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Design, Synthesis, and Rearrangement Studies of *Gem*-dimethyl Containing Cage Systems

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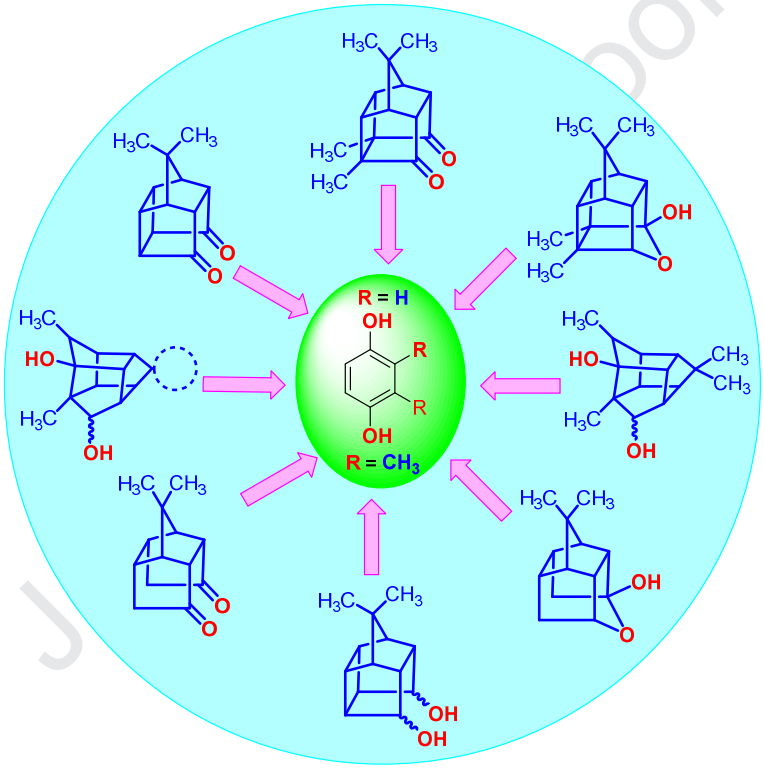
Abstract



A variety of functionalized cage compounds and D_3-trishomocubane derivatives have been assembled via the Diels–Alder strategy, with reductive cleavage of the cyclopropane ring and metal promoted ring rearrangement as key steps. We have installed the *gem*-dimethyl moiety on the norbornane ring system containing a cage framework by a late-stage synthetic manipulation involving the hydrogenolysis of the cyclopropane ring with the aid of Adams' catalyst (PtO_2). Several cage molecules containing methyl substituents were synthesized by starting with inexpensive and commercially available materials such as 2,3-dimethylhydroquinone, Zn/AcOH, and *endo*-dicyclopentadiene. These cage pentacycloundecane frameworks assembled here are

difficult to synthesize by conventional routes. Some of these *gem*-dimethyl cage systems and D_3-trishomocubane derivative was firmly supported on the basis of single-crystal X-ray diffraction studies.

Keywords

Adams' catalyst; D_3-trishomocubanes; hydrogenolysis; pentacycloundecane; cage rearrangement; reductive cleavage

Introduction

The design and synthesis of theoretically interesting polycycles has been considered as a challenging task in organic syntheses. In the beginning carbocyclic cage molecules were assembled as academic curiosity.[1-2] Many of these cage systems are useful synthons to assemble complex natural products. Cage molecules act as useful precursors to design high-density fuels and biologically active molecules.[3-4] Special structural features such as deformation of bond angles, rigid molecular architecture and inherent ring strain of these systems are general reasons for their synthetic appeal.[5] Synthesis of these molecules has become a worthwhile exercise because of their utility as high energy materials.[6]

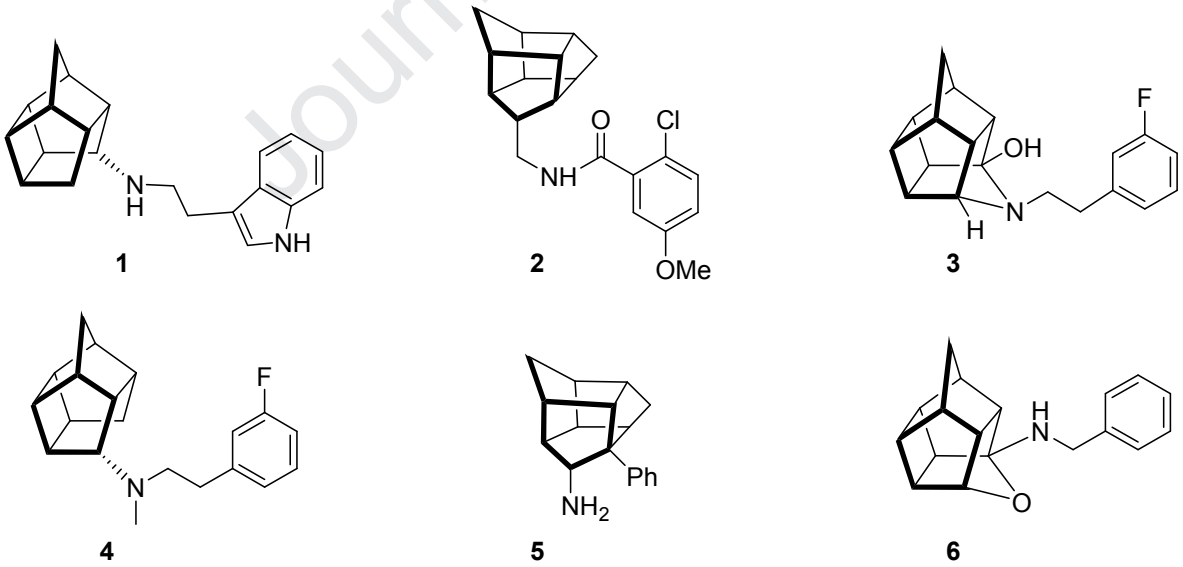


Figure 1. Selected examples of biologically active cage molecules (**1**-**6**) containing PCUD and D_3-trishomocubyl moiety.

Moreover, due to the high strain energy associated with the cage propellanes they can be used as suitable substrates for interesting molecular rearrangements. Rearrangement studies of cage diones and cage propellanes have provided new synthetic routes to a variety of interesting polycycles.[7] Selected D_3-trishomocubane frameworks prepared by rearrangement approaches produced various biologically active as well as medicinally important compounds.[8-9] Representative examples of biologically important cage molecules **1-6** containing pentacycloundecane (PCUD) and D_3-trishomocubane skeleton are shown in Figure 1.[10]

A variety of ring expansion, ring-contraction, ring-fragmentation, and ring-rearrangement processes provide new cage frameworks in an unusual fashion.[11] The rearrangement process enable the relief of the ring strain.[12-13] Some examples of polycycles **7-10** which are derived from a metal-mediated reductive cleavage approach are illustrated in Figure 2.[13] Our main objective in this field is to expand the chemical space of unusual cage polycycles and D_3-trishomocubanes via the rearrangement strategy and in this regard, we studied metal-catalyzed (PtO_2/H_2) reductive cleavage of the cyclopropane ring and rearrangements associated with the pentacycloundecane system.

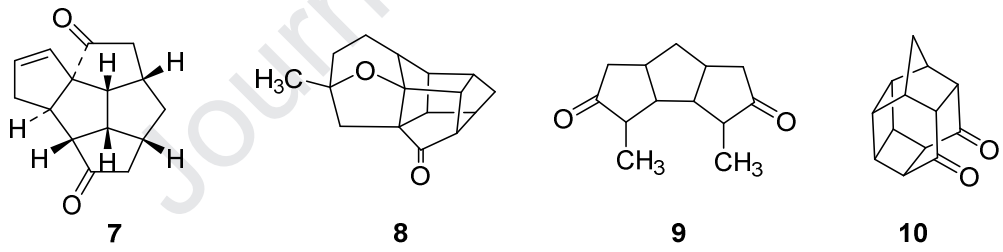
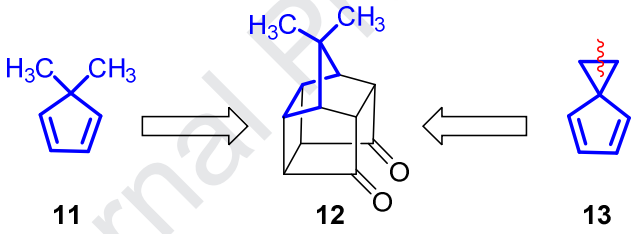


Figure 2. List of various polycycles **7-10** assembled via metal-mediated reductive cleavage.

Results and discussion

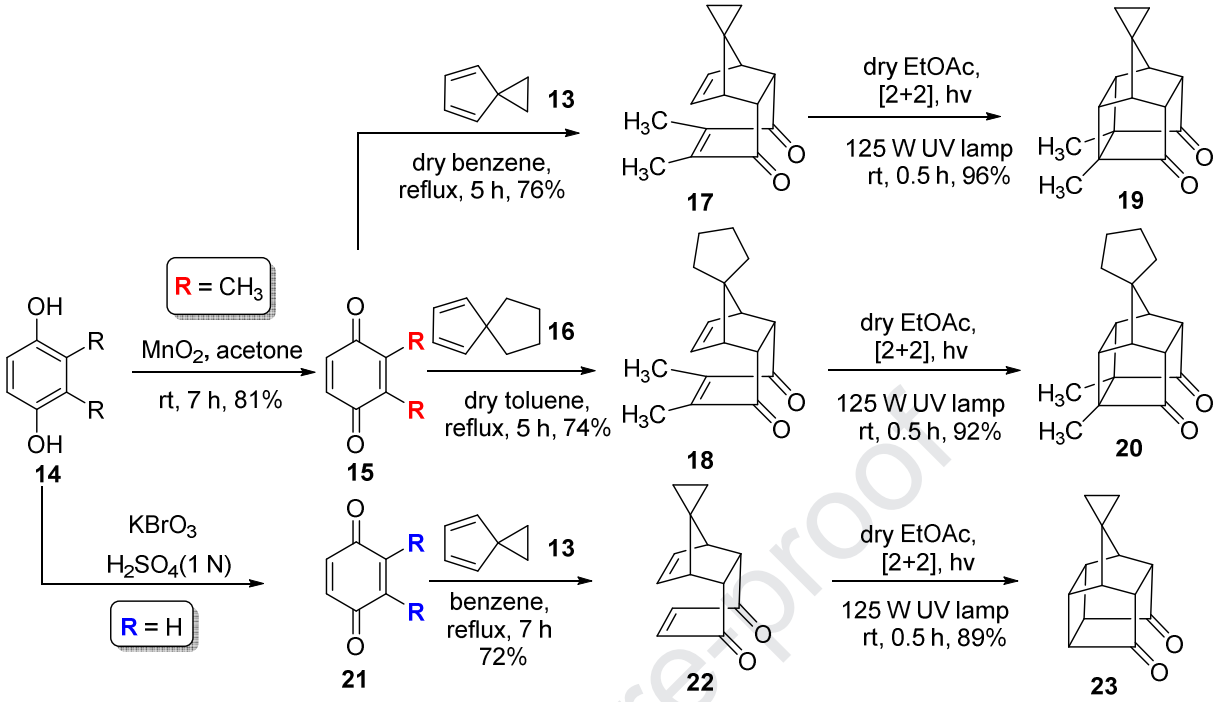
Here, our aim is to design new polycyclic cage molecules containing a *gem*-dimethyl moiety at the C_7 position of the norbornane ring system. These categories of methyl-substituted PCUD frameworks are considered as suitable precursors to design high-density fuels. Also, some *gem*-dimethyl cage frameworks containing amine groups were tested for anti-influenza activity.[14] There are two possible synthetic routes to assemble *gem*-dimethyl substituted PCUD cage frameworks as shown in Scheme 1. For example, compound **12** can be synthesized from 5,5-

dimethylcyclopentadiene (**11**) and spiro[2.4]hepta-4,6-diene (**13**). Preparation of the diene **11**[15] involves a multistep synthetic sequence. Whereas the preparation of the spiro diene **13** requires only one step from readily accessible cyclopentadiene. Therefore, we chose a simple route to synthesize *gem*-dimethyl substituted cage dione **12** from spirodiene **13**. Late-stage metal-mediated reductive cleavage of the cyclopropane ring was planned as a key step to introduce the *gem*-dimethyl group. In this regard, reductive cleavage of cyclopropane rings may be accomplished by use of PtO_2/H_2. The increased *p*-character of the cyclopropane C–C bonds shows a higher affinity towards the metal surface, which accelerates the reaction as compared with simple alkane derivatives. The cleavage of the cyclopropane ring generally proceeds with high regioselectivity. Hydrogenolysis of the cyclopropane ring is feasible because of the low activation energy involved in the cleavage of the cyclopropane C–C bond. The relief of ring strain provides the driving force for hydrogenolysis of C–C bonds in the strained systems containing a cyclopropane ring.



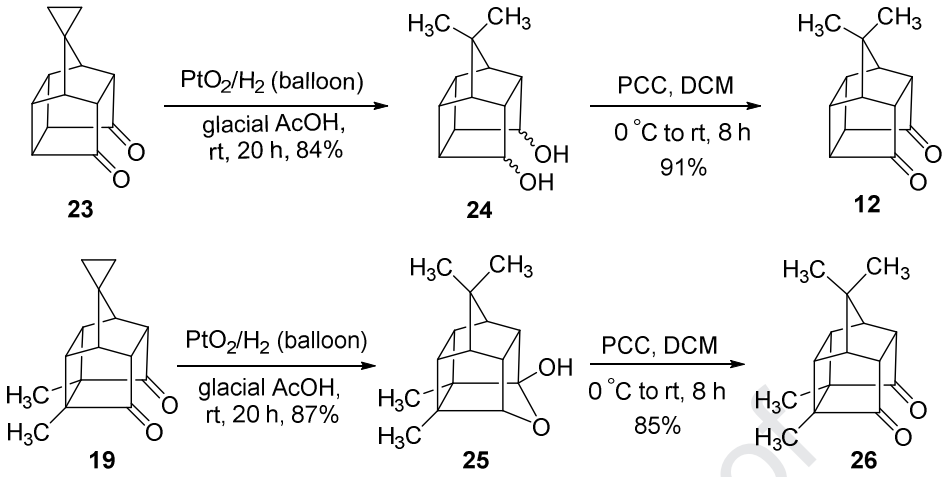
Scheme 1. The synthetic plan of PCUD cage dione **12** constitutes *gem*-dimethyl moiety.

In view of our interest in designing new polycyclic cage frameworks, here we report the synthesis of hexacyclic cage diones bearing cyclopropane and cyclopentane ring system with the Diels–Alder (DA) reaction and [2+2] photocycloaddition as key steps. The synthesis of the target cage compound commenced with the preparation of key building blocks such as 2,3-dimethyl-1,4-benzoquinone **15** (Scheme 2). The quinone derivative **15**[16] was prepared by MnO_2 oxidation of the 2,3-dimethylhydroquinone **14** in acetone (81% isolated yield).

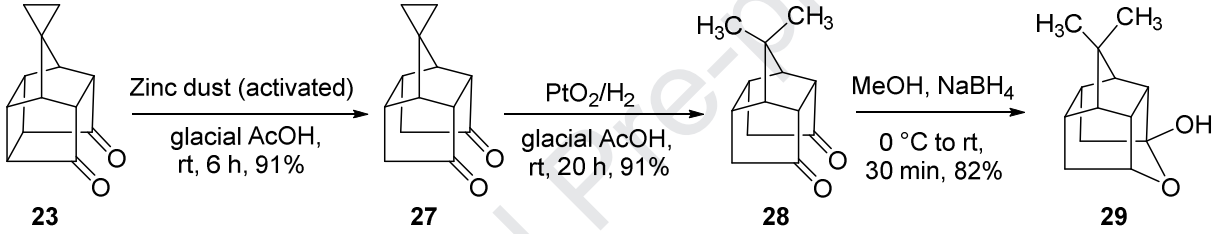


Scheme 2. Synthesis of spiro cage diones **19**, **20**, and **23**.

Having the DA precursors **15** and **21** in hand, next our efforts were directed towards the preparation of cage diones **19**, **20**, **23**, and **27** using intramolecular [2+2] photocycloaddition as a key step. In this context, the DA adduct **22** (72%) was prepared by [4+2] cycloaddition of freshly prepared spirodiene **13** and 1,4-benzoquinone **21** under reflux conditions (Scheme 2).[17] Along similar lines, the other DA adducts **17** and **18** were assembled in good yields (74-76%) by thermal cycloaddition of the quinone **15** with freshly generated spirodienes[17]such as **13** and **16**. Afterward, *endo*-adducts **17**, **18**, and **22** were prepared from quinones **15** and **21**. They were then subjected to intramolecular [2+2] photocycloaddition by irradiation with 125W UV light through a pyrex immersion well for 30 min under N_2 atmosphere to deliver the cage systems **19**, **20**, and **23**[17] in excellent yields. The structures of these cage diones **19**, **20**, and **23**[17] were fully supported on the basis of IR, ^{1}H NMR, ^{13}C NMR, APT spectroscopy and further established using HRMS data.



Scheme 3. Synthesis of PCUD cage frameworks **12** and **26** bearing *gem*-dimethyl group.



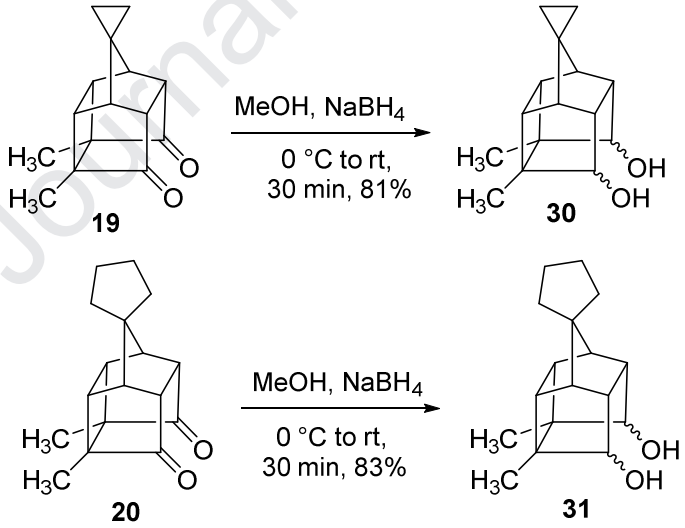
Scheme 4. Synthesis of cage hemiketal **29** bearing *gem*-dimethyl group.

Having the cage diones **19, 23,** and **27** in hand, next we directed our efforts towards the metal-catalyzed reductive cleavage of the cyclopropane ring[18] to generate cage diones containing a *gem*-dimethyl group. In this context, the cage diones such as **19** and **23** bearing cyclopropane ring were treated with PtO_2 in glacial acetic acid under hydrogen (balloon) atmosphere at room temperature for 20 h produced the *gem*-dimethyl substituted cage diol **24** and cage hemiketal **25** in 84 and 87% yields respectively (Schemes 3). Steric strain associated with the presence of methyl groups and the proximity of the two carbonyl groups in the cage dione facilitates the formation of hemiketal **25**.

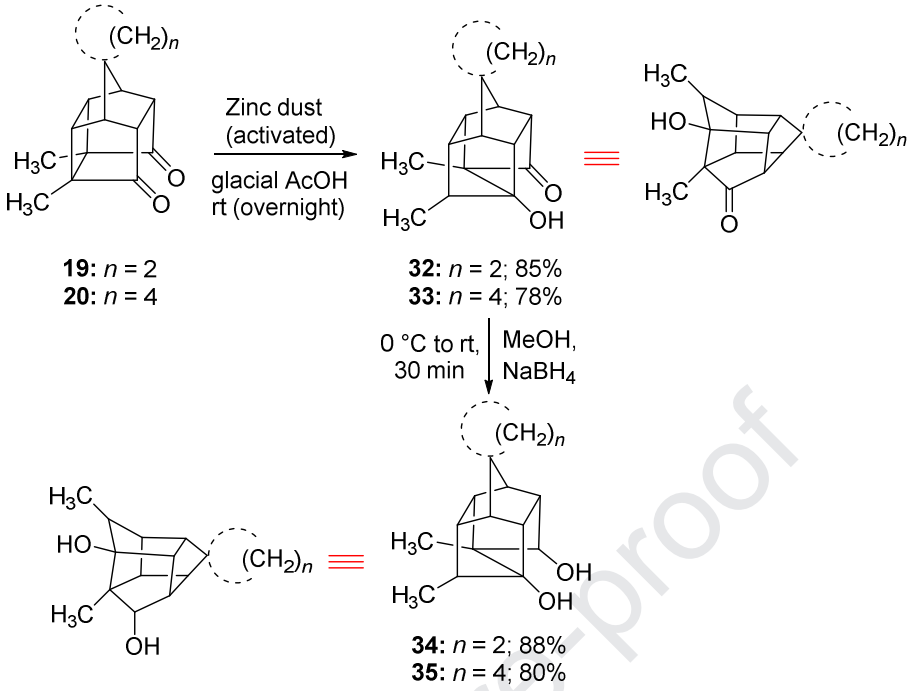
Additionally, **19** also facilitates the formation of hemiketal **25**. The structure of these compounds **24** and **25** were confirmed on the basis of IR, ^{1}H NMR, and ^{13}C NMR, APT, DEPT-135 and HRMS data. Also, the structure of the transannular product **25** (hemiketal) was further confirmed by single-crystal X-ray diffraction data (Figure 3).[19] The ring-opened products **24** and **25** by reductive C–C bond cleavage with PtO_2 on further treatment with PCC in DCM delivered the

cage diones **12** and **26** in excellent yields (Schemes 3). The structure of the cage dione bearing *gem*-dimethyl group **12** was further established by single-crystal X-ray diffraction data (Figure 3). [19]

Pentacyclic cage dione **23** bearing cyclopropane was also subjected to reductive C–C bond cleavage of the cyclobutane ring. To this end, the dione **23** was reacted with activated zinc powder in glacial acetic acid at room temperature to give the tetracyclic cage dione **27** in 91% yield (Scheme 4). Next, the tetracyclic dione **27** was further subjected to reductive cleavage with PtO_2 in glacial acetic acid under hydrogen (balloon) atmosphere at room temperature for 20 h to produce the *gem*-dimethyl substituted tetracyclic cage dione **28** in 91% yield (Scheme 4). Finally, the tetracyclic dione **28** was converted to the corresponding cage hemiketal **29** (82%) by $NaBH_4$ reduction in methanol at 0 °C to rt (Scheme 4). The hemiketal structure **29** was characterized by spectroscopy (IR, ^{1}H NMR, ^{13}C NMR, and HRMS data). Subsequently, spiro cage diones **19** and **20** were treated with $NaBH_4$ in methanol to produce the cage diols **30** and **31** in good yields (Scheme 5). The structures of these cage diols **30** and **31** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, APT, and DEPT spectroscopy followed by HRMS.



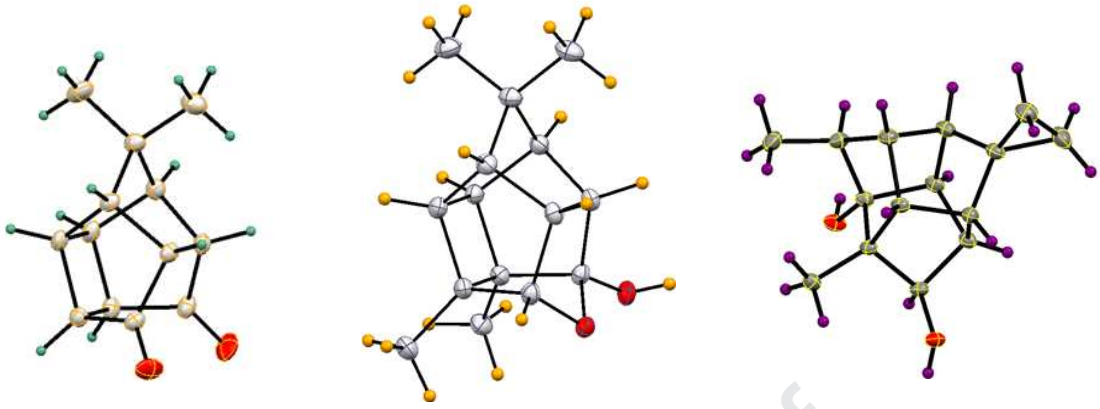
Scheme 5. Synthesis of hexacyclic cage diols bearing spiro systems **30**-**31**.



Scheme 6. Zn/AcOH promoted rearrangement of spiro cage diones **19** and **20**.

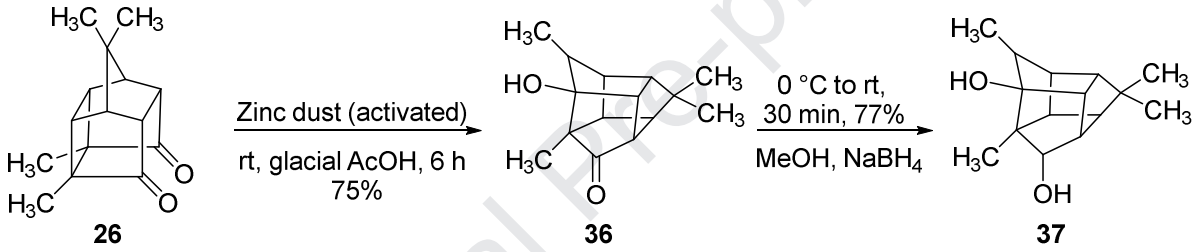
Cage PCUD systems containing a succinyl bonds are prone to undergo skeletal rearrangement to produce unusual cage structures. To expand the rearrangement approach in cage frameworks, we studied metal-mediated rearrangements starting with cage diones bearing methyl substituents. In this context, we studied the zinc-mediated rearrangement of cage compounds **19**, **20**, and **26**.

To design various functionalized D_3-trishomocubane derivatives by Zn/AcOH catalyzed rearrangement, we also examined the ring rearrangement approach in substituted cage diones such as **19** and **20** bearing spiro linkages. In this context, the diones **19** and **20** containing a spiro linkage were reacted with activated Zn dust in glacial acetic acid and this delivered the rearranged cage hydroxyketones **32** and **33** in good yields (78-85%). The cage hydroxyketones **32** and **33** were then treated with $NaBH_4$ in methanol to afford the desired D_3-trishomocubanediols **34** and **35** in excellent yields (Scheme 6). The structure of the cage diol **34** was further established by single-crystal X-ray diffraction data (Figure 3). [19]



12 (CCDC-**1908378**) . **25** (CCDC-**1908389**) . **34** (CCDC **1919869**)

Figure 3. X-ray crystallographic structures of compounds **12**, **25**, and **34**.



Scheme 7. Zn/AcOH promoted rearrangement of tetra substituted cage dione **26**.

We also recognized that the cage dione **26** bearing *gem*-dimethyl group is also a useful candidate for creating new functionalized D_3-trishomocubane frameworks via the ring rearrangement approach. Having tetramethyl cage dione **26** in hand, next, it was subjected to acid-catalyzed rearrangement with activated zinc dust in glacial acetic acid to deliver the tetramethyl D_3-trishomocubane **36** in 75% yield (Scheme 7). Subsequent $NaBH_4$ reduction of compound **36** produced the tetramethyl D_3-trishomocubanediol **37**. The structures of these D_3-trishomocubane derivatives **36** and **37** were confirmed by ^{1}H NMR, ^{13}C NMR, APT, DEPT spectroscopy and HRMS data (Scheme 7).

Conclusions

To conclude, we have efficiently utilized a hydrogenolysis route to create *gem*-dimethyl containing polycyclic cage frameworks involving reductive cleavage of the cyclopropane ring in a PCUD system. Also, several D_3-trishomocubane frameworks bearing cyclopropane and cyclopentane ring systems, as well as substituted cage ketals, were synthesized successfully in

this sequence. The design and synthesis of *gem*-dimethyl substituents at the 7th position of the norbornane ring in the PCUD framework requires a lengthy synthetic sequence by conventional strategy. These *gem*-dimethyl substituted cage frameworks may function as promising candidates for high-density fuels and also inspire further research in this area.

Experimental Section

General Experimental Details (methods/materials)

Essential reagents, required chemicals and solvents were used directly as obtained from commercial suppliers. Thin-layer chromatography (TLC) plates were made on 10 × 5 glass plates layered with commercial-grade Acme's silica gel (GF-254) containing 13% $CaSO_4$ which acts as a binder. Reaction progress was analyzed by a chromatographic technique (TLC analysis) with suitable solvent systems (ethyl acetate/pet ether) and observation was done by UV, iodine spray and immersion in $KMnO_4$ solution. All dry/anhydrous (moisture sensitive) reactions were done in oven-dried glassware under nitrogen/argon atmosphere by using syringe-septum techniques. Column purification was executed with 100-200 mesh silica gel in all cases with suitable solvent systems. Dry benzene and DCM were distilled over CaH_2 and ethyl acetate was dried with anhydrous K_2CO_3. Spiro dienes **13**[17] and **16**[17] were prepared according to known literature procedures.

IR samples were recorded with DCM and chloroform as solvents on a Nicolet Impact-400 FTIR spectrometer. NMR spectra (^{1}H, ^{13}C, and DEPT 135) were recorded on 400 and 500 MHz spectrometers (Bruker) with $CDCl_3$ solvent and chemical shifts (δ ppm) are reported relative to an internal standard such as TMS. The *J* values (coupling constants) are given in Hz. Mass spectra (HRMS) have been recorded under positive ion electrospray ionization (ESI/Q-TOF) mode. X-ray crystal analysis was performed on a diffractometer equipped with graphite monochromated Mo Kα radiation and the structure was solved by direct methods shelxl-97 and refined by full-matrix least-squares against F^2 using shelxl-97 software.

Experimental procedures and characterization data

2,3-dimethylcyclohexa-2,5-diene-1,4-dione (15)[16]

To a stirred solution of the 2,3-dimethyl benzene-1,4-diol **14** (5.0 g, 36.2 mmol) in acetone (70 mL) was added an excess amount of MnO_2 (25.2 g, 289.6 mmol) portion-wise. The resulting reaction mixture was stirred at room temperature for 7 h and then manganese dioxide was removed by filtration of the crude mixture through Celite pad and washed twice with acetone. The solvent was evaporated under reduced pressure followed by purification (100-200 mesh, silica gel) with 2% ethyl acetate in petroleum ether as an eluent to afford the compound **15** as a yellow crystalline solid. Yield: 81% (4.13 g); Mp: 58-60 °C (lit. 54-55 °C);[16] ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) = 6.70 (s, 2H); 2.01 (s, 6H), ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 187.5, 141.1, 136.4, 12.3.

Synthesis of [4+2] cycloadducts 17, **18**, and **22: General procedure[7f, 12b]for the Diels–Alder (DA) reaction**

To a stirred solution of quinone derivatives such as 2,3-dimethyl-1,4-benzoquinone **15** (1 g, 7.34 mmol, 1 equiv for **17** and **18**), 1,4-benzoquinone **21** (500 mg, 4.63 mmol for **22**) was added freshly made spiro[2.4]hepta-4,6-diene **13** (14.68 mmol, 2 equiv, 1.5 mL for **17** and 9.25 mmol, 1.0 mL for **22**), spiro[4.4]nona-1,3-diene **16** (14.68 mmol, 2 equiv, 1.9 mL for **18**) in dry benzene/toluene (20 mL) and thus was kept under reflux for 5 h (reaction progress was monitored by TLC). After completion of the reaction by TLC, the solvent was evaporated under reduced pressure and the crude residue was purified by column chromatography (silica gel, 100-200 mesh) using an appropriate mixture of ethyl acetate/petroleum ether as an eluent to deliver the pure DA adducts **17**, **18**, and **22**.

Diels–Alder (DA) adduct 17

Prepared according to the above general procedure using 2,3-Dimethyl-1,4-benzoquinone **15** (1 g, 7.34 mmol) and freshly made spiro[2.4]hepta-4,6-diene **13** (14.68, 1.5 mL) in dry benzene (20 mL) under reflux for overnight. Column chromatography (6% ethyl acetate in petroleum ether) afforded the DA adduct **17**.

Pale yellow solid: Yield: 76% (1.27 g); Mp: 120-122 °C; IR (neat, cm^{-1}): υ_{max} = 2958, 2850, 1658, 1622, 1440, 1373, 1284, 944, 765; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 6.06 (t, J = 1.8

Hz, 2H), 3.36-3.35 (m, 2H), 2.85 (s, 2H), 1.90 (s, 6H), 0.58-0.55 (m, 2H), 0.48-0.45 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 198.6, 147.8, 135.4, 53.8, 49.2, 44.7, 13.2, 8.0, 6.9; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{16}NaO_2$ $[M + Na]^+$ 251.1043; found: 251.1043.

Diels–Alder adduct 18

Prepared according to the above general procedure using 2,3-Dimethyl-1,4-benzoquinone **15** (1 g, 7.34 mmol) and freshly made spiro[4.4]nona-1,3-diene **16** (14.68 mmol, 1.9 mL) in dry toluene (20 mL) under reflux for overnight. Column chromatography (5% ethyl acetate in petroleum ether) afforded the DA adduct **18**.

Pale yellow solid; Yield: 74% (1.39 g); Mp: 109-111 °C; IR (neat, cm^{-1}): υ_{max} = 3061, 2962, 2850, 1657, 1374, 1264, 1124; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.92 (s, 2H), 3.23 (s, 2H), 3.04 (s, 2H), 1.85 (s, 6H), 1.56-1.38 (m, 8H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ (ppm) = 199.1, 147.7, 136.1, 68.8, 56.3, 48.4, 31.9, 31.6, 25.9, 25.3, 13.1; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{17}H_{20}KO_2$ $[M + K]^+$ 295.1095; found: 295.1095.

Diels–Alder adduct 22 [17]

Prepared according to the above general procedure using 1,4-benzoquinone **21** (500 mg, 4.63 mmol) and freshly made spiro[2.4]hepta-4,6-diene **13** (1.0 mL, 9.25 mmol) in dry benzene (20 mL) under reflux for overnight. Column chromatography (30% ethyl acetate in petroleum ether) afforded the DA adduct **22**. Pale yellow solid; Yield: 72% (655 mg); Mp: 105-107 °C; (Lit. Mp: 110 °C).

Synthesis of cage diones 19, 20, and 23: General procedure[7f, 12b] for [2+2] photocycloaddition

The [4+2] cycloadducts (DA adducts) **17**, **18**, and **22** (500 mg to 1.0 g, 2.50-4.38 mmol) in 250 mL of dry ethyl acetate were degassed with nitrogen and then irradiated in a pyrex immersion well by using 125W medium pressure UV mercury-vapor lamp (homemade) for 30 min at room temperature under nitrogen atmosphere. The reaction progress was monitored by TLC, the solvent was removed under reduced pressure and the crude reaction mixture was purified from column chromatography (on 100-200 mesh silica gel) using appropriate mixture of ethyl acetate in petroleum ether as an eluent to furnish the cage diones **19**, **20**, and **23**.

Cage dione 19

Prepared according to the above general procedure using DA adduct **17** (1.0 g, 4.38 mmol) in dry ethyl acetate under UV irradiation for 0.5 h. Column chromatography (6-8% ethyl acetate in petroleum ether) afforded the pure cage dione **19**.

Colourless crystalline solid; Mp: 152-154 °C; prepared from DA adduct **17** (1 g, 4.38 mmol); Yield: 969 mg (96%); IR (neat, cm^{-1}): υ_{max} = 3062, 2970, 2929, 2866, 1747, 1732, 1455, 1381, 1302, 1227, 1184, 1158, 1104, 1049, 1016, 958, 903, 875, 864; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.91 (d, J = 13.7 Hz, 4H), 2.15 (d, J = 1.4 Hz, 2H), 1.02 (s, 6H), 0.65-0.64 (m, 2H), 0.62-0.60 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 213.9, 55.2, 51.0, 49.1, 44.5, 37.8, 11.6, 5.4, 4.0; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{16}NaO_2$ $[M + K]^+$ 267.0782; found: 267.0780.

Cage dione 20

Prepared according to the above general procedure using DA adduct **18** (1.0 g, 3.90 mmol) in dry ethyl acetate under UV irradiation for 0.5 h. Column chromatography (8-10% ethyl acetate in petroleum ether) afforded the pure cage dione **20**.

Colourless crystalline solid; Mp: 134-136 °C; Yield: 920 mg (92%); IR (neat, cm^{-1}): υ_{max} = 2976, 2945, 2854, 1747, 1730, 1452, 1446, 1383, 1268, 1232, 1119, 1053, 878; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.88 (d, J = 12.8 Hz, 4H), 2.38 (d, J = 1.5 Hz, 2H), 1.63-1.49 (m, 8H), 1.00 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 213.8, 65.4, 54.6, 51.1, 50.2, 44.4, 32.2, 28.4, 25.6, 25.5, 11.6; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{17}H_{20}NaO_2$ $[M + Na]^+$ 279.1356; found: 279.1357.

Cage dione 23[17]

Prepared according to the above general procedure using DA adduct **22** (500 mg, 2.5 mmol) in 250 mL of dry ethyl acetate under UV irradiation for 0.5 h. Column chromatography (40% ethyl acetate in petroleum ether) afforded the pure cage dione **23**; Colourless crystalline solid; Yield: 445 mg (89%); Mp: 152-154 °C; (Lit. Mp: 152 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.32 (s, 2H), 2.89 (s, 2H), 2.85-2.84 (m, 2H), 2.24 (s, 2H), 0.72-0.69 (m, 2H), 0.67-0.63 (m, 2H) ppm; ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 212.2, 55.3, 50.4, 44.6, 39.1, 37.3, 5.5, 4.2 ppm.

Reductive cleavage of cyclopropane ring with PtO_2/AcOH: General procedure[18]

To a stirred solution of compounds **19**, **23**, and **27** (0.50-1.31 mmol) in 5 mL of glacial acetic acid was added PtO_2 (0.05-0.13 mmol). The resulting reaction mixture was stirred at room temperature under H_2 atmosphere (balloon pressure) for 20 h. After completion of the reaction by TLC monitoring, the metal catalyst was removed through the Celite pad with ethyl acetate washing. The solvent was diluted with water, quenched by aqueous $NaHCO_3$ solution and 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 obtained crude residues were purified by column chromatography (on 100-200 mesh silica gel) using an appropriate mixture of ethyl acetate in petroleum ether as an eluent to deliver the *gem*-dimethyl cage compounds **24**, **25**, and **28**.

Cage diol 24

Prepared according to the above general procedure using cage dione **23** (200 mg, 1 mmol) and Adams' catalyst (22 mg, 0.1 mmol) in glacial acetic acid (5 mL) stirred under rt for 20 h. Column chromatography (20% ethyl acetate in petroleum ether) afforded the cage diol **24**.

White colour solid; Yield: 173 mg (84%); Mp: 116-118 °C; IR (neat, cm^{-1}): υ_{max} = 3314, 2952, 2867, 1450, 1277, 1168, 1145, 1087, 1042; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.89 (t, J = 4.1 Hz, 1H), 2.79 (q, J = 6.4 Hz, 1H), 2.72-2.59 (m, 3H), 2.55-2.46 (m, 2H), 2.31 (d, J = 11.9 Hz, 1H), 1.72 (t, J = 3.7 Hz, 1H), 1.66 (t, J = 3.7 Hz, 1H), 1.57 (s, 2H), 1.13 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 74.7, 56.7, 52.5, 46.9, 45.5, 42.4, 41.4, 40.2, 38.3, 35.4, 29.1, 23.7, 21.5; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{13}H_{18}KO_2$ $[M + K]^+$ 245.0938; found: 245.0936.

Cage hemiketal 25

Prepared according to the above general procedure using cage dione **19** (300 mg, 1.31 mmol) and Adams' catalyst (30 mg, 0.13 mmol) in glacial acetic acid (5 mL) stirred under rt for 20 h. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage hemiketal **25**.

White solid; Yield: 267 mg (87%); Mp: 110-112 °C; IR (neat, cm^{-1}): υ_{max} = 3454, 2972, 2962, 2864, 1639, 1457, 1368, 1329, 1213, 1053, 1002; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.85 (d, *J* = 4.4 Hz, 1H), 3.39 (s, 1H), 3.00-2.96 (m, 1H), 2.65-2.62 (m, 1H), 2.45 (t, *J* = 2.3 Hz, 2H), 1.95 (t, *J* = 3.8 Hz, 2H), 1.09 (s, 3H), 1.04 (s, 3H), 0.98 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 81.8, 54.3, 53.8, 52.9, 52.6, 51.7, 50.2, 48.0, 46.7, 44.9, 23.3, 20.4, 16.5, 11.6; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{20}KO_2$ $[M + K]^+$ 271.1095; found: 271.1093.

Cage dione 28

Prepared according to the above general procedure using cage dione **27** (100 mg, 0.5 mmol) and Adams' catalyst (11 mg, 0.05 mmol) in glacial acetic acid (5 mL) stirred under rt for 20 h. Recrystallization of the crude mixture from ethyl acetate in petroleum ether afforded the pure *gem*-dimethyl cage dione **28**.

Colourless crystalline solid; Yield: 92 mg (91%); Mp: 148-150 °C; IR (neat, cm^{-1}): υ_{max} = 2966, 2949, 1749, 1722, 1463, 1422, 1265, 1180, 1120, 1081; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.90 (s, 4H), 2.28-2.24 (m, 4H), 2.16-2.13 (m, 2H), 1.21 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 217.9, 58.4, 57.2, 46.3, 40.3, 38.2, 22.9, 20.1; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{13}H_{16}NaO_2$ $[M + Na]^+$ 227.1043; found: 227.1041.

Synthesis of *gem*-dimethyl cage diones 12 and 26: General procedure (PCC oxidation)

To a stirred solution of the cage diol **24** and cage hemiketal **25** (100 to150 mg, 0.48-0.64 mmol) in anhydrous DCM (10 mL) was added pyridinium chlorochromate (PCC, 5 equiv). Then, the reaction mixture was stirred for 8 h at room temperature under nitrogen atmosphere. After completion of the reaction by TLC monitoring, the reaction mixture was filtered on a Celite bed and washed twice with DCM (10 mL). The filtrate was evaporated under reduced pressure and the crude product was purified by column chromatography (on 100-200 mesh, silica gel) using an appropriate mixture of ethyl acetate in petroleum ether as an eluent system to furnish the *gem*-dimethyl cage diones **12** and **26**.

Cage dione 12

Prepared according to the above general procedure using cage diol **24** (100 mg, 0.48 mmol) and PCC (521 mg, 2.42 mmol) in anhydrous DCM (10 mL) stirred under rt for 8 h. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage dione **12.**

Colourless crystalline solid; Yield: 89 mg (91%); Mp: 176-178 °C; IR (neat, cm^{-1}): υ_{max} = 2948, 2861, 1736, 1464, 1369, 1052; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.33 (s, 2H), 2.90 (s, 2H), 2.82 (s, 2H), 2.35 (s, 2H), 1.13 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 212.1, 54.4, 53.5, 53.4, 43.7, 39.0, 23.1, 18.2; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{13}H_{14}NaO_2$ $[M + Na]^+$ 225.0886; found: 225.0886.

Cage dione 26

Prepared according to the above general procedure using cage hemiketal **25** (150 mg, 0.64 mmol) and PCC (695 mg, 3.22 mmol) in anhydrous DCM (10 mL) stirred under rt for 8 h. Column chromatography (8% ethyl acetate in petroleum ether) afforded the cage dione **26**.

Colourless crystalline solid; Yield: 127 mg (85%); Mp: 135-137 °C; IR (neat, cm^{-1}): υ_{max} = 2983, 2935, 1742, 1730, 1461, 1386, 1369, 1300, 1232, 1169, 1075, 1059, 875, 782; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.93 (d, *J* = 1.6 Hz, 4H), 2.27 (s, 2H), 1.09 (s, 3H), 1.03 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 213.9, 54.4, 54.1, 52.1, 50.1, 44.6, 22.9, 18.2, 11.7; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{18}NaO_2$ $[M + Na]^+$ 253.1199; found: 253.1200.

General procedure[12b, 13b]for Zn/AcOH promoted rearrangement of cage diones 19, **20, 23**, and **26**

A solution of cage ketones **19**, **20**, **23**, and **26** (0.43-2.00 mmol, 1 equiv) and activated zinc dust (20.0-1.73 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 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 ketones. The resulting crude residue was further purified by column chromatography on silica gel using an appropriate mixture of ethyl acetate in petroleum ether as an eluent to deliver the cage dione **27** and hydroxy ketones **32**, **33**, and **36** in good to excellent yields.

Cage dione 27[17]

Prepared according to the above general procedure using cage dione **23** (400 mg, 2.00 mmol) and activate Zn dust (1.30 g, 20.0 mmol) in glacial acetic acid (10 mL) under rt for overnight.

Recrystallization of the crude mixture from ethyl acetate in petroleum ether afforded the pure cage dione **27**.

Colourless crystalline solid; Yield: 328 mg (91%); Mp: 113-115 °C; (lit. 103-105 °C)[17]; ^{1}H-NMR ($CDCl_3$, 500 MHz): δ (ppm) = 2.91-2.88 (m, 4H), 2.32-2.29 (m, 2H), 2.20-2.15 (m, 4H), 0.74-0.71 (m, 2H), 0.66-0.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 217.8, 59.4, 53.8, 40.3, 39.5, 31.6, 5.6, 4.5.

Cage hydroxy ketone 32

Prepared according to the above general procedure using cage dione **19** (200 mg, 0.87 mmol) and activate Zn dust (230 mg, 3.50 mmol) in glacial acetic acid (5 mL) under rt for overnight. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage hydroxy ketone **32.**

Colourless crystalline solid; Yield: 172 mg (85%); Mp: 136-138 °C; IR (neat, cm^{-1}): υ_{max} = 3437, 3427, 2983, 2955, 2891, 1762, 1456, 1285, 1259, 1225, 1188, 1100, 1005, 983, 931, 865; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 2.55 (t, *J* = 5.6 Hz, 1H), 2.41 (t, *J* = 5.9 Hz, 1H), 2.33 (d, *J* = 5.9 Hz, 2H), 2.08-2.06 (m, 2H), 1.90 (d, *J* = 4.3 Hz, 1H) 1.82 (s, 1H), 1.11 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.59-0.51 (m, 2H), 0.48-0.41 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 217.4, 84.8, 53.1, 52.7, 52.2, 50.3, 50.1, 49.2, 47.0, 45.7, 34.0, 12.7, 10.5, 6.0, 5.3; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{18}NaO_2$ $[M + Na]^+$ 253.1199, found: 253.1199.

Cage hydroxy ketone 33

Prepared according to the above general procedure using cage dione **20** (150 mg, 0.58 mmol) and activate Zn dust (153 mg, 2.34 mmol) in glacial acetic acid (5 mL) under rt for overnight. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage hydroxy ketone **33**.

Colourless crystalline solid; Yield: 119 mg (78%); Mp: 118-120 °C; IR (neat, cm^{-1}): υ_{max} = 3432, 2956, 2943, 1759, 1267, 1050; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.46-2.42 (m, 1H), 2.32-2.27 (m, 3H), 2.14-2.04 (m, 3H), 1.73-1.62 (m, 4H), 1.52-1.38 (m, 5H), 1.11 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 217.2, 84.6, 58.7, 56.0, 52.8, 52.3, 49.7, 49.1, 49.0, 48.9, 45.9, 33.1, 31.3, 26.19, 26.15, 12.8, 10.5; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{17}H_{22}NaO_2$ $[M + Na]^+$ 281.1512, found: 281.1512.

Cage hydroxy ketone 36

Prepared according to the above general procedure using cage dione **29** (100 mg, 0.43 mmol) and activate Zn dust (113 mg, 1.73 mmol) in glacial acetic acid (5 mL) under rt for overnight. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage hydroxy ketone **36**.

Colourless crystalline solid; Yield: 76 mg (75%); Mp: 112-114 °C; IR (neat, cm^{-1}): υ_{max} = 3450, 3420, 2969, 2877, 1757, 1471, 1383, 1368, 1291, 1273, 1251, 1217, 1107, 1073, 1054, 949, 878; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.52-2.48 (m, 1H), 2.40-2.35 (m, 3H), 2.07-2.00 (m, 2H), 1.91 (s, 1H), 1.84 (s, 1H), 1.11 (s, 3H), 1.07 (d, J = 7.1 Hz, 3H), 0.97 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 217.5, 84.6, 56.4, 55.6, 53.0, 52.6, 50.1, 49.3, 48.4, 47.2, 45.6, 23.1, 20.9, 12.8, 10.5; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{20}NaO_2$ $[M + Na]^+$ 255.1356, found: 255.1358.

Synthesis of cage hemiketal 29, **cage diols 30**, **31**, **34**, **35**, **and 37: General procedure[12b, 13b] ($NaBH_4$ reduction)**

To a mechanically stirred solution of cage ketones **19**, **20**, **26**, **32**, **33**, and **36** (0.49-0.21 mmol) in dry methanol (10 mL), $NaBH_4$ (4 equiv) was added at 0 °C in small portions over a period of 10 min. Later on, the reaction mixture was stirred for another 20-30 min at room temperature. 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 obtained crude residues were purified by column chromatography (on 100-200 mesh silica gel) using an appropriate mixture of ethyl acetate in petroleum ether as an eluent to deliver the cage hemiketal **29** and diols **30**, **31**, **34**, **35**, and **37**.

Cage hemiketal 29

Prepared according to the above general procedure using cage dione **28** (100 mg, 0.49 mmol) and $NaBH_4$ (74 mg, 1.95 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (25% ethyl acetate in petroleum ether) afforded the cage hemiketal **29**.

Colourless crystalline solid; Mp: 94-96 °C; Yield: 83 mg (82%); IR (neat, cm^{-1}): υ_{max} = 3349, 2955, 2942, 1463, 1339, 1280, 1246, 1166, 1129, 1071, 1003, 983, 937, 841; ^{1}H NMR (400

MHz, $CDCl_3$): δ (ppm) = 4.62 (t, *J* = 6.5 Hz, 1H), 3.08-3.02 (m, 1H), 2.99 (s, 1H), 2.56-2.52 (m, 1H), 2.44 (s, 2H), 2.08 (d, *J* = 13.4 Hz, 1H), 2.00 (d, *J* = 3.9 Hz, 1H), 1.90 (dd, *J* = 13.4, 4.5 Hz, 1H), 1.84 (d, *J* = 14.3 Hz, 1H), 1.73 (d, *J* = 3.9 Hz, 1H), 1.64-1.58 (m, 1H), 1.07 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 115.3, 80.8, 59.0, 58.8, 56.7, 53.4, 49.9, 43.3, 41.8, 40.9, 37.8, 23.1, 22.5; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{13}H_{18}NaO_2$ $[M + Na]^+$ 229.1199; found: 229.1193.

Cage diol 30

Prepared according to the above general procedure using cage dione **19** (50 mg, 0.22 mmol) and $NaBH_4$ (33 mg, 0.87 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (15% ethyl acetate in petroleum ether) afforded the cage diol **30**.

Colourless liquid; Yield: 41 mg (81%); IR (neat, cm^{-1}): υ_{max} = 3192, 2953, 2867, 1459, 1350, 1258, 1241, 1134, 1111, 1083, 1058, 990, 962; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.77 (s, 2H), 3.32 (s, 2H), 2.53 (s, 2H), 2.22 (s, 2H), 1.53 (s, 2H) 1.10 (s, 6H), 0.48-0.42 (s, 2H), 0.27-0.20 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 77.9, 47.8, 46.7, 45.5, 45.4, 31.4, 18.2, 5.1, 4.4; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{20}NaO_2$ $[M + Na]^+$ 255.1356; found: 255.1358.

Cage diol 31

Prepared according to the above general procedure using cage dione **20** (75 mg, 0.29 mmol) and $NaBH_4$ (44 mg, 1.17 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (20% ethyl acetate in petroleum ether) afforded the cage diol **31.**

Colourless liquid; Yield: 63 mg (83%); IR (neat, cm^{-1}): υ_{max} = 3345, 3244, 3162, 2936, 2853, 1463, 1216, 1107; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 4.22 (s, 2H), 3.38 (s, 2H), 2.50 (s, 2H), 2.19 (s, 2H), 1.83 (s, 2H), 1.58-1.39 (s, 6H), 1.18-1.13 (m, 8H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 78.2, 57.5, 49.9, 46.0, 45.4, 44.8, 32.3, 29.8, 25.8, 25.6, 18.3 ppm; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{17}H_{24}NaO_2$ $[M + Na]^+$ 283.1669; found: 283.1668.

Cage diol 34 (*D*$_3$-Trishomocubanediol)

Prepared according to the above general procedure using cage hydroxy ketone **32** (100 mg, 0.43 mmol) and $NaBH_4$ (65 mg, 1.73 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (30% ethyl acetate in petroleum ether) afforded the cage diol **34**.

Colourless crystalline solid; Mp:181-183 °C; Yield: 89 mg (88%); IR (neat, cm^{-1}): υ_{max} = 3346, 3328, 2972, 2954, 1361, 1344, 1287, 1244, 1197, 1156, 1080, 1061, 1049, 1006; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) = 3.92 (s,1H), 2.37 (d, *J* = 4.9 Hz, 1H), 2.10-2.06 (m, 4H), 1.86 (q, *J* = 7.1 Hz, 1H), 1.60 (s, 3H), 1.16 (s, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 0.47-0.44 (m, 2H), 0.39-0.37 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 87.1, 80.1, 56.4, 52.4, 52.1, 51.6, 51.0, 49.1, 48.3, 45.1, 31.5, 13.4, 12.7, 5.7, 5.3; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{20}NaO_2$ $[M + Na]^+$ 255.1356, found: 255.1353.

Cage diol 35 (D_3-Trishomocubanediol)

Prepared according to the above general procedure using cage dione cage hydroxy ketone **33** (100 mg, 0.38 mmol) and $NaBH_4$ (58 mg, 1.54 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (25% ethyl acetate in petroleum ether) afforded the cage diol **35.**

Colourless crystalline solid; Mp: 199-201 °C; Yield: 81 mg (80%); IR (neat, cm^{-1}): υ_{max} = 3363, 2928, 2851, 1456, 1402, 1185, 1050; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.90 (d, *J* = 1.9 Hz, 1H), 2.33 (t, *J* = 5.4 Hz, 2H), 2.05-1.96 (m, 3H), 1.86 (q, *J* = 7.1 Hz, 2H), 1.63-1.61 (m, 2H), 1.52 (s, 3H), 1.44-1.41 (m, 5H), 1.14 (s, 3H), 1.05 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 86.8, 80.2, 55.9, 55.7, 55.49, 55.45, 51.2, 49.8, 48.5, 47.6, 45.1, 33.1, 32.4, 26.26, 26.21, 13.3, 12.7; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{17}H_{24}NaO_2$ $[M + Na]^+$ 283.1669, found: 283.1668.

Cage diol 37 (D_3-Trishomocubanediol)

Prepared according to the above general procedure using cage hydroxy ketone **36** (50 mg, 0.21 mmol) and $NaBH_4$ (32 mg, 0.86 mmol) in methanol (10 mL) under 0 °C to rt for 30 min. Column chromatography (50% ethyl acetate in petroleum ether) afforded the cage diol **37**.

Colourless crystalline solid; Mp: 163-165 °C; Yield: 39 mg (77%); IR (neat, cm^{-1}): υ_{max} = 3420, 3355, 2969, 1242, 1217, 1053, 1032; ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.91 (d, *J* = 2.2

Hz, 1H), 2.43-2.42 (m, 1H), 2.20-2.16 (m, 2H), 2.09 (t, *J* = 5.6 Hz, 1H), 2.03 (t, *J* = 5.5 Hz, 1H), 1.84 (q, *J* = 7.1 Hz, 1H), 1.75-1.74 (m, 1H), 1.14 (s, 3H), 1.06 (d, *J* = 7.3 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ (ppm) = 86.7, 80.2, 55.9, 55.86, 55.82, 51.4, 49.1, 48.7, 47.0, 44.8, 44.4, 23.2, 22.5, 13.4, 12.8; HRMS (ESI/Q-ToF): *m/z* calcd for $C_{15}H_{22}NaO_2$ $[M + Na]^+$ 257.1512, found: 257.1511.

Notes

The authors declare no competing financial interests.

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Appendix A. Supplementary data

The supporting information is available free of charge on the journal website. Copies of ^{1}H, ^{13}C, ^{13}C-APT, DEPT-135 NMR spectral plots of all new products and X-Ray data of products **12**, **25**, and **34** (refinement data and ORTEP diagrams) are available in supplementary information (SI) file.

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(19) CCDC 1908378 (**12**), CCDC 1908389 (**25**), and CCDC 1919869 (**34**) of rearranged compounds contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For ORTEPs of products **12**, **25**, and **34**, please see the SI file.

Design, Synthesis, and Rearrangement Studies of *Gem*-dimethyl Containing Cage Systems

Highlights

- A short synthetic route to Gem-dimethyl substituted cage frameworks and D_3-trishomocubane derivatives have been established by metal-mediated reductive cleavage.
- These PCUD cage frameworks were assembled by starting with commercially available materials such as 2,3-dimethylhydroquinone, PtO_2, Zn dust/AcOH, and *endo*-dicyclopentadiene.
- The design of *gem*-dimethyl substituents at 7^{th} position of the norbornane ring in PCUD system requires lengthy synthetic sequence by conventional approach.
- These *gem*-dimethyl substituted cage frameworks may function as a promising candidates for high energy density materials.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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