strain involved in macrocyclic ring generation (Scheme 5). Our initial attempts to realize the RCM of compounds **11a–d**, **12a–d**, **13a** and **13b** by treatment with the Grubbs 1st generation catalyst were not successful. We also failed to achieve the cyclized product with substrates such as **11a**, **11b**, **12a**, **12b**, **13a** and **13b** under the same reaction conditions involving Grubbs 2nd generation catalyst. From these results, it appears that the substrates containing a shorter terminal olefin tether (n = 1 or 2), as in **11** and **13**, are not good precursors for the RCM sequence.

When the RCM protocol was carried out with substrates **10c**, **10d**, **11c**, **11d**, **12c**, **12d**, **13c** and **13d** with Grubbs 2nd generation catalyst in toluene at reflux temperature, the corresponding RCM products **14c**, **14d**, **15c**, **15d**, **16c**, **16d**, **17c** and **17d** were obtained (Figure 2). However, substrates **14–17** with longer olefin tethers (n = 3 and 4), underwent RCM to generate the product as a mixture of *cis*/*trans* isomers of the [12] and [14]cyclophane derivatives (Scheme 6).[15]



[12]paracyclophane

14c R = OMe, E^2 = E^1 = CO_2Et, (*E*) only
15c R = H, E^2 = E^1 = CO_2Et, (*E*) only
16c R = OMe, E^2 = COMe, E^1 = CO_2Et, (*E*/*Z* 1.6:1)
17c R = OMe, E^2 = H, E^1 = CO_2Et, (*E*/*Z* 1.6:1)

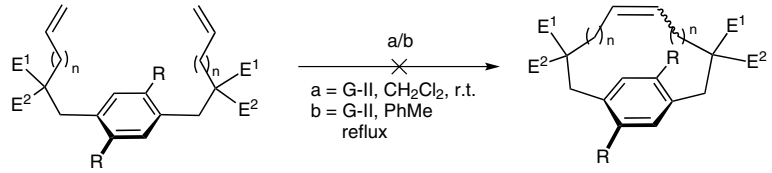


[14]paracyclophane

14d R = OMe, E^2 = E^1 = CO_2Et, (*E*/*Z* 3.7:1)
15d R = H, E^2 = E^1 = CO_2Et, (*E*/*Z* 3.7:1)
16d R = OMe,E^2 = COMe, E^1 = CO_2Et, (*E*/*Z* 1.7:1)
17d R = OMe, E^2 = H, E^1 = CO_2Et, (*E*/*Z* 1.7:1)

Figure 2 List of prepared macrocyclic cyclophanes

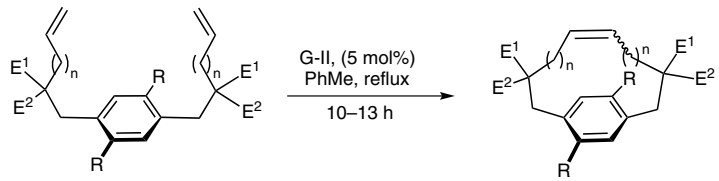
Toward the synthesis of quinone-containing cyclophane **19**, the required RCM precursor **18** was obtained (67% yield) by using silica gel supported CAN oxidation of **13c** in dichloromethane at room temperature (Scheme



11a (n = 1), R = H, E^2 = E^1 = CO_2Et
11b (n = 2), R = H, E^2 = E^1 = CO_2Et
12a (n = 1), R = OMe, E^2 = COMe, E^1 = CO_2Et
12b (n = 2), R = OMe, E^2 = COMe, E^1 = CO_2Et
13a (n = 1), R = OMe, E^2 = H, E^1 = CO_2Et
13b (n = 2), R = OMe, E^2 = H, E^1 = CO_2Et

15a (n = 1), R = H, E^2 = E^1 = CO_2Et
15b (n = 2), R = H, E^2 = E^1 = CO_2Et
16a (n = 1), R = OMe, E^2 = COMe, E^1 = CO_2Et
16b (n = 2), R = OMe, E^2 = COMe, E^1 = CO_2Et
17a (n = 1), R = OMe, E^2 = H, E^1 = CO_2Et
17b (n = 2), R = OMe, E^2 = H, E^1 = CO_2Et

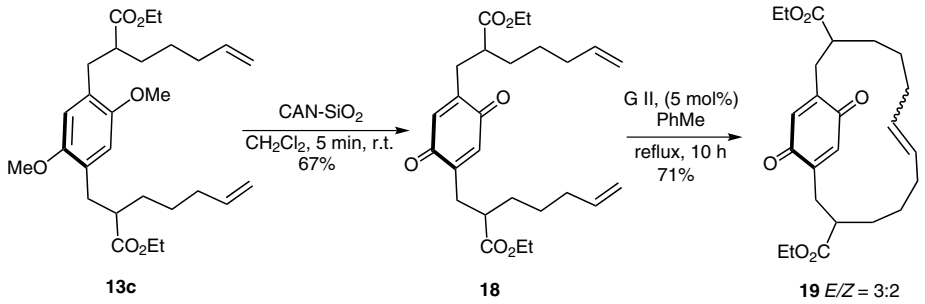
Scheme 5 Attempted synthesis of RCM products



10c (n = 3), R = OMe, E^2 = E^1 = CO_2Et
10d (n = 4), R = OMe, E^2 = E^1 = CO_2Et
11c (n = 3), R = H, E^2 = E^1 = CO_2Et
11d (n = 4), R = H, E^2 = E^1 = CO_2Et
12c (n = 3), R = OMe, E^2 = COMe, E^1 = CO_2Et
12d (n = 4), R = OMe, E^2 = COMe, E^1 = CO_2Et
13c (n = 3), R = OMe, E^2 = H, E^1 = CO_2Et
13d (n = 4), R = OMe, E^2 = H, E^1 = CO_2Et

14c (n = 3), R = OMe, E^2 = E^1 = CO_2Et, 77%
14d (n = 4), R = OMe, E^2 = E^1 = CO_2Et, 78%
15c (n = 3), R = H, E^2 = E^1 = CO_2Et, 82%
15d (n = 4), R = H, E^2 = E^1 = CO_2Et, 80%
16c (n = 3), R = OMe, E^2 = COMe, E^1 = CO_2Et, 83%
16d (n = 4), R = OMe, E^2 = COMe, E^1 = CO_2Et, 81%
17c (n = 3), R = OMe, E^2 = H, E^1 = CO_2Et, 80%
17d (n = 4), R = OMe, E^2 = H, E^1 = CO_2Et, 83%

Scheme 6 Macrocyclic cyclophane derivatives by RCM



Scheme 7 Synthesis of quinone-containing cyclophane derivative **19**

7).[16] Subsequently, the olefinic precursor **18** was subjected to RCM in the presence of Grubbs 2nd generation catalyst under toluene reflux conditions to give the cyclized product **19**, containing the macrocyclic frame of longithorone C, in 71% yield. The structure of cyclophane **19** was confirmed by ^{1}H, ^{13}C NMR spectral data and further supported by HRMS data.

In conclusion, we have developed a novel synthetic route for the synthesis of various macrocyclic compounds (**14c–d**, **15c–d**, **16c–d** and **17c–d**) and also the quinone-containing derivative **19**, which is related to the longithorone C framework, via RCM reaction as a key step.[18] We have used simple starting materials such as malonic ester, hydroquinone, unsaturated bromides, and, more importantly, the approach did not require the use of protecting groups. Moreover, the methodology reported here is armed with several diversity points and is amenable to the production of a library of cyclophane derivatives.

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References and Notes

(1) A portion of this work has been presented at the 19th International Symposium on Olefin Metathesis and Related Chemistry (ISOM XIX), July 10, 2011, Rennes, France.

(2) (a) Fu, X.; Hossain, M. B.; van der Helm, D.; Schmitz, F. J. *J. Am. Chem. Soc.* **1994**, *116*, 12125. (b) Fu, X.; Hossain, M. B.; Schmitz, F. J.; van der Helm, D. *J. Org. Chem.* **1997**, *62*, 3810. (c) Fu, X.; Ferreira, M. L.; Schmitz, F. J. *J. Nat. Prod.* **1999**, *62*, 1306. (d) Davis, R. A.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **1999**, *62*, 158. (e) Davis, R. A.; Carroll, A. R.; Watters, D.; Quinn, R. J. *Nat. Prod. Res., Part B* **2006**, *20*, 1277.

(3) Kato, T.; Nagae, K.; Hoshikawa, M. *Tetrahedron Lett.* **1999**, *40*, 1941.

(4) (a) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (b) Morales, C. A.; Layton, M. E.; Shair, M. D. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12036.

(5) Zakarian, J. E.; El-Azizi, Y.; Collins, S. K. *Org. Lett.* **2008**, *10*, 2927.

(6) (a) Fürstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. (b) Grubbs, R. H. *Handbook of Metathesis*; Vol. 1-3; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2003**. (c) Castarlenas, R.; Fischmeister, C.; Bruneau, C.; Dixneuf, P. H. *J. Mol. Catal. A: Chem.* **2004**, *213*, 31. (d) Mori, M. *J. Mol. Catal. A: Chem.* **2004**, *213*, 73. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. (f) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4490. (g) Astruc, D. *New J. Chem.* **2005**, *29*, 42. (h) Schrock, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 3748. (i) Chauvin, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 3740. (j) Collins, S. K. *J. Organomet. Chem.* **2006**, *691*, 5122. (k) Grubbs, R. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 3760. (l) Grubbs, R. H.; Schrock, R. R.; Fürstner, A. *Adv. Synth. Catal.*; Vol. 349; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2007**, 1–265. (m) Kotha, S.; Lahiri, K. *Synlett* **2007**, 2767. (n) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (o) Clavier, H.; Grela, K.; Kirschning, A.; Mauduit, M.; Nolan, S. P. *Angew. Chem. Int. Ed.* **2007**, *46*, 6786. (p) Kotha, S.; Shah, V.; Mandal, K. *Adv. Synth. Catal.* **2007**, *349*, 1159. (q) Kotha, S.; Meshram, M.; Tiwari, A. *Chem. Soc. Rev.* **2009**, *38*, 2065. (r) Cossy, J.; Arseniyadis, S.; Meyer, C. *Metathesis in Natural Product Synthesis; Strategies, Substrates and Catalysts*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2010**. (s) Grela, K. *Beilstein J. Org. Chem.* **2010**, *6*, 1089. (t) Kang, S. Y.; Kim, J. M.; Lee, J. S.; Lee, J. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3759.

(7) (a) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792. (b) Grubbs, R. H.; Lee, C. W. *J. Org. Chem.* **2001**, *66*, 7155. (c) Chuchuryukin, A. V.; Dijkstra, H. P.; Suijkerbuijk, B. M. J. M.; Gebbink, R. J. M. K.; van Klink, G. P. M.; Mills, A. M.; Spek, A. L.; van Koten, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 228. (d) Gradillas, A.; Pérez-Castells, J. *Angew. Chem. Int. Ed.* **2006**, *45*, 6086. (e) Albrecht, M.; Yeni; Fröhlich, R. *Synlett* **2007**, 2295. (f) El-Azizi, Y.; Zakarian, J. E.; Bouillerand, L.; Schmitzer, A. R.; Collins, S. K. *Adv. Synth. Catal.* **2008**, *350*, 2219. (g) Diederich, F.; Stang, P. J.; Tykwinski, R. R. *Modern Supramolecular Chemistry: Strategies for Macrocycle Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2008**, 29–67. (h) Abell, A. D.; Alexander, N. A.; Aitken, S. G.; Chen, H.; Coxon, J. M.; Jones, M. A.; McNabb, S. B.; Muscroft-Taylor, A. *J. Org. Chem.* **2009**, *74*, 4354. (i) Muthusamy, S.; Azhagan, D. *Tetrahedron* **2010**, *66*, 8196. (j) Jarikote, D. V.; Murphy, P. V. *Eur. J. Org. Chem.* **2010**, 4959. (k) Bolduc, P.; Jacques, A.; Collins, S. K. *J. Am. Chem. Soc.* **2010**, *132*, 12790.

(8) (a) Diederich, F. *Cyclophanes*; Royal Society of Chemistry: Cambridge, **1991**. (b) Vögtle, F. *Cyclophane Chemistry: Synthesis, Structures, and Reactions*; John Wiley and Sons: Chichester, **1993**. (c) Weber, E. *Cyclophanes*, Vol. 172; Springer Verlag: Berlin, **1994**. (d) Takemura, H. *Cyclophane Chemistry for the 21st Century*; Research Signpost: Trivandrum, **2002**. (e) Gleiter, R.; Hopf, H. *Modern Cyclophane Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, **2004**. (f) Davis, F.; Higson, S.

Macrocycles: Construction, Chemistry and Nanotechnology Applications; John Wiley and Sons Ltd: Chichester, **2011**.

(9) (a) Jimenez, L.; Diederich, F. *Tetrahedron Lett.* **1989**, *30*, 2759. (b) Diederich, F.; Lutter, H. D. *J. Am. Chem. Soc.* **1989**, *111*, 8438. (c) Seel, C.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 528. (d) Newman, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215. (e) Fürstner, A. *Eur. J. Org. Chem.* **2004**, 943. (f) Rajakumar, P.; Rasheed, A. M. A.; Rabia, A. I.; Chamundeeswari, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6019. (g) Rajakumar, P.; Rasheed, A. M. A.; Balu, P. M.; Murugesan, K. *Bioorg. Med. Chem.* **2006**, *14*, 7458. (h) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discovery* **2008**, *7*, 608. (i) Huang, M.; Song, L.; Liu, B. *Org. Lett.* **2010**, *12*, 2504. (j) Yoshinari, T.; Ohmori, K.; Schrems, M. G.; Pfaltz, A.; Suzuki, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 881. (k) Kotha, S.; Krishna, N. G.; Halder, S.; Misra, S. *Org. Biomol. Chem.* **2011**, *9*, 5597.

(10) (a) Bodwell, G. J.; Nandaluru, P. R. *Isr. J. Chem.* **2012**, *52*, 105. (b) Mohan, A.; Sankararaman, S. *Isr. J. Chem.* **2012**, *52*, 92.

(11) (a) Kotha, S.; Halder, S.; Damodharan, L.; Pattabhi, V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1113. (b) Kotha, S.; Behera, M.; Kumar, R. V. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 105. (c) Kotha, S.; Mandal, K.; Arora, K. K.; Pedireddi, V. R. *Adv. Synth. Catal.* **2005**, *347*, 1215. (d) Kotha, S.; Behera, M.; Shah, V. *Synlett* **2005**, 1877. (e) Kotha, S.; Halder, S. *ARKIVOC* **2005**, *(iii)*, 56. (f) Kotha, S.; Mandal, K. *Eur. J. Org. Chem.* **2006**, 5387. (g) Kotha, S.; Lahiri, K. *Eur. J. Org. Chem.* **2007**, 1221. (h) Kotha, S.; Mandal, K. *Chem. Asian J.* **2009**, *4*, 354. (i) Kotha, S.; Chavan, A. S.; Mobin, S. *J. Org. Chem.* **2012**, *77*, 482.

(12) Weng, X.; Ren, L.; Weng, L.; Huang, J.; Zhu, S.; Zhou, X.; Weng, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 8020.

(13) (a) Yamazaki, T.; Kasatkin, A.; Kawanaka, Y.; Sato, F. *J. Org. Chem.* **1996**, *61*, 2266. (b) Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998. (c) Oppolzer, W.; Pitteloud, R.; Strauss, H. F. *J. Am. Chem. Soc.* **1982**, *104*, 6476. (d) Williams, R. M.; Lee, B. H.; Miller, M. M.; Anderson, O. P. *J. Am. Chem. Soc.* **1989**, *111*, 1073. (e) Saint-Dizier, A. C.; Kilburn, J. D. *Tetrahedron Lett.* **2002**, *43*, 6201.

(14) (a) Miyazawa, N.; Ogasawara, K. *Synlett* **2002**, 1065. (b) Grenning, A. J.; Tunge, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 14785; and the references cited therein.

(15) Mori, K.; Ohmori, K.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 5638.

(16) Fisher, A.; Henderson, G. N. *Synthesis* **1985**, 641.

(17) We have determined the *E*/*Z* ratio of RCM products **16**–**19** (Figure 2), based on ^{1}H NMR spectral data. In most of the cases, we observed *E*-configured compounds as the major product; this assumption was based on our earlier experience on cyclophane derivatives. See reference 11i.

(18) **Alkene Derivatives of Malonate Ester; General Procedure:** To a suspension of NaH (3 equiv) in THF was added **3** (1 equiv) dropwise at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. Bromide **5c** (1.1 equiv) was added and the reaction mixture was stirred at r.t. for 12 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with H_2O and extracted with diethyl ether. 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; EtOAc–petroleum ether, 4%) to afford **6c** (67%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.22 (m, 6 H), 1.35–1.40 (m, 2 H), 1.81–1.90 (m, 2 H), 2.01–2.05 (m, 2 H), 3.26 (t, *J* = 7.2 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 4 H), 4.88–4.97 (m, 2 H), 5.66–5.70 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.90, 26.38, 28.02, 33.14, 51.69, 61.05, 114.83, 137.77, 169.23. IR (neat): 2929, 2859, 1741, 1640, 1464, 1368, 1183 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + Na] calcd for $C_{12}H_{20}O_4Na$: 251.1259; found: 251.1265.

Alkylation of Ethyl Acetoacetate; General Procedure: In a 100 mL round-bottomed flask equipped with a nitrogen gas inlet, ethyl acetoacetate **4** (1 equiv) was added dropwise at r.t. to K_2CO_3 (4 equiv) in acetonitrile and the mixture was stirred for 1 h. Bromide **5c** (1.1 equiv) was added and the reaction mixture was stirred at r.t. for 12 h under a nitrogen atmosphere. At the conclusion of the reaction (TLC monitoring), the crude mixture was filtered through a Celite pad and extracted with diethyl ether. The organic layer was washed with brine and dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 4%) to afford alkylated ethyl acetoacetate derivative **8c** (68%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.2 Hz, 3 H), 1.32–1.44 (m, 2 H), 1.80–1.92 (m, 2 H), 2.00–2.10 (m, 2 H), 2.22 (s, 3 H), 3.41 (t, *J* = 7.4 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.94–5.04 (m, 2 H), 5.72–5.82 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.16, 26.64, 27.62, 28.82, 33.41, 59.77, 61.37, 115.13, 137.96, 169.88, 203.24. IR (neat): 2991, 2934, 1742, 1716, 1641, 1448, 1360, 1216 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{11}H_{19}O_3$: 199.1334; found: 199.1334.

General Procedure for 10c: To a suspension of NaH (3 equiv) in THF was added alkylated malonate ester **6c** (1 equiv) dropwise at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. Dibromide **1** (0.5 equiv) was added and the reaction mixture was stirred at r.t. for 12 h under nitrogen. 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; EtOAc–petroleum ether, 8%) to afford bis-alkene malonate derivative **10c** (65%) as a white solid material. Mp 60–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 12 H), 1.34–1.41 (m, 4 H), 1.70–1.74 (m, 4 H), 1.99 (q, *J* = 7.1 Hz, 4 H), 3.24 (s, 4 H), 3.64 (s, 6 H), 4.08–4.23 (m, 8 H), 4.89–5.00 (m, 4 H), 5.70–5.81 (m, 2 H), 6.52 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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. IR (neat): 3054, 2989, 1729, 1641, 1422, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{34}H_{51}O_{10}$: 619.3482; found: 619.3499.

General Procedure for 11c: To a suspension of NaH (3 equiv) in THF was added alkylated malonate ester **6c** (1 equiv) dropwise at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. *p*-Xylylene dibromide **2** (0.5 equiv) was added and the reaction mixture was stirred at r.t. for 12 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction was quenched with H_2O and extracted with diethyl ether. 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; EtOAc–petroleum ether, 8%) to afford bis-alkene malonate ester derivative **11c** (62%) as a white solid material. Mp 60–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (t, *J* = 7.2 Hz, 12 H), 1.34–1.40 (m, 4 H), 1.73–1.77 (m, 4 H), 2.04 (q, *J* = 7.2 Hz, 4 H), 3.19 (s, 4 H), 4.10–4.22 (m, 8 H), 4.97–5.03 (m, 4 H), 5.78–5.80 (m, 2 H), 6.95 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.22, 23.72, 31.54, 33.90, 37.87, 58.90, 61.33, 115.16, 129.92, 134.97, 138.21, 171.45. IR (neat): 3054, 2989, 1729, 1641, 1422, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{32}H_{47}O_8$:

559.3271; found: 559.3286.

General Procedure for 12c: In a 100 mL round-bottomed flask equipped with a nitrogen gas inlet, K_2CO_3 (4 equiv) in acetonitrile was added to alkylated ethyl acetoacetate **8c** (1 equiv) dropwise at r.t. and stirred for 1 h. Dibromo compound **1** (0.5 equiv) was added and the reaction mixture was stirred at r.t. for 12 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the crude mixture was filtered through a Celite pad and extracted with diethyl ether. 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; EtOAc–petroleum ether, 6%) to afford the alkylated ethyl acetoacetate derivative **12c** (72%) as a solid. Mp 60–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–1.25 (m, 6 H), 1.29–1.37 (m, 4 H), 1.64–1.76 (m, 4 H), 2.03 (q, *J* = 7.0 Hz, 4 H), 2.11 (s, 6 H), 3.06–3.31 (m, 4 H), 3.62 (s, 6 H), 4.09–4.26 (m, 4 H), 4.91–5.01 (m, 4 H), 5.69–5.80 (m, 2 H), 6.50 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.20, 23.76, 27.15, 31.30, 31.66, 34.22, 55.53, 61.32, 64.32, 114.29, 115.05, 124.30, 138.28, 151.66, 172.61, 205.10. IR (neat): 2979, 2911, 1739, 1717, 1531, 1212 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + Na] calcd for $C_{32}H_{46}O_8Na$: 581.3090; found: 581.3105.

General procedure for 13c: To a suspension of NaH (3 equiv) in THF was added alkylated ethyl acetoacetate **8c** (1 equiv) dropwise at 0 °C. The reaction mixture was warmed to r.t. and stirred for 1 h. Dibromide **1** (0.5equiv) was added to the reaction mixture, which was stirred at r.t. for 12 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction was quenched with H_2O and extracted with diethyl ether. 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; EtOAc–petroleum ether, 10%) to afford bis-alkylated derivative **13c** (66%) as a white solid. Mp 60–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.15 (m, 6 H), 1.33–1.45 (m, 4 H), 1.45–1.54 (m, 2 H), 1.59–1.70 (m, 2 H), 2.00–2.07 (m, 4 H), 2.65–2.75 (m, 2 H), 2.75–2.85 (m, 4 H), 3.74 (s, 6 H), 4.00–4.08 (m, 4 H), 4.90–5.00 (m, 4 H), 5.71–5.82 (m, 2 H), 6.59 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 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. IR (neat): 2931, 2860, 1726, 1506, 1211 cm^{-1}. HRMS (Q-Tof): *m*/*z* calcd: for $C_{28}H_{43}O_6$ [M + H]: 475.3060; found 475.3060.

General Procedure for 14c and 15c: To a degassed solution of bis-alkylated derivative **10c** or **11c** in anhydrous toluene (5 mL) was added Grubbs 2nd generation catalyst (5 mol%) at r.t., and 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, 5%) to afford cyclophane derivatives **14c** and **15c**.

Compound 14c: Yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.14 (m, 4 H), 1.23–1.30 (m, 12 H), 1.44 (td, *J* = 13.4, 4.4 Hz, 2 H), 1.59 (td, *J* = 13.4, 4.4 Hz, 2 H), 1.76–1.77 (m, 2 H), 1.92–1.95 (m, 2 H), 3.13 (s, 1 H), 3.17 (s, 1 H), 3.62 (s, 1 H), 3.66 (s, 1 H), 3.67 (s, 6 H), 4.14–4.30 (m, 8 H), 5.06 (t, *J* = 3.9 Hz, 2 H), 6.63 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.26, 23.50, 31.27, 32.43, 33.27, 55.78, 57.63, 61.13, 114.36, 124.43, 130.34, 151.71, 172.40. IR (neat): 2931, 2860, 1730, 1510, 1212 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{32}H_{47}O_{10}$: 591.3169; found: 591.3160.

Compound 15c: Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (m, 4 H), 1.28 (m, 12 H), 1.46–1.48 (m, 4 H), 1.83–1.88 (m, 4 H), 3.30 (s, 4 H), 4.25 (m, 8 H), 5.07–5.09 (m, 2 H), 7.02 (s, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.27, 23.49, 31.53, 32.49, 39.06, 58.15, 61.50, 129.75, 130.53, 135.36, 172.06. IR (neat): 2982, 2940, 1732, 1446, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{30}H_{43}O_8$: 531.2958; found: 531.2957.

General Procedure for 18: In a 100 mL round-bottomed flask was charged flash chromatographic-grade silica gel (6 g). A solution of CAN (5 mol%) in water (2.5 mL) was added dropwise until a free-flowing yellow solid was obtained. CH_2Cl_2 (25 mL) was added and the bis-alkylated derivative **13c** dissolved in CH_2Cl_2 (2 mL) was added dropwise. At the conclusion of the reaction (TLC monitoring), the crude mixture was filtered through a Celite pad (washed with CH_2Cl_2) and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; EtOAc–petroleum ether, 5%) to afford bis-alkylated quinone derivative **18** (67%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.22 (m, 6 H), 1.37–1.45 (m, 4 H), 1.49–1.56 (m, 2 H), 1.63–1.70 (m, 2 H), 2.06 (q, *J* = 7.0 Hz, 4 H), 2.59–2.65 (m, 6 H), 4.07–4.12 (m, 4 H), 4.94–5.02 (m, 4 H), 5.71–5.81 (m, 2 H), 6.54 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 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. IR (neat): 2931, 2858, 1728, 1464, 1266 cm^{-1}. HRMS (Q-Tof): *m*/*z* [M + H] calcd for $C_{26}H_{37}O_6$: 445.2590; found: 445.2601.

