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Synthesis of Functionalized Cage Propellanes and D_3-Trishomocubanes via the Ring-Closing Metathesis and Acid-Promoted Rearrangement

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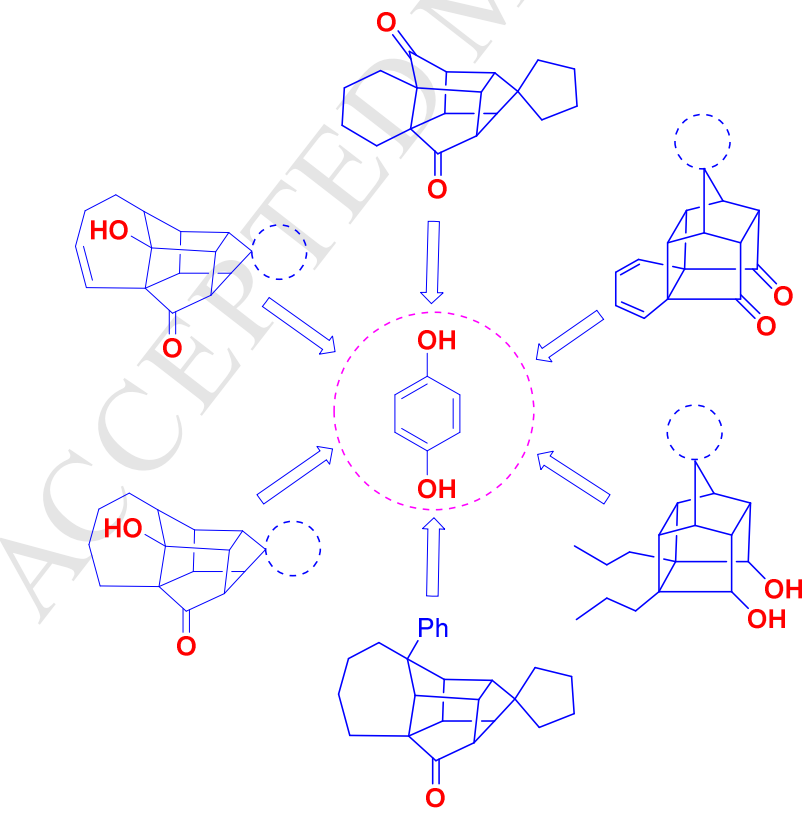
Abstract

Several functionalized cage propellanes and D_3-trishomocubanes containing spiro linkage have been reported starting with commercially available materials such as 1,4-hydroquinone and dicyclopentadiene. In this regard, Claisen rearrangement, Diels–Alder reaction (DA), ring-closing metathesis (RCM) and acid-promoted rearrangement have been used as key steps. The strategies described here, opens up new opportunities to assemble intricate cage systems that are difficult to construct by conventional methods. Carbocation intermediates generated during the rearrangement process play a prominent role in designing unusual cage systems. One of the rearranged cage compound's structure was unambiguously established by single crystal X-ray diffraction studies.



Key words

Claisen rearrangement, Diels–Alder reaction, [2+2] photocycloaddition, ring-closing metathesis, acid-catalyzed rearrangement, cage [4.4.2]propellane, and D_3-trishomocubanes.

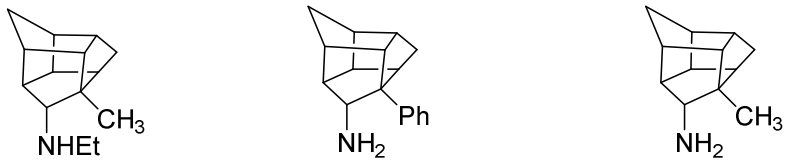
1. Introduction

D_3-Trishomocubane **1** is a stable and chiral molecule with an empirical formula of $C_{11}H_{14}$. It is made up of fused five membered rings with high degree of symmetry (Figure 1). Derivatives of D_3-trishomocubanes are useful frameworks for pharmaceutical applications, medicinal chemistry and organocatalysis.[1-6] Due to their distinctive properties such as high lipophilicity and conformational rigidity, they are useful substrates in drug discovery.[2-6]

1

Figure 1. Structure of D_3-trishomocubane **1**

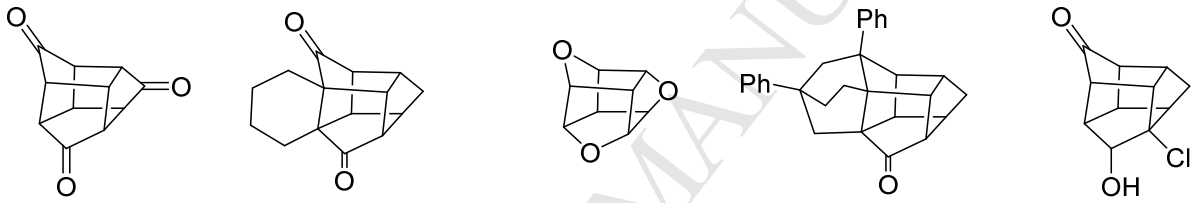
D_3-Trishomocubane derivatives are important targets for synthetic as well as medicinal chemists.[2] Because of their inherent gyrochirality (e.g. D_3-streoisomerism) these compounds provides an opportunity for further investigations in chemical and biological sciences.[3] D_3-trishomocubyl amines (Figure 2) shows interesting activities against tuberculosis, neurodegenerative, and anti-viral diseases.[4] For example, amino substituted trishomocubane derivatives such as 4-amino-(D_3)-trishomocubanes **2-3** exhibits significant anti-viral properties against Herpes simplex I and II, Influenza A_2/Taiwan and Rhino 1A virus when compared with the standard drugs like acyclovir and amantadine.[5] Trishomocubylamine **4** [6] displays potential anti-cataleptic and anti-cholinergic activity (Figure 2).



2 **3** **4**

Figure 2. Examples of biologically active D_3-trishomocubyl amines

Cage propellane containing succinyl bond is prone to skeletal rearrangement to produce unusual cage structures.[7] Moreover, strained propellanes undergo ring-rearrangement process providing a variety of intricate cage systems that are difficult to design by direct synthetic approaches.[8] The stability of the carbocation intermediate generated during the ring-rearrangement play a crucial role in assembling trishomocubane skeleton.[9]



5 **6** **7** **8** **9**

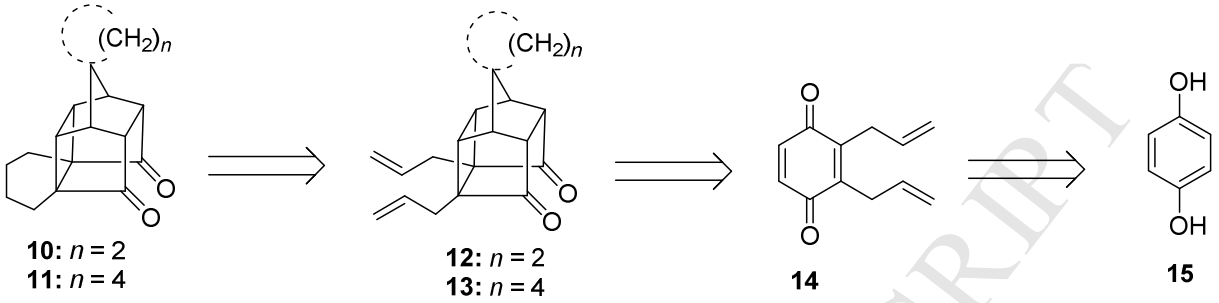
Figure 3. Selected examples of D_3-trishomocubanes assembled by rearrangement approach

Selected examples of D_3-trishomocubane[8,9] derivatives **5**-**9** prepared by rearrangement approaches are shown in Figure 3.[10] Recently, we reported a new synthetic approach to functionalized D_3-trishomocubane derivatives via acid-catalyzed rearrangement starting with cage [4.3.2]propellane and cage [4.4.2]propellane system having methyl substituent in cyclohexene ring. [10d, 11]

2. Results and Discussions

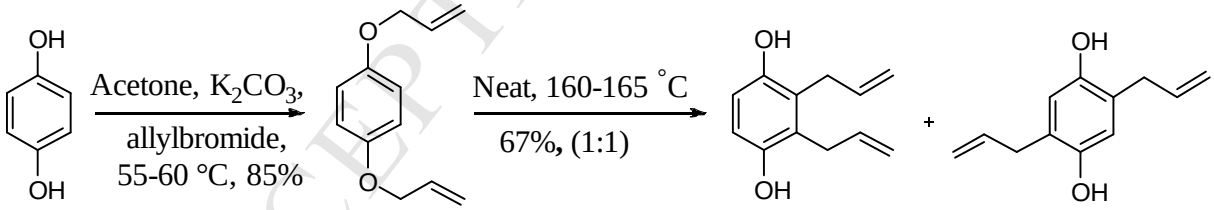
Our retrosynthetic approach to cage [4.4.2]propellanes **10** and **11** containing spiro linkage is depicted in Scheme 1. We anticipated that the required diones **10** and **11** could be constructed from a di-allyl cage diones **12** and **13** by adopting a ring-closing metathesis (RCM) and reduction. The heptacyclic diones **12** and **13** may be obtained from 2,3-diallyl-1,4-benzoquinone **14** via the Diels–Alder (DA) reaction followed by [2+2] photocycloaddition. The quinone derivative **14** can be synthesized from a readily available 1,4-hydroquinone **15** by known

methods[12, 13] involving di *O*-allylation, double Claisen rearrangement followed by oxidation (Scheme 1).



Scheme 1. Retrosynthetic approach to cage propellanes **10** and **11**

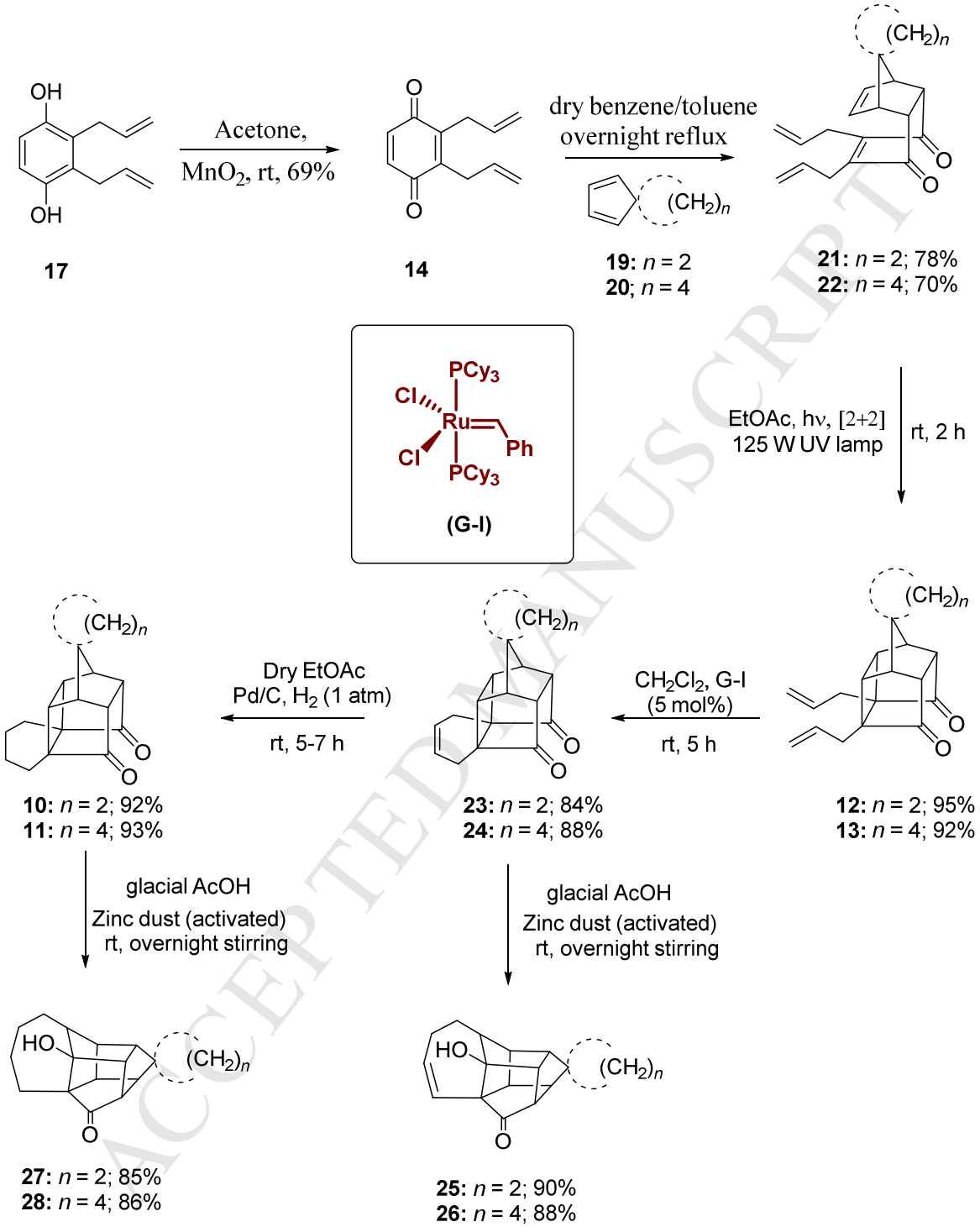
Several cage systems are used as high energy materials and in this context, we explored rearrangement approach to trishomocubane derivatives containing spiro linkage starting with cage [4.4.2]propellanes **10** and **11**. To this end, we recognized cage diones such as **12** and **13** as key precursors. These cage diones **12-13** were prepared[12] via a quinone derivative **14**[13a] by adopting a two-step synthetic sequence involving DA reaction starting with suitable spiro-dienes **19**[13b]and **20**[13c] and [2+2] photocycloaddition. 2,3-Diallyl-1,4-benzoquinone **14,**[13a] readily prepared from commercially available 1,4-hydroquinone **15** (Scheme 2).[12, 13a]



Scheme 2. Synthesis of diallyl hydroquinones **17** and **18**.

Cage propellanes containing cyclohexene ring may be assembled with dione units such as **23** and **24** via ring-closing metathesis (RCM) starting with a suitable synthons using [2+2] photoadducts **12** and **13** which are derived from DA adducts **21** and **22**. In this context, ring-closing metathesis (RCM)[14] of di-allyl cage diones **12** and **13** was accomplished with the Grubbs first generation (G-I) catalyst in dry DCM to produce the symmetrical diones **23** and **24** in good yields (84 and

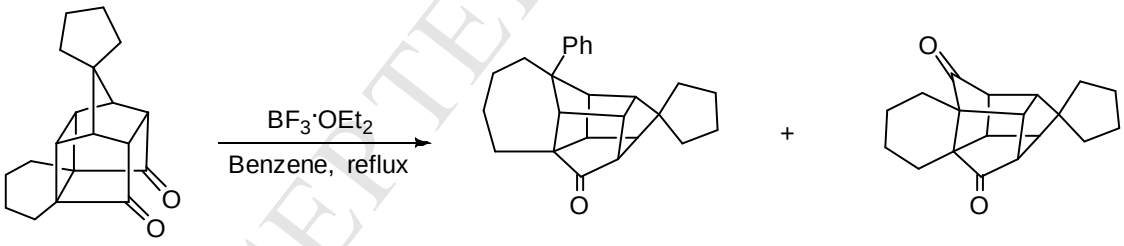
88%). Subsequent hydrogenation of the RCM products **23** and **24** in the presence of H_2 with 10% Pd/C in dry ethyl acetate furnished the saturated diones **10** (92%) and **11** (93%) (Scheme 3).



Scheme 3. Reduction of cage propellane diones **10, 11, 23,** and **24** with Zn/AcOH

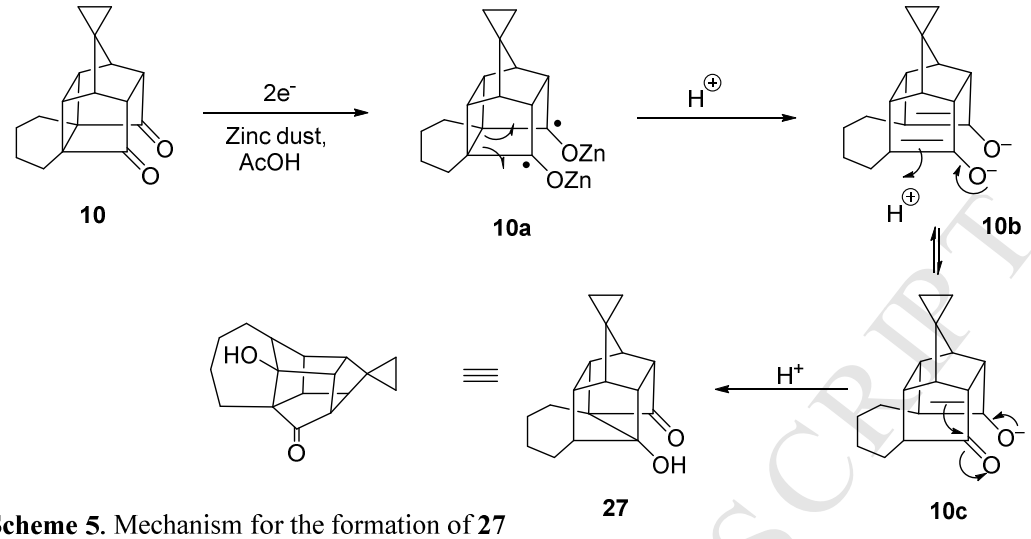
To assemble cage propellanes and D_3-trishomocubanes containing spiro system, we attempted acid-catalyzed rearrangement of cage [4.4.2]propellanes **10**, **11**, **23**, and **24** with the aid of $BF_3{\cdot}OEt_2$ and Zn/AcOH. Having the cage diones **10**, **11**, **23** and **24** in hand, the reductive C-C bond cleavage of cyclobutane ring present in the cage diones (**10**, **11**, **23**, and **24**) was achieved in the presence of activated zinc in glacial acetic acid at room temperature. Thus, the rearranged cage hydroxyketones such as **25**, **26**, **27** and **28** were produced in good yields (Scheme 3). The structures of these hydroxyketones **25, 26, 27,** and **28** have been supported by ^{1}H NMR, ^{13}C NMR, APT, DEPT spectroscopic data and HRMS details. Finally, the structure of ring rearranged cage hydroxyketone **28** was confirmed by it's single-crystal X-ray diffraction studies (Figure 4).[15]

Based on Lewis acid-catalyzed rearrangements data of cage compounds, [10d, 11] we identified that spiro dione **11** as a suitable substrate for carbocation rearrangement. In this regard, compound **11** (n = 4) was treated with $BF_3{\cdot}OEt_2$ in dry benzene under reflux conditions to afford the solvent (benzene) incorporated product **29** (23%) along with the rearranged cage dione **30** (41%). The structures of these cage ketones **29** and **30** have been confirmed on the basis of ^{1}H NMR, ^{13}C NMR, APT spectral parameters, and further supported by HRMS data (Scheme 4).



11 **29** (23%) **30** (42%)

Scheme 4. $BF_3{\cdot}OEt_2$-Promoted rearrangement of cage dione **11**



Scheme 5. Mechanism for the formation of **27**

We proposed a possible reaction mechanism for the formation of hydroxyketone **27** (Scheme 5).[7,10d] The reaction was initiated by activated Zn in AcOH to form a diradical species **10a.** Later, cleavage of the strained cyclobutane ring generates the dianion intermediate **10b**. Then, the dianion **10b** is involved in enolization (keto-enol tautomerism) to produce the intermediate **10c,** which on transannular cyclization gave the hydroxyketone (internal aldol product) **27**.

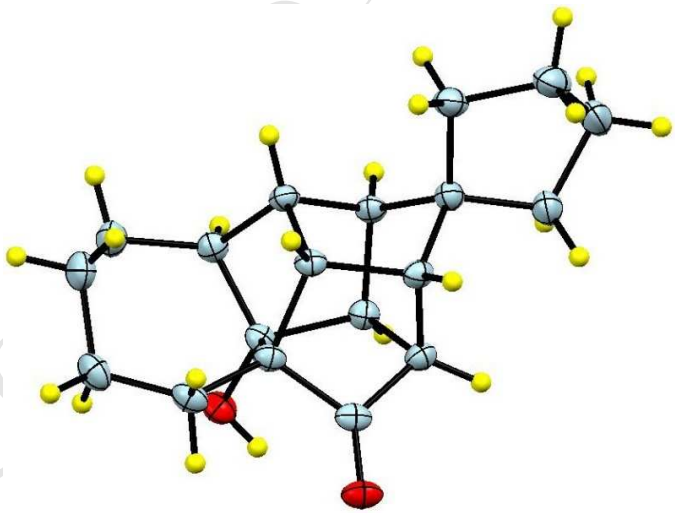
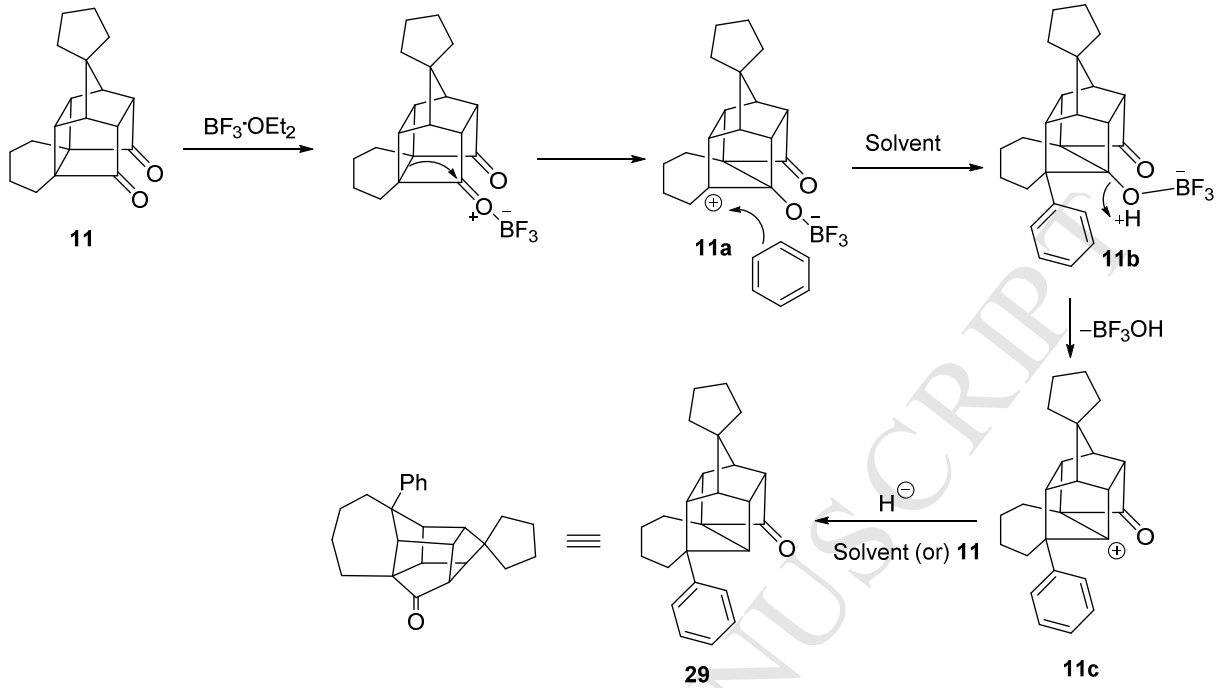
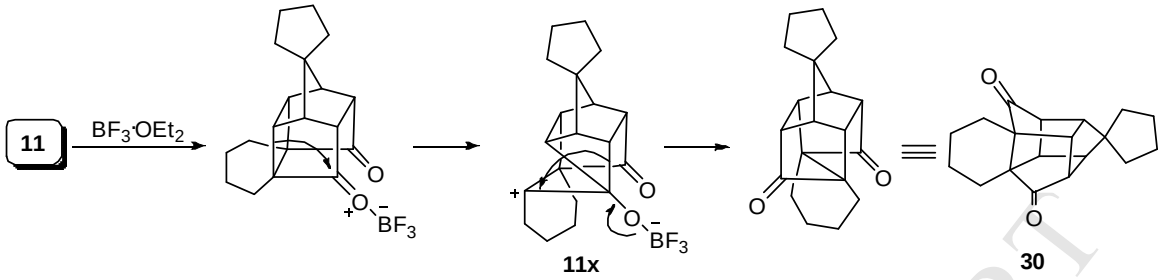


Figure 4. Single crystal X-Ray structure of **28** with thermal ellipsoids drawn at the 50% probability level.



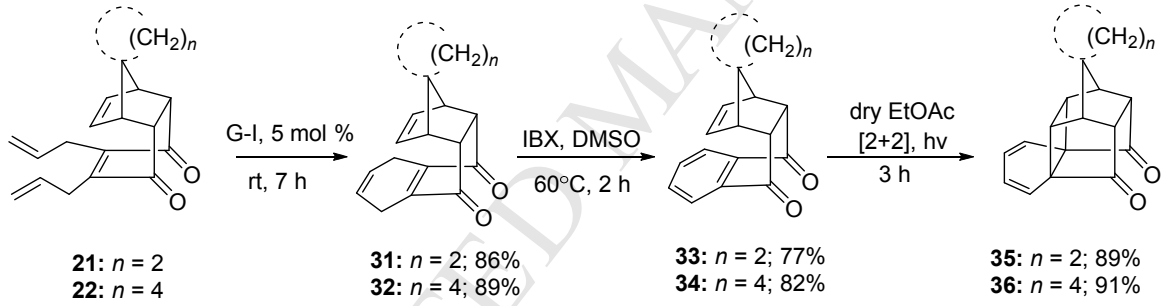
Scheme 6. Mechanism for the rearrangement of cage dione **11** to cage ketone **29**

The conversion of cage dione **11** to the rearranged ketone **29** is based on Lewis acid catalyzed rearrangements with $BF_3.OEt_2$,[10,11] and the proposed mechanism is illustrated in Scheme 6. Initially, coordination of the Lewis acid to the ketone of cage dione **11** would generate carbocation intermediate **11a** via the migration of cyclobutane bond adjacent to the carbonyl carbon. The carbocation **11a** captured with solvent (benzene) and subsequent aromatization followed by hydrogen transfer gives the intermediate **11b**. Afterward, elimination of BF_3OH from **11b** will produce the carbocation **11c**, and further hydride transfers from **11** (or from benzene) delivers the rearranged molecule **29** (Scheme 6). The hydride transfers from solvent or cage hydrocarbon **11** might be due to the disproportionation process under the reaction conditions. At this stage, there is no strong supporting evidence for hydride transfer in the mechanism (Scheme 6).



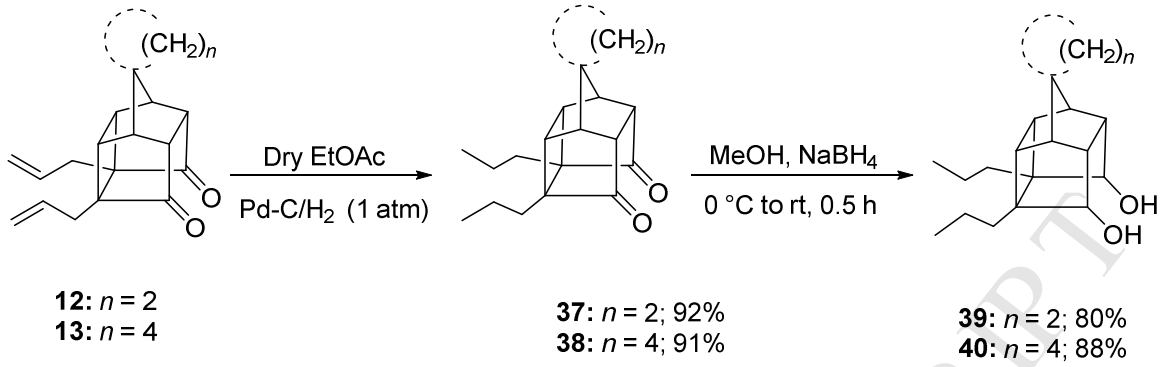
Scheme 7. Plausible mechanism for $BF_3{\cdot}OEt_2$-promoted rearrangement of cage dione **11** to **30**

Along similar lines, compound **11** can generate the rearranged product **29** which involves capture of solvent (benzene) during the rearrangement along with the other rearranged trishomocubane derivative **30**. A plausible mechanism for the transformation of the cage dione **11** to the rearranged dione **30** is depicted in Scheme 7. To start with compound **11,** rearranged by migration of cyclobutane bond which generates the carbocation intermediate **11x**. Later on, a second bond migration from **11x** can give a rearranged dione **30** (Scheme 7).



Scheme 8. Synthesis of hexacyclic cage dione **35** and **36**

Having prepared the DA adducts **21** and **22**, our attention has been shifted towards heptacyclic diones such as **35** and **36** via RCM protocol, IBX mediated dehydrogenation followed [6+2] photocycloaddition. In this regard, [4+2] cycloadducts **21** and **22** were subjected to ring-closing metathesis (RCM) with Grubbs' first generation catalyst (G-I, 5 mol%) to deliver the cyclized products in high yields (up to 86-89%). Subsequently, IBX mediated dehydrogenation of RCM products **31** and **32** in the presence of IBX in DMSO at 60 °C gave the aromatized derivatives **33**[16] and **34**[16] in 77 and 82% yield respectively. Later on, photocycloaddition of aromatized compounds **33** and **34** by irradiation of 125 W UV lamp in dry ethyl acetate for 3 h gave the spiro cage diones **35**[16] and **36**[16] in excellent yields (Scheme 8).



Scheme 9. Synthesis of dialkyl cage diol **39** and **40** via reduction.

Next, we focused our attention on reduction sequence. In this regard, allyl cage derivatives **12** and **13** were subjected to hydrogenation in the presence of 10% Pd/C under hydrogen atmosphere in dry ethyl acetate to produce the saturated cage diones **37** and **38** in 91 to 92% yields respectively (Scheme 9). The structures of these diones **37** and **38** were established by ^{1}H NMR, ^{13}C NMR, APT spectral parameters and further supported by HRMS data. Afterward, reduction of cage diones **37** and **38** in the presence of $NaBH_4$ in dry methanol at room temperature for 0.5 h gave the alkylated cage diols **39** and **40** in excellent yields (Scheme 9).

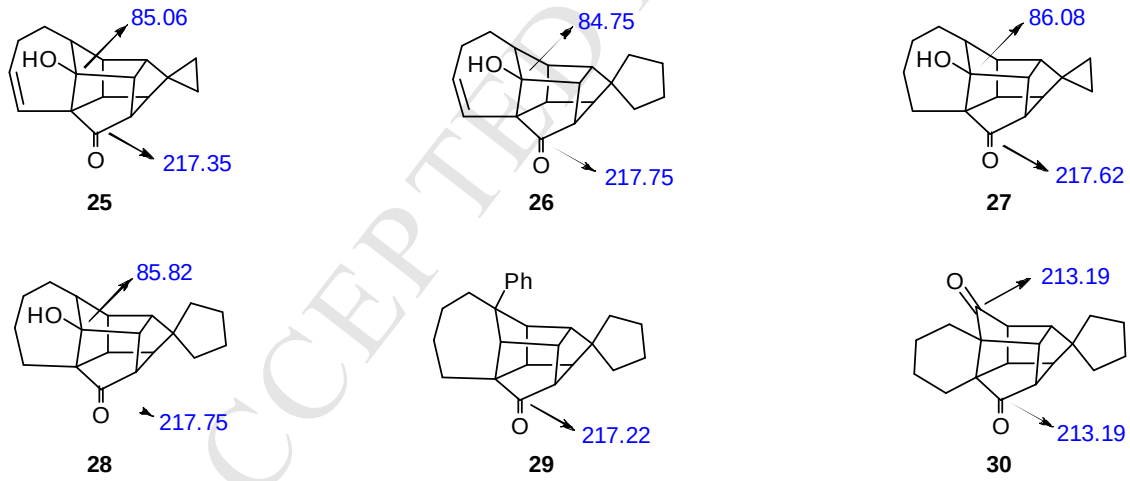


Figure 5. Comparison of 13C NMR value (s) of various D_3-trishomocubanes with respect to carbonyl and OH attached carbons.

We have compared chemical shifts of carbonyl groups and carbons attached to hydroxyl groups of various D_3-trishomocubane derivatives. Surprisingly, the δ value (ppm) of carbonyl carbon in

symmetrical D_3-trishomocubane **30** is of low value (213.19 ppm) as compared with carbonyl group chemical shift value of other D_3-trishomocubane derivatives (Figure 5).

3. Conclusions

In summary, we have successfully synthesized various functionalized cage [4.4.2]propellanediones and D_3-trishomocubane derivatives containing the spiro system from a readily available 1,4-hydroquinone. In this context, RCM protocol and rearrangement reactions are used as key steps. Solvent incorporation as well as ring rearrangement was observed in cage propellane framework during acid promoted rearrangement. We have prepared various functionalized cage hydroxy derivatives as well as alkylated cage diones in this sequence by reduction strategy. Also, we have demonstrated synthetic route to cage [4.4.2]propellanes **35** and **36** using DA precursors such as **21** and **22** via RCM, IBX mediated aromatization followed by [6+2] cycloaddition sequence.

4. Experimental section

4.1. General experimental details

Reagents, chemicals and solvents were purchased from the commercial suppliers and used as without purification unless otherwise stated. Analytical TLC was performed on (10 × 5) glass plates coated with Acme's silica gel (GF-254) containing 13% calcium sulfate as a binder. Reactions were monitored by TLC using suitable solvent system and visualization was done under UV light, exposure to iodine vapour and by dipping in to a solution of $KMnO_4$. Anhydrous reactions were performed in oven dried glassware under nitrogen atmosphere by using standard syringe-septum techniques. Acme's silica gel (100-200 mesh size) was used for column chromatography. Benzene and toluene were distilled from P_2O_5 or CaH_2 and ethyl acetate was dried over K_2CO_3.

IR spectra were collected on a Nicolet Impact-400 FTIR spectrometer and samples were prepared as a thin film between CsCl plates by dissolving the compound in dichloromethane and chloroform and then evaporating the solvent. ^{1}H NMR (400 and 500 MHz), ^{13}C NMR, ^{13}C-APT NMR, DEPT 135 NMR (100 and 125 MHz) spectra were recorded on Bruker spectrometer and samples were prepared in $CDCl_3$ solvent. The chemical shifts are reported in parts per million (ppm) on delta scale with TMS as an internal standard and values for the coupling constants (*J*)

are given in Hz. The standard abbreviations for ^{1}H NMR spin couplings are given as s, d, t, q, dd, dt, td, and m for singlet, doublet, triplet, quartet, doublet of doublet, doublet of triplet, triplet of doublet and multiplet respectively. High-resolution mass spectra (HRMS) were recorded in a positive ion electrospray ionization (ESI-Q-TOF). All melting points were recorded on Veego VMP-CMP melting point apparatus and are uncorrected. spiro dienes such as spiro [2.4] hepta-4,6-diene **19** and spiro[4.4]nona-1,3-diene **20** were prepared according to literature methods.[13]

General procedure for synthesis of Diels-Alder adducts 21[12] and 22[12]

To a stirred solution of 2,3-diallylcyclohexa-2,5-diene-1,4-dione **14** (3.98-3.18 mmol, 1 equiv) and freshly prepared spiro[2.4]hepta-4,6-diene **19** (0.7 mL, 7.17 mmol for **21**) in dry benzene (10 mL) and spiro[4.4]nona-1,3-diene **20** (0.7 mL, 5.72 mmol for **22**) in dry toluene (10 mL) was kept reflux for overnight (progress of reaction monitored by TLC). After completion of the reaction by TLC monitoring, the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography (4-7% EtOAc/PE) to deliver the pure **21** as a yellow liquid and **22** as a yellow semi solid.

DA adduct 21[12]: viscous yellow liquid; obtained from compound **14** (750 mg, 3.98 mmol); Yield: 877 mg (78%); IR (neat, cm^{-1}) 3076, 3012, 2925, 1662, 1422, 1354, 1327, 1269, 1216,1127, 1011, 997, 667; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (t, J = 1.9 Hz, 2H), 5.72-5.62 (m, 2H), 4.99-4.94 (m, 4H), 3.36-3.35 (m, 2H), 3.13 (td, J = 4.0, 2.0 Hz, 4H), 2.84 (t, J = 1.8 Hz, 2H), 0.57-0.53 (m, 2H), 0.46-0.42 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 198.2, 149.2, 135.3, 133.5, 116.8, 53.9, 49.3, 44.7, 31.0, 8.0, 6.9.

DA adduct 22[12]: yellow semi solid; m.p. 47-49 °C; obtained from compound **14** (600 mg, 3.18 mmol); Yield: 687 mg (70%); IR (neat, cm^{-1}): 3016, 2954, 1662, 1354, 1271, 1216, 918; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.96 (s, 2H), 5.72-5.64 (m, 2H), 4.95-5.00 (m, 4H), 3.28 (s, 2H), 3.14 (d, J = 6.1 Hz, 4H), 3.08 (s, 2H), 1.57-1.61 (m, 2H), 1.50-1.42 (m, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.8, 149.2, 136.2, 133.6, 116.8, 69.0, 56.6, 48.8, 32.0, 31.6, 31.0, 25.9, 25.4

General procedure for [2+2] photocycloaddition of DA adducts 21 and 22

The [4+2] adducts **21** and **22** (1.42-2.59 mmol) was dissolved in dry EtOAc (250 mL) and irradiated in a pyrex immersion well by using 125 W UV lamp for 1 h under nitrogen atmosphere at room temperature. After completion of the reaction by TLC analysis, the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel column

chromatography by using 7-10% EtOAc/petroleum ether as an eluent to afford the cage diones **12** and **13** as pure colourless crystalline solids.

Cage dione 12[12]**:** colourless crystalline solid; m.p. 81-83 ºC; obtained from DA adduct **21** (400 mg, 1.42 mmol); Yield: 95% (379 mg); IR (neat, cm^{-1}) 3082, 2982, 1736, 1415, 1273, 1223, 1182, 1080, 1010, 917, 875, 666; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56-5.46 (m, 2H), 5.05-4.97 (m, 4H), 3.05 (t, *J* = 1.3 Hz, 2H), 2.89 (d, *J* = 1.7 Hz, 2H), 2.47 (dd, *J* = 14.0, 5.7 Hz, 2H), 2.20 (dd, *J* = 14.0, 8.3 Hz, 2H), 2.10-2.07 (m, 2H), 0.63 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 213.0, 132.6, 118.6, 56.0, 54.7, 49.2, 41.6, 38.0, 30.2, 5.4, 4.0.

Cage dione 13[12]**:** colourless crystalline solid; m.p. 73-74 ºC; obtained from DA adduct **22** (800 mg, 2.59 mmol); Yield: 92% (740 mg); IR (neat, cm^{-1}): 3081, 2949, 2867, 1752, 1734, 1437, 1117, 918; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49-5.59 (m, 2H), 5.01-5.07 (m, 4H), 2.99 (s, 2H), 2.85 (s, 2H), 2.51 (dd, J_1 = 14.0 Hz, J_2 = 5.6 Hz, 2H), 2.34-2.32 (m, 2H), 2.21 (dd, J_1 = 14.0 Hz, J_2 = 8.4 Hz, 2H), 1.66-1.63 (m,4H), 1.53-1.62 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 25.7, 28.6, 30.3, 32.4, 41.5, 51.3, 54.0, 55.3, 54.0, 55.4, 65.6, 118.6, 132.7, 212.9 ppm

General procedure for synthesis of cage diones 23 and **24 via RCM protocol:**

To a stirred solution of RCM precursors **12** and **13** (1.78-1.29 mmol, 1 equiv) in dry DCM (10 mL) was degassed with nitrogen for 10 min was added G-I catalyst (5 mol%). Later on, the reaction mixture was stirred at room temperature for 2-5 h. After completion of the reaction by monitoring of the TLC, then the solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography using 3-5% EtOAc/PE as an eluent to deliver the RCM products **23** and **24** as a colourless crystalline solids.

Cage dione 23: colourless crystalline solid; m.p. 128-130 ºC; started from [2+2] photo adduct **12** (500 mg, 1.78 mmol); Yield: 84% (380 mg); IR (neat, cm^{-1}): 2962, 2865, 1763, 1270, 781; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95 (d, *J* = 3.2 Hz, 2H), 2.95 (d, *J* = 1.6 Hz, 2H), 2.86 (d, *J* = 1.3 Hz, 2H), 2.35 (d, *J* = 15.7 Hz, 2H), 2.19 (d, *J* = 1.7 Hz, 2H), 1.85-1.81 (m, 2H), 0.72-0.61 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.9, 126.1, 55.2, 52.5, 49.1, 43.2, 37.7, 23.8, 5.5, 4.1; HRMS (ESI, Q-ToF): m/z calcd for $C_{17}H_{16}NaO_2$ $[M + Na]^+$ 275.1043; found: 275.1048.

Cage dione 24: colourless crystalline solid; m.p. 145-147 ºC; started from [2+2] photo adduct **13** (400 mg, 1.29 mmol); Yield: 88% (320 mg); IR (neat, cm^{-1}): 2950, 2857, 1746, 1725, 1444, 1236, 1217, 1100; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97-5.91 (m, 2H), 2.87 (d, *J* = 1.6 Hz, 2H),

2.78-2.77 (m, 2H), 2.42-2.39 (m, 2H), 2.35 (d, J = 15.8 Hz, 2H), 1.85-1.79 (m, 2H), 1.68-1.50 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.8, 126.1, 65.3, 54.6, 51.8, 51.2, 43.1, 32.3, 28.5, 25.7, 25.6, 23.9; HRMS (ESI, Q-ToF): m/z calcd for $C_{19}H_{20}NaO_2$ $[M + Na]^+$ 303.1356; found: 303.1356.

General procedure for synthesis of cage diones 10 and **12 via reduction:**

To a stirred solution of RCM product**s 23** and **24** (0.53-0.79 mmol) in dry ethyl acetate (10 mL) and 10% Pd/C (5 mg) was added. Afterwards, the resulting reaction mixture was stirred at room temperature for 5 h under hydrogen atmosphere (1 atm). After conclusion of the reaction by TLC monitoring, the reaction mixture was filtered through Celite pad and washed with ethyl acetate. The combined washings and filtrate were evaporated under vacuo and the resulting crude residue was purified by silica gel column chromatography using 2-4% ethyl acetate in petroleum ether as an eluent to furnish the hydrogenated products **10** and **12** as white crystalline solids.

Cage dione 10: white crystalline solid; mp 171-173 ºC; started from RCM product **23** (200 mg, 0.79 mmol); Yield: 92% (187 mg); IR (neat, cm^{-1}): 2964, 2833, 1748, 1732, 1438, 1379, 1297, 1277, 1230, 1195, 1168, 1134, 1097, 1066, 1028, 1005, 984, 948, 909, 854, 786; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.0 (s, 2H), 2.93 (d, J = 1.3 Hz, 2H), 2.17 (d, J = 1.4 Hz, 2H), 1.98-1.91 (m, 2H), 1.62-1.50 (m, 4H), 1.36-1.30 (m, 2H), 0.71-0.62 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.7, 55.5, 50.3, 49.3, 44.4, 37.9, 22.8, 19.3, 5.5, 4.1; HRMS (ESI, Q-ToF): m/z calcd for $C_{17}H_{18}KO_2$ $[M + K]^+$ 293.0938; found: 293.0936.

Cage dione 11: white crystalline solid; m.p. 157-159 ºC; started from RCM product **24** (150 mg, 0.53 mmol); Yield: 93% (140 mg); IR (neat, cm^{-1}): 2955, 2939, 2858, 1743, 1728, 1449, 1217, 1095; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.94 (s, 2H), 2.84 (s, 2H), 2.39 (t, J = 1.7 Hz, 2H), 1.95-1.90 (m, 2H), 1.67-1.62 (m, 4H), 1.58-1.47 (m, 8H), 1.33-1.28 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.5, 65.3, 54.8, 51.2, 49.5, 44.2, 32.3, 28.5, 25.7, 25.6, 22.8, 19.3; HRMS (ESI, Q-ToF): m/z calcd for $C_{19}H_{22}NaO_2$ $[M + Na]^+$ 305.1512; found: 305.1510.

General procedure for the synthesis of cage hydroxy ketones 25, 26, 27 and **28 via rearrangement**

A solution of cage diones **10, 11, 23,** and **24** (0.35-0.59 mmol, 1 equiv) and activated zinc dust (1.41-2.36 mmol) in 5 ml glacial acetic acid was stirred at room temperature for overnight.

Insoluble zinc metal and salts were removed by filtration. The resulting filtrate was concentrated, diluted with cold water and extracted with dichloromethane (DCM). The combined organic layers were washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to give the crude rearranged cage hydroxy ketone. The resulting crude residue was further purified by column chromatography on silica gel using 10-15% EtOAc/PE as an eluent to deliver the cage hydroxy ketones **25** and **26** as a colourless liquids and **27** and **28** as a colourless crystalline solids.

Cage hydroxy ketone 25: colourless viscous liquid; prepared from cage dione **23** (150 mg, 0.59 mmol); Yield: 137 mg (90%); IR (neat, cm^{-1}): 3442, 2937, 2862, 1758, 1449, 1305, 1269, 1245, 1159; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.62 (t, *J* = 3.9 Hz, 2H), 2.65-2.63 (m, 1H), 2.44-2.38 (m, 2H), 2.34-2.24 (m, 4H), 2.17 (t, *J* = 3.8 Hz , 1H), 2.13-2.08 (m, 1H), 1.94-1.93 (m, 1H), 1.77-1.76 (m, 1H), 0.57-0.51 (m, 2H), 0.47-0.42 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.3, 129.5, 128.3, 85.0, 55.8, 53.4, 52.2, 50.2, 48.5, 48.4, 46.5, 46.0, 33.8, 26.0, 22.6, 6.0, 5.3 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{17}H_{18}NaO_2$ $[M + Na]^+$ 277.1199; found: 277.1194.

Cage hydroxy ketone 26: colourless viscous liquid; prepared from cage dione **24** (150 mg, 0.53 mmol); Yield: 134 mg (88%); IR (neat, cm^{-1}): 3421, 2962, 1763, 1270, 781; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60 (t, *J* = 3.6 Hz, 2H), 2.82 (s, 1H), 2.52 (t, *J* = 5.6 Hz, 1H), 2.41-2.36 (s, 1H), 2.30-2.24 (m, 4H), 2.17-2.01 (m, 4H), 1.95 (d, *J* = 3.0 Hz, 1H), 1.64-1.59 (m, 2H), 1.48-1.32 (m, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.7, 129.5, 128.3, 84.7, 58.5, 56.5, 55.5. 52.3, 49.1, 49.0, 48.6, 47.2, 45.9, 32.9, 31.1, 26.1, 22.5 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{19}H_{22}NaO_2$ $[M + Na]^+$ 305.1512; found: 305.1518.

Cage hydroxy ketone 27: colourless crystalline solid; m.p. 113-115 ºC; prepared from cage dione **10** (150 mg, 0.59 mmol); Yield: 129 mg (85%); IR (neat, cm^{-1}): 3399, 2975, 1749, 1422, 1226, 1164, 1015, 953, 781; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.53-2.50 (m, 1H), 2.37 (t, *J* = 5.9 Hz, 1H), 2.31-2.29 (m, 1H), 2.25-2.21 (m, 3H), 2.10 (ddd, *J* = 14.8, 6.4, 3.3 Hz, 1H), 1.92-1.91 (m, 1H), 1.85-1.73 (m, 3H), 1.69-1.63 (m, 2H), 1.49-1.40 (m, 1H), 1.35-1.22 (m, 2H), 0.58-0.51 (m, 2H), 0.49-0.41 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.6, 86.0, 57.0, 53.1, 53.0, 50.1, 50.0, 49.9, 48.6, 46.9, 33.6, 28.9, 26.2, 24.82, 24.80, 6.0, 5.3 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{17}H_{20}NaO_2$ $[M + Na]^+$ 279.1353; found: 279.1356.

Cage hydroxy ketone 28: colourless crystalline solid; m.p. 122-124 ºC; prepared from cage dione **11** (100 mg, 0.35 mmol); Yield: 87 mg (86%); IR (neat, cm^{-1}) 3440, 2935, 2861, 1756, 1451, 1308, 1244, 1158; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.41-2.39 (m, 1H), 2.26-2.16 (m, 5H), 2.14-2.06 (m, 2H), 1.99 (s, 1H), 1.82-1.71 (m, 2H), 1.68-1.62 (m, 4H), 1.52-1.34 (m, 7H), 1.31-1.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 217.7, 85.8, 58.3, 56.6, 56.4, 53.2, 50.2, 50.1, 49.6, 48.7, 47.2, 33.0, 31.2, 28.9, 26.2, 26.1, 26.0, 24.85, 24.81; HRMS (ESI) m/z calcd for $C_{19}H_{24}NaO_2$ $[M + Na]^+$ 307.1669; found: 307.1670.

$BF_3{\cdot}OEt_2$-catalyzed rearrangement of cage dione 11

Spiro cage dione **11** (200 mg, 0.70 mmol) was added to a stirred solution of anhydrous $BF_3{\cdot}OEt_2$ (1 mL) in dry benzene (10 mL) at room temperature. Later on, the resulting reaction mixture was refluxed for 2 days. After completion of the reaction by TLC monitoring, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and this was extracted with benzene. The combined organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. After removal of the solvent under vacuo, the resulting crude residue was subjected to silica gel column chromatography by using 5% ethyl acetate/petroleum ether as an eluent to give the desired rearranged cage ketone **29** (57 mg, 23%) containing a phenyl group as a colourless liquid. After continuous elution with 10% ethyl acetate in petroleum ether delivered the rearranged cage dione **30** (82 mg, 41%) as colourless crystalline solid.

Cage ketone 29: colourless liquid; prepared from cage dione **11** (200 mg, 0.70 mmol); Yield: 57 mg (23%); IR (neat, cm^{-1}): 2935, 2337, 1759, 1266; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31-7.15 (m, 5H), 2.82 (d, J = 1.9 Hz, 1H), 2.63-2.61 (m, 1H), 2.50-2.43 (m, 2H), 2.15-2.13 (m, 1H), 2.11-2.01 (m, 2H), 1.70-1.56 (m, 7H), 1.52-1.43 (m, 5H), 1.33-1.27 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.2, 149.6, 128.4, 126.8, 125.3, 60.0, 56.5, 55.3, 54.6, 54.2, 51.6, 50.4, 48.4, 48.1, 43.2, 42.2, 33.0, 32.8, 26.4, 26.2, 26.0, 25.4, 24.3 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{25}H_{28}KO$ $[M + K]^+$ 383.1772; found: 383.1778.

Cage dione 30: colourless crystalline solid; m.p. 136-138 ºC; prepared from cage dione **11** (200 mg, 0.70 mmol); Yield: 82 mg (42%); IR (neat, cm^{-1}) 2926, 2857, 1751, 1450, 1294, 1076; ^{1}H NMR (500 MHz, $CDCl_3$): 2.23-2.26 (m, 6H), 1.83 (d, J = 13.5 Hz, 2H), 1.69-1.62 (m, 2H), 1.49-1.42 (m, 10H), 1.15-1.12 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, δ 213.1, 60.5, 50.6, 48.6,

48.4, 42.8, 32.5, 26.1, 22.0, 21.9 ppm; HRMS (ESI, Q-TOF) *m/z* calcd for $C_{19}H_{22}O_2$ [M + Na] $^+$ 305.1512; found: 305.1514.

General procedure for synthesis of RCM products 31 and **32:**

To a stirred solution of RCM precursors **21** and **22** (0.97-1.24 mmol, 1 equiv) in dry DCM (10 mL) were degassed with nitrogen for 10 min was added G-I catalyst (5 mol%). Later on, the reaction mixture was stirred at room temperature under nitrogen atmosphere for 2-5 h. After completion of the reaction by TLC monitoring, then the solvent was removed under reduced pressure and the crude reaction mixture was purified by silica gel column chromatography using 3-5% EtOAc/PE as an eluent to deliver the RCM products **31** and **32** as a colourless crystalline solids.

Compound 31: colourless crystalline solid; m.p. 138-140 ºC; started from DA adduct **21** (350 mg, 1.24 mmol); Yield: 86% (272 mg); IR (neat, cm^{-1}): 2989, 1654, 1418, 1398, 1276, 1010, 771, 704; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09 (t, *J* = 1.8 Hz, 2H), 5.73 (s, 2H), 3.39-3.38 (m, 2H), 3.00-2.89 (m, 6H), 0.61-0.57 (m, 2H), 0.51-0.47 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.3, 146.0, 135.4, 122.7, 53.9, 49.0, 44.8, 24.7, 8.1, 7.0 ppm ; HRMS (ESI, Q-ToF): m/z calcd for $C_{17}H_{16}NaO_2$ [M + Na]$^+$ 275.1043; found: 275.1045.

Compound 32: colourless crystalline solid; m.p. 143-145 ºC; started from DA adduct **22** (300 mg, 0.97 mmol); Yield: 89% (243 mg); IR (neat, cm^{-1}): 2958, 2854, 1655, 1270, 1259, 772 ; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.00 (t, *J* = 1.9 Hz, 2H), 5.73 (s, 2H), 3.30-3.29 (m, 2H), 3.11 (d, *J* = 1.6 Hz, 2H), 2.96 (s, 4H), 1.63-1.58 (m, 4H), 1.53-1.44 (m, 4H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 198.9, 146.0, 136.2, 122.8, 69.0, 56.6, 48.4, 32.1, 31.6, 26.0, 25.5, 24.7; HRMS (ESI, Q-ToF): m/z calcd for $C_{19}H_{20}NaO_2$ [M + Na]$^+$ 303.1356; found: 303.1353.

General procedure for synthesis of aromatized derivatives 33 and **34 (IBX mediated oxidative dehydrogenation):**

To a stirred solution IBX (1.60-1.98 mmol, 2 equiv) in DMSO (5 mL) were added RCM products **31** and **32** (0.80-0.99 mmol, 1 equiv) under nitrogen atmosphere and kept for heating at 75-85 0°C. After completion of the reaction by TLC monitoring (2 h), the reaction mixture was quenched with water and extracted from ethyl acetate. Then the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution followed by brine. The organic layer was dried

over anhydrous Na_2SO_4 and removal of the solvent under reduced pressure produce the crude products which was charged on silica gel column chromatography using 5-7% EtOAc/petroleum ether as an eluent to affords the aromatized products **33** and **34** as white solids.

Compound 33[16]**:** white solid; m.p. 146-148 ºC; started from RCM product **31** (250 mg, 0.99 mmol); Yield: 77% (192 mg); IR (neat, cm^{-1}): 3067, 2959, 2861, 1676, 1603, 1569, 1451, 1325, 1298, 1273, 1195, 1122, 1020, 912, 883, 856, 836, 778; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.68 (dd, *J* = 5.8, 3.3 Hz, 2H), 6.06 (s, 2H), 3.62 (s, 2H), 3.01 (s, 2H), 0.65-0.61 (m, 2H), 0.57-0.53 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 136.0, 135.5, 134.0, 126.8, 54.3, 50.3, 44.9, 8.1, 7.0 ppm.

Compound 34[16]**:** white solid; m.p. 149-151 ºC; started from RCM product **32** (225 mg, 0.80 mmol); Yield: 82% (185 mg); IR (neat, cm^{-1}): 2980, 2932, 2857, 1675, 1599, 1298, 1277, 1215, 1037, 915, 851, 837; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 2H), 7.68 (s, 2H), 5.97 (s, 2H), 3.53 (s, 2H), 3.23 (s, 2H), 1.61-1.52 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 136.5, 136.2, 134.1, 126.9, 69.2, 57.1, 49.8, 32.2, 31.4, 26.0, 25.5 ppm

General procedure for synthesis of cage diones 35 and **36 via [2+2] photocycloaddition:**

The aromatized derivatives **33** and **34** (0.53-0.69 mmol) was dissolved in dry EtOAc (250 mL) and irradiated in a pyrex immersion well by using 125 W UV lamp for 3 h under nitrogen atmosphere at room temperature. After completion of the reaction by TLC analysis, the solvent was evaporated under reduced pressure and the crude residue was purified by silica gel column chromatography by using 10-15% EtOAc/petroleum ether as an eluent to afford the symmetrical cage diones **35** and **36** as pure colourless solids.

Cage dione 35[16]**:** colourless solid; m.p. 171-173 ºC; obtained from aromatized derivative **33** (175 mg, 0.69 mmol); Yield: 89% (157 mg); IR (neat, cm^{-1}) 2995, 2833, 1741, 1722, 1447, 1308, 1186, 1115; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98-5.94 (m, 2H), 5.40-5.35 (m, 2H), 3.51-3.50 (m, 2H), 2.99 (d, *J* = 1.5 Hz, 2H), 2.30-2.28 (m, 2H), 0.75-0.71 (m, 2H), 0.65-0.61 (m, 2H) ppm;^{13}C NMR (100.6 MHz, $CDCl_3$): δ 210.3, 124.8, 119.9, 55.2, 52.0, 51.0, 49.9, 35.8, 5.3, 4.1.

Cage dione 36[16]**:** colourless solid; m.p. 164-166 ºC; obtained from aromatized derivative **34** (150 mg, 0.53 mmol); Yield: 91% (137 mg); IR (neat, cm^{-1}): 2962, 2328, 1761, 1452, 1219; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97-5.95 (m, 2H), 5.39-5.37 (m, 2H), 3.43-3.40 (m, 2H), 2.91 (d, *J* =

1.6 Hz, 2H), 2.53-2.50 (m, 2H), 1.68-1.60 (m, 8H) ppm; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 210.3, 124.8, 120.0, 63.1, 54.5, 52.05, 52.01, 50.2, 32.5, 28.2, 25.7, 25.6.

General procedure for synthesis of di-alkyl cage diones 37 and **38 via reduction:**

To a stirred solution of di-allyl cage diones **12** and **13** (0.48-0.71 mmol) in dry ethyl acetate (10 mL) and 10% Pd/C was added. Afterwards, the resulting reaction mixture was stirred at room temperature for 3-5 h under hydrogen atmosphere (1 atm). After conclusion of the reaction by TLC monitoring, the reaction mixture was filtered through Celite pad and washed with ethyl acetate. The combined washings and filtrate were evaporated under vacuo and the resulting crude residue was purified by silica gel column chromatography using 12-15% ethyl acetate in petroleum ether as an eluent to furnish the di-alkyl cage diones **37** and **38** as white solids.

Di-alkyl cage dione 37: white solid; m.p. 99-101 ºC; obtained from di-allyl cage dione **12** (200 mg, 0.71 mmol); Yield: 92% (187 mg); IR (neat, cm^{-1}) 3166, 2949, 1742, 1723, 1523, 1437, 1351, 1258, 1154; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (s, 2H), 2.90 (d, *J* = 1.5 Hz, 2H), 2.12 (d, *J* = 1.4 Hz, 2H), 1.69-1.60 (m, 2H), 1.49-1.41 (m, 2H), 1.15-1.07 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6H), 0.68-0.64 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 214.1, 56.3, 56.2, 49.5, 42.0, 38.1, 27.8, 17.1, 14.8, 5.5, 4.1; HRMS (ESI) m/z calcd for $C_{19}H_{24}NaO_2$ $[M + Na]^+$ 307.1669; found: 307.1664.

Di-alkyl cage dione 38: white solid; m.p. 81-83 ºC; obtained from di-allyl cage dione **13** (150 mg, 0.48 mmol); Yield: 91% (138 mg); IR (neat, cm^{-1}) 3179, 2949, 2957, 2803, 2378, 1747, 1525, 1217,1131, 981, 768, 675; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (s, 2H), 2.82 (d, *J* = 1.4 Hz, 2H), 2.35-2.34 (m, 2H), 1.67-1.61 (m, 6H), 1.57-1.56 (m, 4H), 1.45-1.39 (m, 2H), 1.16-1.06 (m, 4H), 0.87 (t, *J* = 7.3 Hz, 6H) ppm;^{13}C NMR (125 MHz, $CDCl_3$): δ 214.1, 65.7, 55.6, 55.4, 51.5, 41.8, 32.4, 28.7, 27.8, 25.7, 25.6, 17.0, 14.8; HRMS (ESI) m/z calcd for $C_{21}H_{28}NaO_2$ $[M + Na]^+$ 335.1982; found: 335.1983.

General procedure for synthesis of di-alkyl cage diols 39 and **40 via reduction:**

A solution of di-alkyl cage diones **37** and **38** (0.40-0.52 mmol) in dry methanol (10 mL), $NaBH_4$ (1.60-2.08 mmol) was added at 0 °C in small portions over a period of 10 min. Afterwards, the reaction mixture was stirred for another 20 min at the room temperature. After completion of the reaction (the progress of the reaction monitored by TLC), methanol was removed under vacuo

and the crude residue was quenched by addition of water and it was extracted with ethyl acetate. The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude products were obtained after evaporation of solvent followed by purified by column chromatography on silica gel using 20-25% EtOAc in petroleum ether as an eluent to deliver the cage diols **39** and **40** as a colourless solids.

Di-alkyl cage diol 39: white solid; m.p. 140-142 ºC; obtained from di-alkyl cage dione **37** (150 mg, 0.52 mmol); Yield: 80% (123 mg); IR (neat, cm^{-1}) 3181, 2955, 1466, 1228, 1113, 1090, 1058, 993, 962, 806; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (s, 2H), 3.64 (s, 2H), 2.59 (s, 2H), 2.33 (s, 2H), 1.70-1.53 (m, 6H), 1.33-1.24 (m, 2H), 1.22-1.16 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 6H), 0.51-0.48 (m, 2H), 0.29-0.26 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.8, 49.4, 48.2, 46.4, 43.4, 31.6, 31.5, 17.2, 15.1, 5.1, 4.4; HRMS (ESI) m/z calcd for $C_{19}H_{28}NaO_2$ $[M + Na]^+$ 311.1982; found: 311.1985.

Di-alkyl cage diol 40: white solid; m.p. 137-139 ºC; obtained from di-alkyl cage dione **38** (125 mg, 0.40 mmol); Yield: 88% (112 mg); IR (neat, cm^{-1}) 3369, 3186, 2951, 1496, 1269, 1017; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.37 (s, 2H), 3.63 (s, 2H), 2.50 (s, 2H), 2.23 (s, 2H), 1.76 (s, 2H), 1.68-1.62 (m, 2H), 1.59-1.52 (m, 6H), 1.49 (t, *J* = 6.9 Hz, 2H), 1.31-1.24 (m, 3H), 1.17 (t, *J* = 7.3 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.9, 57.6, 50.3, 48.7, 45.7, 43.3, 32.3, 31.6, 29.8, 25.8, 25.6, 17.1, 15.1; HRMS (ESI) m/z calcd for $C_{21}H_{32}NaO_2$ $[M + Na]^+$ 339.2295; found: 339.2297.

Notes

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Appendix A. Supplementary data

The supporting information is available free of charge on the journal website. Characterization data of ^{1}H, ^{13}C, ^{13}C-APT, DEPT-135 NMR spectra of all new products (PDF) and X-Ray data (ORTEP diagrams) are available in supplementary information (SI) file.

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Synthesis of Functionalized Cage Propellanes and D_3-Trishomocubanes via the Ring-Closing Metathesis and Acid-Promoted Rearrangement

Highlights

1. Functionalized cage propellanes and D_3-trishomocubanes have been reported by Claisen rearrangement, Diels–Alder reaction (DA), ring-closing metathesis (RCM) and acid-promoted rearrangement.
2. The strategies described here, opens up new opportunities to design intricate cage systems via RCM and rearrangement approach.
3. Solvent incorporation as well as ring rearrangement was observed in cage [4.4.2]propellane framework during the acid promoted rearrangement.
4. Functionalized cage hydroxy derivatives as well as alkylated cage diones have been assembled by reduction.