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Molecular acrobatics in polycyclic frames: Synthesis of functionalized D_3-trishomocubanes via rearrangement approach

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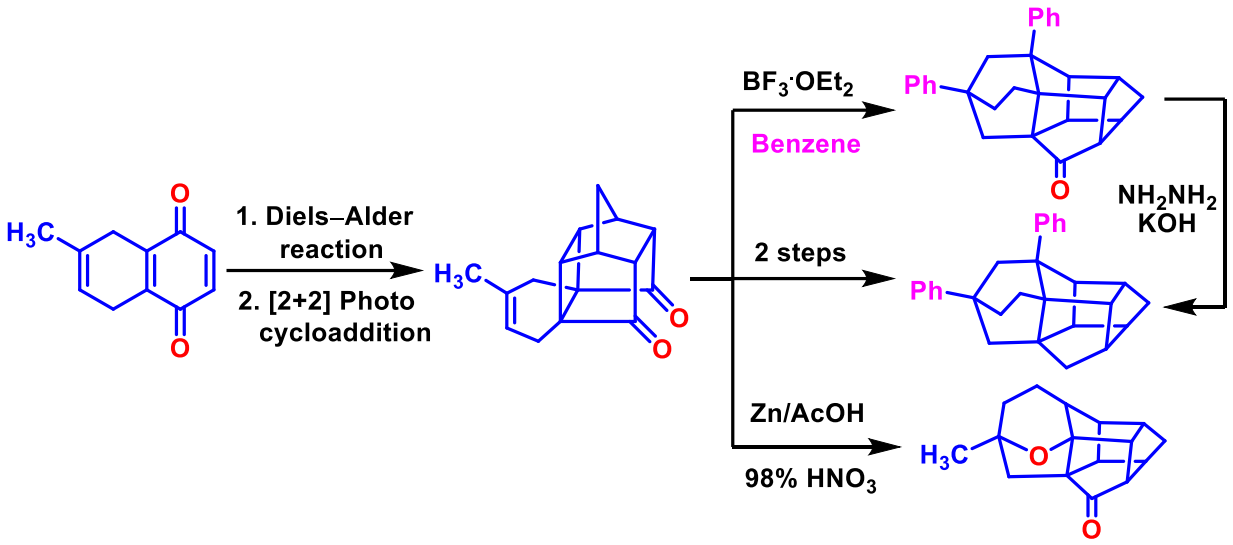
Abstract



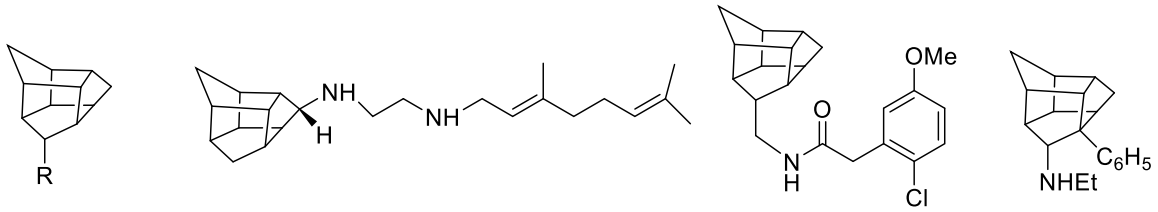
A new synthetic route to D_3-trishomocubanone and oxa- D_3-trishomocubane derivatives has been established by rearrangement approach. Remotely located methyl substituent in the six membered ring contributed to the acid catalyzed rearrangement of cage dione in an unusual fashion. This rearrangement approach provided an attractive route to extended D_3-trishomocubanes which are not accessible by conventional multi-step synthetic sequence. For the first time, two phenyl groups were incorporated from the solvent in strained trishomocubane skeleton in an unprecedented manner via carbocation-mediated rearrangement with the aid of $BF_3{\cdot}OEt_2$. Interestingly, oxa-bridged trishomocubane skeleton was also formed during acid-promoted rearrangement.

Introduction

D_3-Trishomocubane **1** ($C_{11}H_{14}$) is known to be a stable hydrocarbon with a planar chiral cage structure with a high degree of symmetry.[1-2] Its enhanced lipophilicity, propeller chirality combined with extended cage size (5.5 Å) and a rigid architecture makes it a worthwhile scaffold

for further investigation. Several trishomocubane derivatives show improved pharmacokinetic properties as drugs and they are also useful substrates for organocatalysis.[3-5]

Functionalized trishomocubane [6,7] has attracted the attention of synthetic chemists because of their significant biological activities. For example, amino substituted trishomocubane derivatives show prominent pharmacological properties against tuberculosis, neurodegenerative, and anti-viral diseases. [6,7] Moreover, amino derivatives, such as trishomocubyl 1-4-amine **2** [8] acts as NMDA receptor antagonist, trishomocubyl derivative **3** [9] shows potent anti-TB activity, D_3-trishomocubyl benzamide **4** [10] acts as P2X7 receptor antagonist, and substituted trishomocubylamine **5** [11] exhibits anti-Parkinson activity (Figure 1).



1; R = H; (D_3-Trishomocubane)
2; R = NH_2

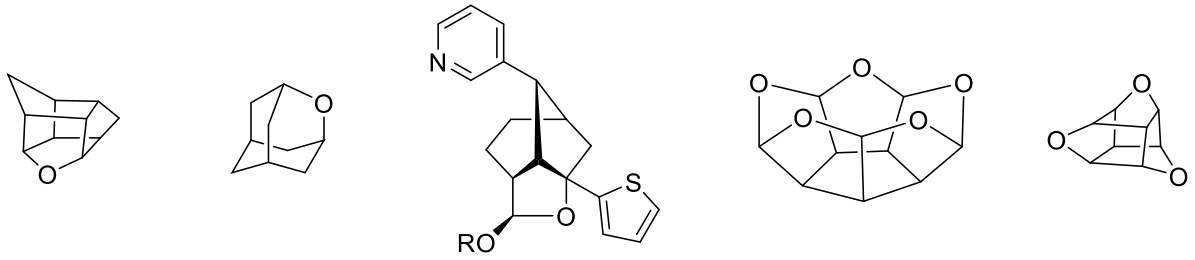
3 **4** **5**

Figure 1. Examples of biologically active D_3-trishomocubane derivatives

Several methodologies have been developed to design D_3-trishomocubane and its derivatives based on rearrangement strategies.[12] Recently, Sharapa *et al*. reported chloro-D_3-trishomocubane derivatives via Diels–Alder (DA) reaction followed by chlorosulfation of Cookson's dione.[13] In view of our continued interest in cage polycyclic systems,[14] we developed a new synthetic approach to D_3-trishomocubane derivatives via Lewis acid-catalyzed rearrangement starting with cage [4.3.2]propellane system.[14d] Additionally, we also described a unique method to oxa-cage propellanes via ring-closing metathesis (RCM) strategy.[15] Now, we report a new synthetic strategy to functionalized trishomocubanes and oxa-trishomocubane by acid-promoted rearrangement. We have included selected examples of recently reported oxa-cage frameworks **6-10** (Figure 2).[16]

In view of the ring strain and rigid architecture, cage moiety containing 1,4-dicarbonyl system is a suitable substrate for ring-rearrangement, ring-fragmentation and ring-opening approaches by acid, or metal catalysts. [17] Most of the acid-catalyzed rearrangements in polycyclic cage systems are generally driven by a concomitant release of strain via formation of a stable carbocation

intermediate which play a prominent role in assembling unusual cage frameworks in an unprecedented manner.

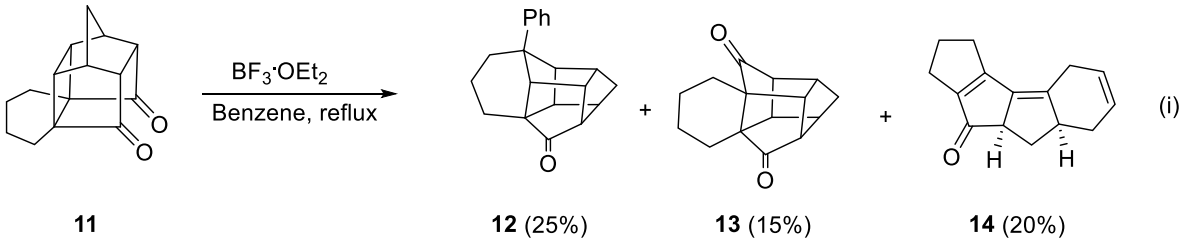


6 **7** **8** **9** **10**

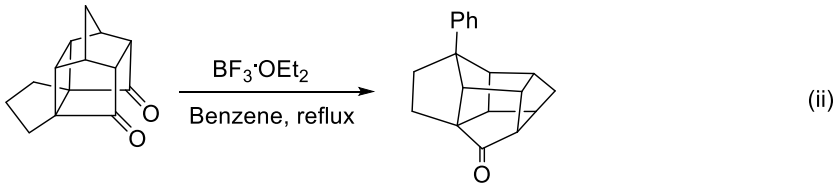
Figure 2. Some representative oxa-cages reported in the literature by rearrangement approach

Scheme 1. $BF_3{\cdot}OEt_2$-Promoted rearrangement approach to various polycycles.

Previous works[14d,18]

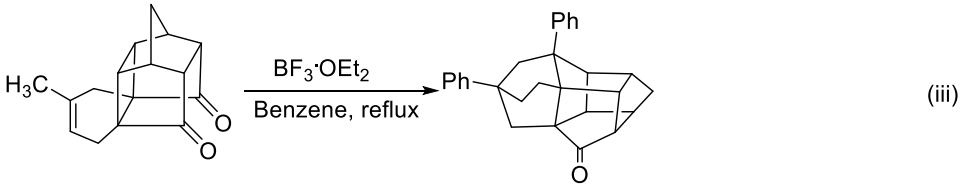


11 **12** (25%) **13** (15%) **14** (20%)



15 **16** (60%)

This work



17 **18** (53%)

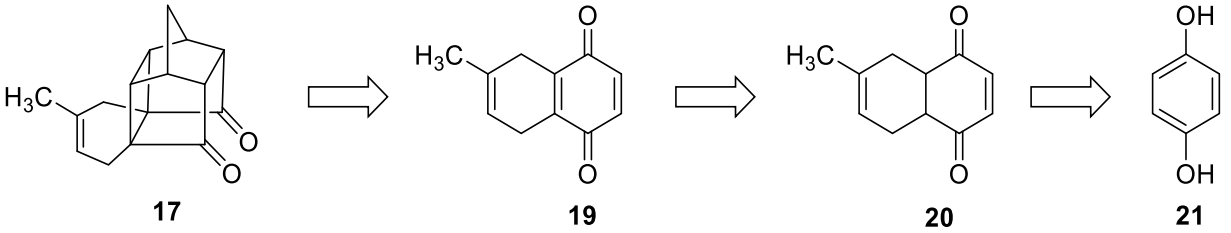
In view of our recent report on the rearrangement of the [4.3.2]propellane derivative **15** under Lewis acid conditions, [14d] now, we studied the rearrangement of the unsaturated cage

[4.4.2]propellane **17** containing methyl substituent in cyclohexene ring to generate the D_3-trishomocubane derivative **18** involving a carbocation rearrangement.

Results and Discussion

Previously (Scheme 1, eq i), [18] the Lewis acid promoted rearrangement of the compound **11** was studied with $BF_3{\cdot}OEt_2$ in benzene to deliver compounds **12**, **13** and **14**. Recently, [14] we also reported (Scheme 1, eq ii) a carbocation-mediated rearrangement of the cage [4.3.2]propellanedione **15** using $BF_3{\cdot}OEt_2$ in benzene under reflux conditions to produce the ketone **16** in a moderate to good yield. Now, we disclose an interesting and unusual ring rearrangement approach to the trishomocubane derivatives starting with a substituted cage dione **17** (Scheme 1, eq iii) with the aid of Lewis acid such as $BF_3{\cdot}OEt_2$. Here, the methyl substituent located in one of the unsaturated cyclohexane ring in cage dione **17** play a critical role in the carbocation formation and incorporation of two phenyl groups by the ring rearrangement process is unexpected with the aid of Lewis acid.

Scheme 2. Retrosynthetic analysis of hexacyclic cage dione 17

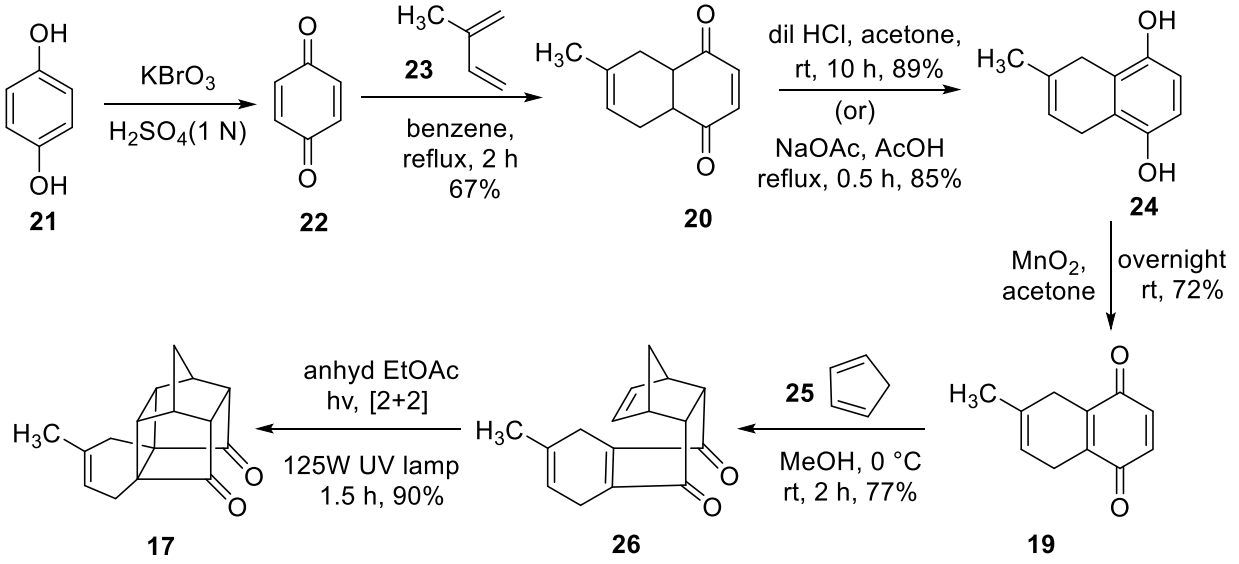


Our retrosynthetic analysis to hexacyclic dione **17** is shown in Scheme 2. In this regard, the synthesis of the cage dione **17** may be accomplished from dihydronaphthalene-1,4-dione **19** upon Diels–Alder reaction (DA) followed by a [2+2] photocycloaddition of the cycloadduct. The DA precursor **19** may be assembled from the tetrahydronaphthalene-1,4-dione **20** via aromatization followed by oxidation. Finally, the required cycloadduct **20** could readily be prepared starting with commercially available hydroquinone **21** in two steps involving a [4+2] cycloaddition and oxidation sequence.

To realize the strategy shown in Scheme 2, our journey towards the synthesis of the hexacyclic dione **17** was commenced with the preparation of the DA precursor such as the dihydronaphthalene-1,4-dione **19** from inexpensive and commercially available hydroquinone

21[19] (Scheme 3). In this context, [4+2] cycloaddition of 1,4-benzoquinone **22** prepared from the hydroquinone **21** was treated with 2-methyl 1,3-butadiene **23** (isoprene) under reflux conditions in anhydrous benzene to deliver the cycloadduct **20** in good yield (67%). Aromatization of the DA adduct **20** in the presence of dil. HCl at room temperature furnished the 1,4-naphthalenediol **24** in 89% yield. Alternatively, the diol **24** was also prepared from the enone **20** in 85% yield by aromatization in the presence of NaOAc and AcOH under reflux conditions.[19] Subsequently, oxidation of the hydroquinone **24** in the presence of MnO_2 delivered the quinone **19** in 72% isolated yield after column chromatography (Scheme 3).[19]

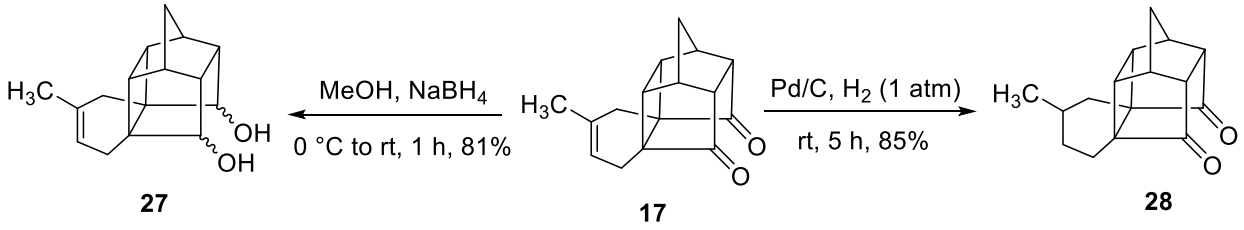
Scheme 3. Synthesis of hexacyclic cage dione 17



Having prepared the DA precursor **19**, our attention was directed to assemble the cage dione **17** using [4+2] cycloaddition[20] and intramolecular [2+2] photocycloaddition[21] as key steps. To this end, [4+2] cycloaddition of the quinone derivative **19** was accomplished by reacting with a freshly cracked 1,3-cyclopentadiene **25** at 0 °C to furnish the desired cycloadduct **26** in 77% yield. The structure of the DA adduct **26** was established on the basis of ^{1}H NMR, ^{13}C NMR spectroscopic evidence and further supported by the HRMS data. The stereochemistry of the cycloadduct **26** was found to be *endo* and it was confirmed later by an intramolecular [2+2] photocycloaddition reaction. The DA adduct **26** underwent intramolecular [2+2] photocycloaddition by irradiation with UV light (125 W-homemade) gave the hexacyclic cage dione **17** in 90% yield (Scheme 3).

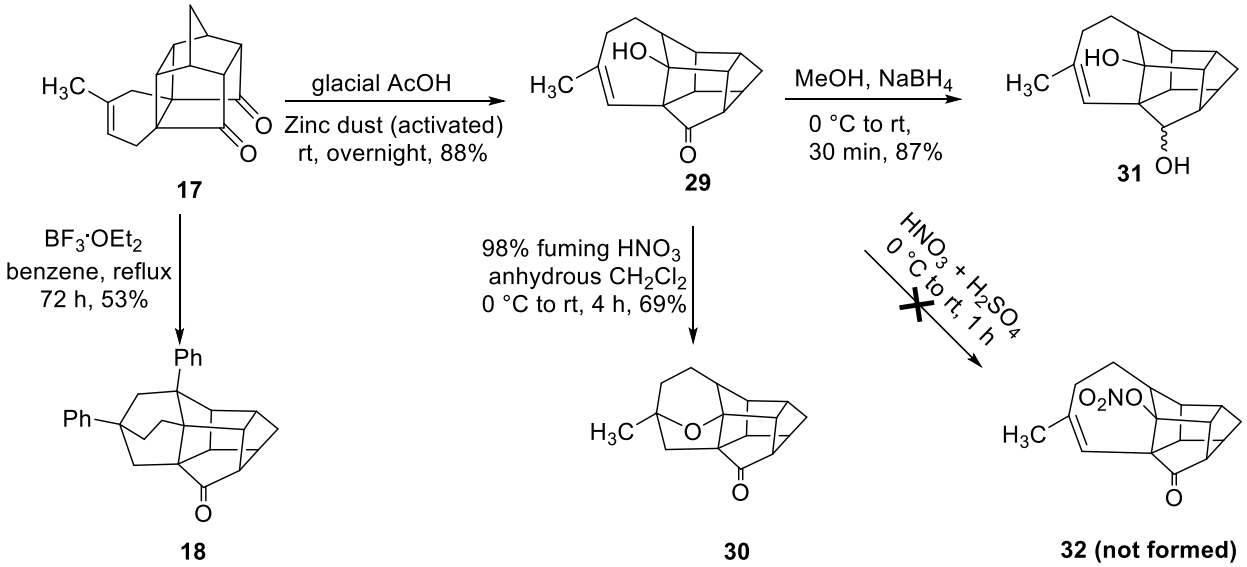
The structure of the cage dione **17** was established on the basis of ^{1}H NMR, ^{13}C NMR, APT, and further supported by HRMS data.

Scheme 4. Synthesis of hexacyclic cage diol 27 and cage dione 28 by reduction



Having the cage dione **17** in hand, we next attempted the synthesis of cage diol **27** as well as saturated hexacyclic dione **28** by reduction. In this regard, the cage dione **17** was treated with $NaBH_4$ in methanol to produce the cage diol **27** in 81% yield. Along similar lines, hydrogenation of the cage dione **17** in the presence of 10% Pd/C in dry ethyl acetate delivered the saturated dione **28** in 85% yield (Scheme 4). Structures of the cage diol **27** and hexacyclic dione **28** were confirmed by spectroscopic and analytical data (^{1}H NMR, ^{13}C NMR, APT and HRMS).

Scheme 5. Synthesis of cage ketone 18 and oxa-cage ketone 30 via acid catalyzed rearrangement



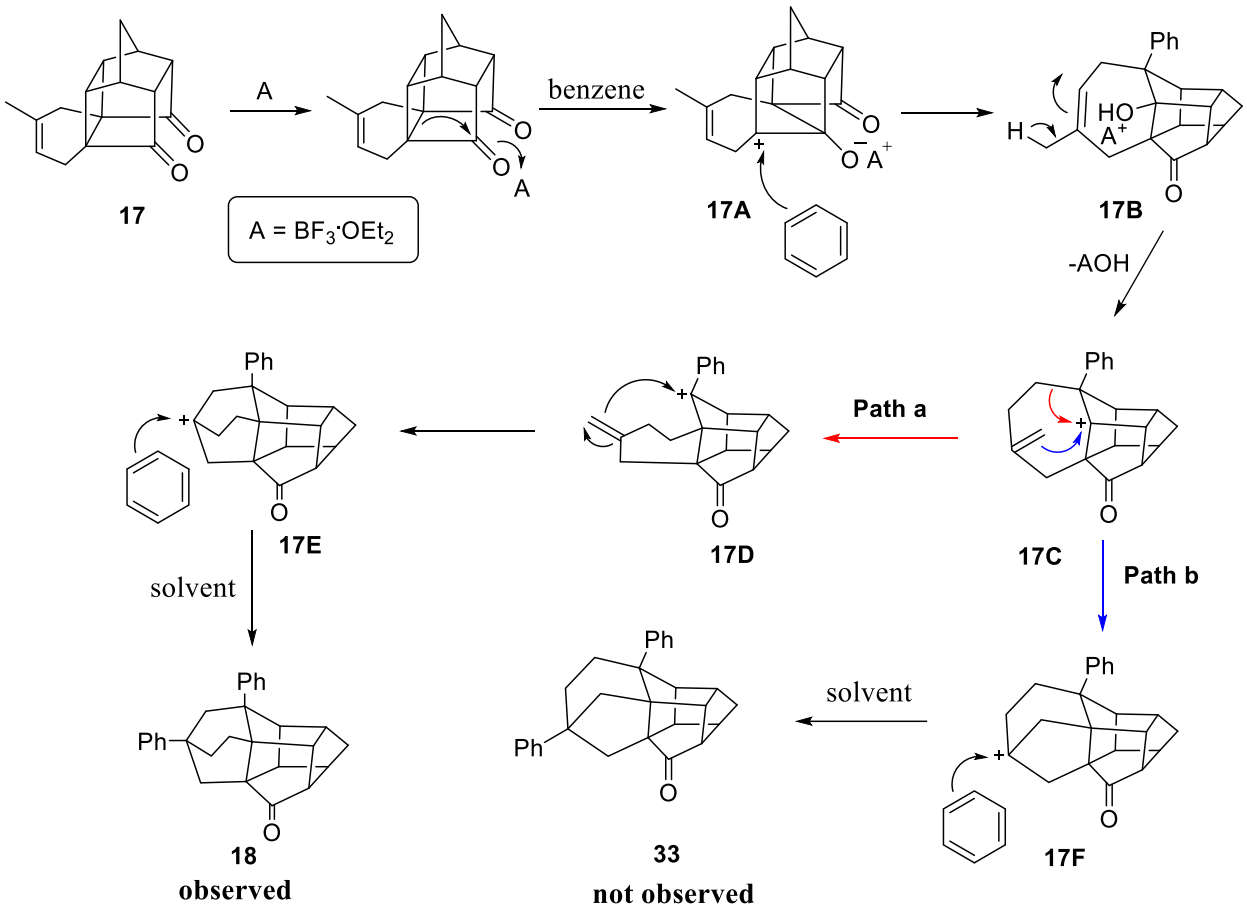
In view of our interest to design new polycyclic systems via rearrangement approach, the cage dione **17** was treated with $BF_3{\cdot}OEt_2$ in anhydrous benzene under reflux conditions. We found that the rearranged cage ketone **18** (trishomocubanone) was produced in moderate yield (Scheme 5). The solvent incorporated product **18** was derived by an extensive reorganization of carbon skeleton

of the strained [4.4.2]propellane framework **17** through the generation of carbocation intermediates. The carbocation intermediate generated in the sequence incorporate the two phenyl groups from the solvent (benzene). Initially, the structure of the rearranged ketone **18** (D_3-trishomocubanone) was indicated by the spectral data and later it was confirmed by its single-crystal X-ray diffraction data (see the Supporting Information).[22]

To create diverse frameworks by rearrangement approach, our efforts are also diverted towards the synthesis of D_3-trishomocubane derivatives via a reductive C-C bond cleavage reaction. In this regard, the 1, 4-dicarbonyl system adjacent to the cyclobutane ring present in the cage dione **17** has a tendency to undergo rearrangement in the presence of metal/ acid media to release the ring strain. Therefore, the reductive cleavage of C-C bond present in cage dione **17** was carried out using activated zinc powder in glacial acetic acid at room temperature. After overnight stirring the rearranged hydroxyketone **29** was formed in 88% yield (Scheme 5). The structure of the hydroxyketone **29** was established on the basis of ^{1}H NMR and ^{13}C NMR, APT, DEPT-135 and HRMS data. Based on the spectroscopic data of the compound **29,** it appears that, it is an inseparable mixture of two compounds such as **29** and **34** (Schemes 5 & 7).

Later on, the hydroxyketone **29** was treated with 1:1 Conc.H_2SO_4 + Conc.HNO_3 mixture to produce the nitrito derivative **32**. Unfortunately, the desired nitrito derivative **32** was not formed. Interestingly, unexpected oxa-derivative **30** was obtained instead of the nitrito derivative **32** in poor yield. Then the yield of oxa-cage compound **30** was improved (69%) by treatment with HNO_3 in anhydrous CH_2Cl_2. To the best of our knowledge, this is the first observation where oxa-bridged cage frame work **30** was assembled by nitric acid (HNO_3) treatment. The structure of the oxa-cage compound **30** was conformed on the basis of ^{1}H NMR, ^{13}C NMR, APT, and HRMS data. DEPT 135 NMR spectrum of cage ether **30** indicates the disappearance of two distinctive signals at δ = 89.9 and 96.3 which are quaternary carbons and both of them are connected to an oxygen atom (ether linkage). This data indicates that the two carbons are joined through a bridgehead oxygen atom. Further, we unambiguously confirmed the structure of the oxa derivative **30** by a single-crystal X-ray diffraction studies (see the Supporting Information).[22] Next, the hydroxyketone **29** was converted to the corresponding cage diol **31** in 87% yield by treatment with $NaBH_4$ in methanol at 0 °C to rt (Scheme 5).

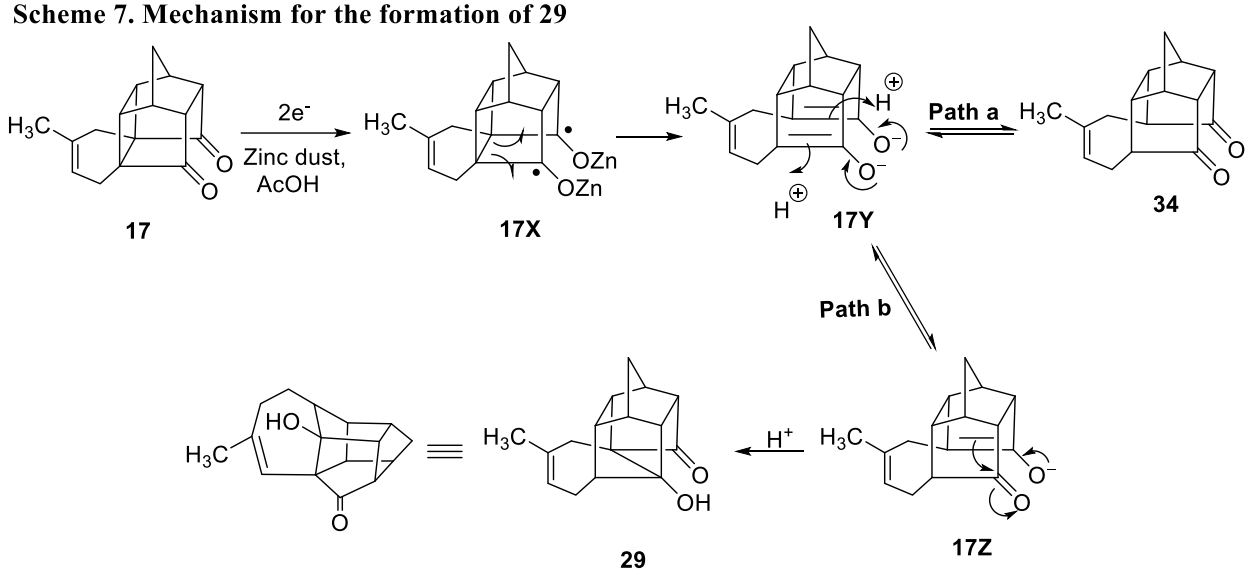
Scheme 6. Proposed mechanism for the rearrangement of cage dione 17 to cage ketone 18



Based on the earlier Lewis acid catalyzed rearrangements with $BF_3.OEt_2$,[14d,18] the proposed mechanism for the transformation of cage dione **17** to the rearranged ketone **18** is shown in Scheme 6. Initially, coordination of the Lewis acid to the ketone of cage dione **17** would generate carbocation intermediate **17A** via the migration of cyclobutane bond adjacent to the carbonyl carbon. The carbocation **17A** is captured by solvent (benzene) and subsequent aromatization affords the intermediate **17B**. Later, elimination of AOH followed by involvement of the olefin from methyl group in **17B** in the presence of $BF_3.OEt_2$ gives another carbocation **17C**. Intermediate **17C** may cyclize in two different modes (path a & b) to form the carbocation **17D** and **17F** through the migration of alternate C-C bonds as shown in Scheme 6. Intermediate **17D** is a highly resonance-stabilized benzylic carbocation, which follows the path a to generate the carbocation

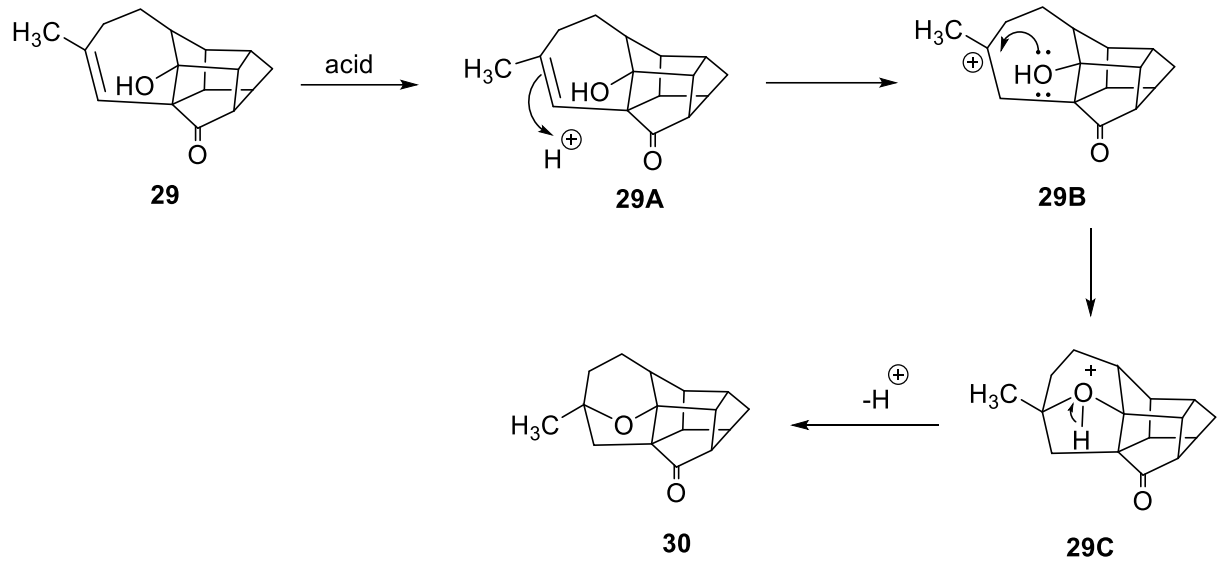
intermediate **17E** and trapped with benzene to furnish the rearranged cage ketone **18**. **17F** is expected to deliver the compound **33**.

Scheme 7. Mechanism for the formation of 29



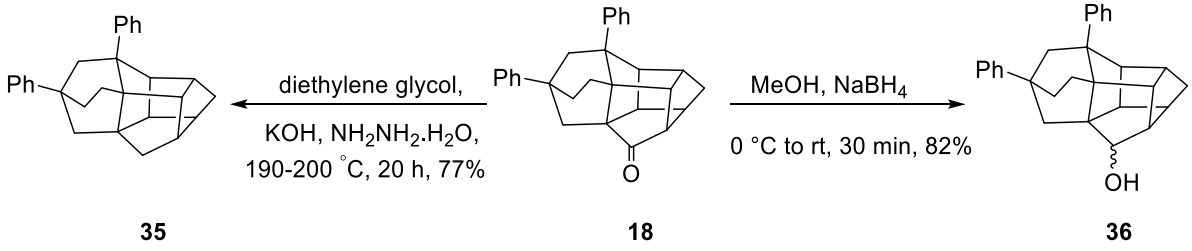
Based on earlier studies, [17e] and our experimental results, we have proposed a possible mechanism for the formation of hydroxyketone **29** (Scheme 7). The reaction was initiated by activated Zn in AcOH to form a diradical species **17X.** Later, cleavage of strained cyclobutane ring generates the dianion intermediate **17Y**. In path a, the dianion **17Y** involved in enolization (keto-enol tautomerism) to produce the cage dione **34.** In path b, the intermediate **17Y** underwent enolization gave **17Z** followed by cyclization to afford the hydroxyketone (internal aldol product) **29**.

Scheme 8. A Plausible mechanism for formation of 30



A proposed mechanism for the formation of cyclic ether **30** from compound **29** is illustrated in Scheme 8. Initially, in the presence of nitric acid, a stable carbocation intermediate **29B** is generated**.** Further the intermediate **29B** on cyclization gave the oxa-bicyclic cage system **30** through **29C.**

Scheme 9. Synthesis of D_3- trishomocubane 35 and D_3- trishomocubanol 36



Having established a new strategy to trishomocubanone **18**, we next focused our attention to prepare other D_3-trishomocubane derivatives such as **35** and **36**. In this regard, compound **18** was subjected to Wolff–Kishner reduction in the presence of hydrazine hydrate under basic condition at 200 °C in diethylene glycol to produce the corresponding cage hydrocarbon **35** in 77% yield. Finally, trishomocubanol **36** was obtained as a diastereomeric mixture in 82% yield from trishomocubanone **18** by the treatment of $NaBH_4$ in methanol (Scheme 9). The structure of these

two compounds **35** and **36** were established from ^{1}H NMR and ^{13}C NMR, APT, DEPT-135, and further supported from HRMS data. The structure of the cage hydrocarbon (D_3-trishomocubane) **35** has been firmely established from the DEPT-135 NMR spectrum, which clearly indicates the presence of six -CH_2 -groups in aliphatic region clearly indicate that the carbonyl group has been reduced to methylene group.

Conclusions

In conclusion, we have successfully demonstrated a new synthetic strategy to functionalized D_3-trishomocubane derivatives via carbocation-mediated rearrangement under acidic conditions such as Zn/AcOH, fuming HNO_3 and $BF_3{\cdot}OEt_2$. For the first time, two phenyl groups were incorporated from the solvent in strained trishomocubanone system **18** in an unprecedented manner via Lewis acid catalyzed rearrangement with the help of $BF_3{\cdot}OEt_2$. Surprisingly, we also isolated oxa-trishomocubane derivative **30** through carbocation generation starting with cage dione **17**. Oxygenated trishomocubane system containing fused tetrahydropyran and tetrahydrofuran was generated with the aid of fuming HNO_3. It looks like that, the ring-rearrangement of cage dione **17** to trishomocubane framework is driven by a concomitant release of strain due to involvement of most stable carbocation intermediate through an acid-catalyzed rearrangement. In this strategy, we reported six new substituted D_3-trishomocubane derivatives along with three cage compounds. Further efforts to obtain interesting and unusual cage systems by rearrangement approach are currently in progress.

EXPERMENTAL SECTION

General Experimental Details

All the required reagents, chemicals and solvents were purchased from the commercial suppliers and used as without any further purification. Analytical TLC was performed on (10×5) glass plates coated with Acme's silica gel (GF-254) containing 13% calcium sulfate as a binder. All the 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 $KMnO_4$. Dry reactions were performed in oven dried glassware under nitrogen atmosphere by using standard syringe-septum techniques. Acme's silica gel (100-200 mesh size) and neutral alumina was used for column

chromatography and solvents were concentrated under vacuo on rotary evaporator. Benzene and DCM were distilled from P_2O_5 or CaH_2 and ethyl acetate was dried by using 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 DCM 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. All reported yields are isolated yields of the products after column purification. X-ray data were recorded on diffractometer equipped with graphite monochromated Mo Kα radiation and structure was solved by direct methods shelxl-97 and refined by full-matrix least-squares against F^2 using shelxl-97 software.

6-Methyl-4a,5,8,8a-tetrahydronaphthalene-1,4-dione (20)[19]

To a solution of 1,4-benzoquinone **22** (2g, 18.5 mmol) in anhydrous benzene (20 mL) was added 2-methyl-1,3-butadiene **23** (2.8 mL, 28 mmol) at room temperature. Later on, the resulting reaction mixture was stirred at 50 °C until all the starting material was consumed. After the reaction was completed (2.5 h, TLC analysis), the solvent was evaporated under vacuo and the crude residue was crystallized from petroleum ether and ethyl acetate (4:1) to afford the adduct **20** as a pure yellow crystalline solid.

Yield: 67% (2.2 g); mp 73-75 °C; (lit. reported [19] mp. 78-83 °C), IR (neat, cm^{-1}) 2932,2352, 1686, 1659, 1451, 1307, 1268, 1090, 942, 883, 854; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.62 (d, *J* = 5.1 Hz, 2H), 5.35 (d, *J* = 1.3 Hz, 1H), 3.22 (t, *J* = 5.27 Hz, 1H), 3.14 (t, *J* = 5.70 Hz, 1H), 2.42-2.34 (m, 2H), 1.64 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 200.4, 200.0, 139.4, 136.6, 131.7, 118.4, 46.9, 46.2, 28.8, 24.7, 23.4 ppm.

6-Methyl-5,8-dihydronaphthalene-1,4-diol (24) [19]

Method 1

To a stirred solution of compound **20** (1g, 5.7 mmol) in glacial acetic acid (10 mL), NaOAc (47 mg, 0.57 mmol) was added and the reaction mixture was heated at reflux for 1 h. After completion of the reaction (monitored by TLC), the cooled reaction mixture was poured in water and extracted with ethyl acetate. The combined organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the resulting brown colour residue was purified by column chromatography (silica gel, petroleum ether/EtOAc, 3:1) to give aromatized hydroquinone **24** as a white colour solid. Yield: 85% (850 mg).

Method 2

To a stirred solution of compound **20** (1g, 5.7 mmol) in acetone was treated with dil. HCl (20 mL) at room temperature for overnight. At the end of the reaction (monitored by TLC), the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The obtained crude residue was purified by silica gel column chromatography (petroleum ether/EtOAc, 3:1) to afford aromatized hydroquinone **24** as a white colour solid. Yield: 89% (890 mg).

Yield: 89% (2.2 g); mp 173-175 °C (lit.[19] mp 177-178 °C), IR (neat, cm^{-1}): 3271, 2969,2325, 1485, 1425, 1361, 1329, 1241, 1156, 1012, 807, 787; ^{1}H NMR (500 MHz, DMSO-d6): δ = 8.50 (s, 1H), 8.46 (s, 1H), 6.43 (s, 2H), 5.53 (s, 1H), 3.09 (br. s, 2H), 3.00 (d, J = 4.5 Hz, 2H), 1.75 (s, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d6): δ = 146.8, 146.7, 130.2, 121.6, 121.2, 118.0, 115.5, 111.4, 29.1, 25.1, 23.1 ppm.

6-Methyl-5, 8-dihydronaphthalene-1,4-dione (19) [19]

To a stirred solution of hydroquinone **24** (500 mg, 2.83 mmol) in acetone (20 mL) manganese dioxide (MnO_2) was added in excess amount (8 equiv) at room temperature for overnight. After completion of the reaction (monitored by TLC), the MnO_2 in reaction mixture was filtered off using Celite pad and filtrate was removed by vacuo to give the yellow colour solid **19**. The crude product **19** was purified by silica gel column chromatography (3% EtOAc/PE) to deliver the quinone **19** as a yellow crystalline solid. Quinone **19** is sensitive to light and was immediately

subjected to next step [4+2] cycloaddition (Diels–Alder) reaction. Yield: 72% (355 mg): mp 133-135 °C.

Yield: 72% (355 mg); mp 133-135 °C; IR (neat, cm^{-1}): 2891, 1647, 1634, 1444, 1418, 1296, 1115, 841, 782; ^1H NMR (500 MHz, $CDCl_3$): δ = 6.71 (s, 2H), 5.49 (t, *J* = 1.4 Hz, 1H), 3.06-3.04 (d, *J* = 6.9 Hz, 2H), 2.95 (t, *J* = 7.98 Hz, 2H), 1.76 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.2, 187.1, 139.7, 139.5, 136.4, 130.2, 116.9, 28.6, 25.1, 23.0 ppm.

Diels–Alder adduct (26)

To a stirred solution of Diels–Alder precursor (quinone) **19** (700 mg, 4.01 mmol) in anhydrous dichloromethane (10 mL) was added freshly cracked cyclopentadiene **25** (0.5 mL, 6.0 mmol) in dropwise manner at 0 °C. The reaction mixture was stirred at room temperature for 2 h. After the reaction was complete (progress of the reaction monitored by TLC), the solvent was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography (5% EtOAc/PE) to afford Diels–Adduct **26** as a pure yellow crystalline solid.

Yield: 77% (750 mg); mp 103-105 °C; IR (neat, cm^{-1}) 2969, 1659, 1446, 1415, 1334, 1296, 1269, 705; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.94 (s, 2H), 5.35 (d, *J* = 1.4 Hz, 1H), 3.46 (s, 2H), 3.16 (d, *J* = 1.5 Hz, 2H), 2.85-2.98 (m, 2H), 2.72-2.84 (m, 2H),1.66 (s, 3H), 1.38, 1.46 (ABq, *J* = 8.7 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 198.4, 198.3, 145.7, 145.5, 135.2, 129.9, 116.7, 48.95, 48.94, 48.93, 48.2, 48.1, 29.2, 25.7, 22.7 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{16}KO_2$ $[M + K]^+$ 279.0782; found: 279.0781.

Hexacyclic Cage Propellanedione (17)

A solution of the Diels–Alder adduct **26** (500 mg, 2.08 mmol) in 250 mL of anhydrous EtOAc was degassed with nitrogen and irradiated in Pyrex immersion well by using 125 W medium pressure UV mercury-vapor lamp (homemade) for 1.5 h at room temperature. After completion of the reaction (by TLC monitoring), the solvent was removed under vacuo and the crude product was purified from column chromatography on silica gel using 5% EtOAc in petroleum ether as an eluent to deliver cage dione **17** as a white crystalline solid.

Yield: 90% (450 mg); mp 139-141 °C; IR (neat, cm^{-1}): 2959, 1747, 1730, 1440, 1295, 1227, 1098; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.57-5.59 (m, 1H), 2.84 (t, *J* = 1.5 Hz, 2H), 2.71 (s, 2H), 2.60-

2.66 (m, 2H), 2.25-2.34 (m, 2H), 1.85, 2.00 (ABq, J = 11.0 Hz, 2H), 1.76 (s, 3H), 1.73 (s, 1H), 1.63 (d, J = 15.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.3, 213.0, 133.9, 118.8, 54.9, 54.8, 52.3, 51.4, 43.5, 43.4, 42.88, 42.85, 41.1, 28.9, 24.4, 23.9 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{17}O_2$ $[M + H]^+$ 241.1223; found: 241.1226.

Hexacyclic Cage Propellanediol (27)

To the stirred solution of cage dione **17** (50 mg, 0.20 mmol) in anhydrous methanol (5 mL), $NaBH_4$ (30 mg, 0.80 mmol) was added at 0 °C in small portions over a period of 10 min. The resultant reaction mixture was stirred for another 50 min at the room temperature. After completion of the reaction (the progress of the reaction monitored by TLC, 1 h), 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 product obtained after evaporation of solvent was purified from column chromatography on silica gel using 10% EtOAc in petroleum ether as an eluent to deliver the cage diol **27** as a colourless liquid.

Yield: 81% (41 mg); IR (neat, cm^{-1}): 3213, 2952, 2871, 2332, 2091, 1861, 1649, 1483, 1115; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.63 (d, J = 4.7 Hz, 1H), 5.03 (s, 2H), 3.46 (s, 2H), 2.23-2.38 (m, 6H), 1.88-1.94 (m, 2H), 1.78 (s, 3H), 1.74 (d, J = 8.6 Hz, 1H), 1.63 (d, J = 15.4, 1H), 1.56 (d, J = 10.4 Hz, 1H), 1.01 (d, J = 10.2 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.1, 120.8, 75.5, 75.3, 47.3, 46.4, 46.2, 46.1, 43.6, 43.5, 41.68, 41.63, 35.2, 34.9, 29.9, 24.7 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{20}NaO_2$ $[M + Na]^+$ 267.1356; found: 267.1355.

Hexacyclic Cage Propellanedione (28) via catalytic hydrogenation

To a solution of cage dione **17** (50 mg, 0.20 mmol) in anhydrous EtOAc (5 mL) was added catalytic amount of 10% Pd/C (9 mg). The dione was hydrogenated using hydrogen balloon at atmospheric pressure at room temperature for 3-4 h. After completion of the reaction by TLC monitoring, the reaction mixture was filtered off with the aid of Celite pad and filtrate was concentrated under reduced pressure. The obtained crude residue was purified by column chromatography on silica gel using 4% EtOAc in petroleum ether as an eluent to furnish the hydrogenated product **28** as a colourless liquid.

Yield: 85% (43 mg); IR (neat, cm^{-1}): 2952, 2335, 1740, 1456; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.83-2.89 (m, 2H), 2.72-2.78 (m, 4H), 2.11-2.16 (m, 1H), 1.89, 2.02 (ABq, J = 11.4 Hz, 2H), 1.67-1.74 (m, 2H), 1.46 (td, J = 11.9, 1.6 Hz, 1H), 1.25-1.31 (m, 2H), 0.93 (d, J = 4.9 Hz, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.9, 213.5, 55.06, 55.01, 51.0, 48.6, 45.7, 43.5, 43.1, 41.3, 31.9, 28.6, 26.4, 25.1, 22.95, 22.92 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{18}H_{20}NaO_2$ $[M + Na]^+$ 291.1356; found: 291.1351.

$BF_3{\cdot}OEt_2$-Catalyzed Rearrangement of Cage Propellanedione (17)

Boron trifluoride etherate **(**$BF_3{\cdot}OEt_2$) in excess amount (5 mL) was added to a stirred solution of cage dione **17** (300mg, 1.24 mmol) in anhydrous benzene (20 mL) under nitrogen atmosphere and the reaction mixture was refluxed for 72 h. After conclusion of the reaction (progress of the reaction monitored by TLC evident), the reaction mixture was cooled to room temperature. Afterwards, it was quenched by the addition of saturated aqueous $NaHCO_3$ solution, and was extracted with benzene. The combined organic layers were washed with water, brine solution and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure followed by silica gel column chromatography of the resultant crude residue using 3% ethyl acetate in petroleum ether as an eluent furnished the desired rearranged caged molecule **18** (with two phenyls) as a pure colourless crystalline solid.

Yield: 53% (249 mg); mp 195-197 °C; IR (neat, cm^{-1}): 2938, 2315, 1762, 1468, 1274, 1032, 705; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.36 (m, 4H), 7.27-7.31 (m, 4H), 7.19-7.22 (m, 1H), 7.14-7.18 (m, 1H), 2.61-2.62 (m, 1H), 2.53 (t, J = 5.5 Hz, 1H), 2.40-2.42 (m, 1H), 2.33 (dd, J = 12.8, 3.0 Hz, 1H), 2.23-2.32 (m, 5H), 2.01-2.03 (m, 1H), 1.65-1.70 (m, 2H), 1.62 (dd, J = 10.3, 1.8 Hz, 2H), 1.53 (dd, J = 13.1, 2.5 Hz, 1H), 1.47 (d, J = 10.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.8, 149.2, 148.2, 128.27, 127.1, 125.9, 125.69, 125.62, 62.0, 57.0, 54.2, 51.4, 50.4, 48.2, 48.0, 47.8, 44.7, 41.1, 37.7, 36.9, 33.2, 33.1, 20.5 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{28}H_{27}O$ $[M + H]^+$ 379.2056; found: 379.2056.

Zn/AcOH reduction of cage propellanedione (17)

Mixture of hexacyclic cage propellanedione **17** (300 mg, 1.24 mmol) and activated zinc dust (300 mg, 4.55 mmol) in 5 ml glacial acetic acid was stirred at room temperature for 10 h. 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 at reduced pressure to give the crude rearranged cage hydroxyketone. The resulting crude residue was further purified by column chromatography on silica gel using 15% ethyl acetate in petroleum ether as an eluent to afford the inseparable mixture of cage hydroxyketone **29** as a colourless liquid.

Yield: 88% (265 mg); IR (neat, cm^{-1}): 3413, 2976, 2966, 2332, 1752, 1442, 1308, 1288, 1246, 1161, 858; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.36 (dd, J = 16.4, 7.6 Hz, 1H), 2.56 (s, 1H), 2.27-2.49 (m, 5H), 2.08-2.23 (m, 3H), 1.86-2.05 (m, 3H), 1.68 (s, 3H), 1.42, 1.54 (ABq, J = 10.6, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.9, 217.8, 137.2, 136.9, 122.9, 122.1, 84.5, 84.4, 55.3, 54.7, 51.36, 51.30, 49.7, 48.54, 48.50, 48.39, 48.32, 47.31, 47.2, 45.0, 40.5, 40.4, 37.07, 37.05, 31.0, 27.6, 27.1, 27.0, 25.1, 21.5 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{18}NaO_2$ $[M + Na]^+$ 265.1199; found: 265.1196.

Synthesis of Oxa Cage Compound (30)

To a stirred solution of cage hydroxyketone **29** (100 mg, 0.41 mmol) in dichloromethane (10 mL) was added a solution of 98% fuming HNO_3 (0.2 mL) in dropwise manner over a period of 5 min under ice bath temperature. Then, the resulting reaction mixture was allowed to room temperature and further stirred for 4 h. After reaction was complete (4 h, TLC), the reaction mixture was diluted with water and extracted with dichloromethane (DCM). The organic layer was washed with water, brine solution and dried with anhydrous Na_2SO_4. Evaporation of the solvent under vacuo followed by column chromatography of the crude mixture on silica gel using 5-7% EtOAc in petroleum ether as an eluent afforded the oxa cage compound **30** as a pure colourless crystalline solid.

Yield: 69% (69 mg): mp 102-104 °C; IR (neat, cm^{-1}): 2959, 1766, 1451, 1295; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.68 (q, J = 5.9 Hz, 2H), 2.53-2.55 (m, 2H), 2.12-2.16 (m, 2H), 2.04 (d, J = 12.6, 1H), 1.80-1.88 (m, 2H), 1.62-1.69 (m, 2H), 1.46-1.60 (m, 3H), 1.38-1.44 (m, 1H), 1.32 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 214.4, 96.3, 89.9, 61.7, 50.2, 47.4, 44.1, 43.6, 41.9, 41.1, 38.3, 35.4, 32.2, 25.7, 22.4 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{18}NaO_2$ $[M + Na]^+$ 265.1199; found: 265.1193.

$NaBH_4$ Reduction of Cage Hydroxyketone (29)

A solution of cage hydroxyketone **29** (50 mg, 0.20 mmol) in anhydrous methanol (5 mL), $NaBH_4$ (15 mg, 0.40 mmol) was added at 0 °C in small portions over a period of 10 min. The resultant 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 the addition of water and was extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained after evaporation of solvent was purified from column chromatography on silica gel using 15% EtOAc in petroleum ether as an eluent delivered the cage diol **31** as a white colour solid.

Yield: 87% (44 mg); mp 142-144 °C; IR (neat, cm^{-1}): 3359, 2938, 2966, 2833, 2515, 2040, 1454, 1029, 680; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.34-5.43 (m, 1H), 3.98 (s, 1H), 2.60 (s, 1H), 2.32-2.45 (m, 1H), 2.27-2.30 (m, 1H), 2.14-2.22 (m, 1H), 2.09-2.13 (m, 1H), 2.01-2.07 (m, 1H), 1.94-1.98 (m, 3H), 1.77 (s, 3H), 1.70-1.72 (m, 4H), 1.33 (q, J = 10.4, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 137.7, 137.0, 123.2, 122.9, 87.2, 87.1, 78.6, 78.4, 58.6, 58.0, 51.38, 51.33, 49.79, 49.74, 48.2, 48.0, 47.3, 47.1, 46.76, 46.71, 44.68, 44.4, 44.3, 34.75, 34.71, 31.1, 30.1, 27.7, 27.5 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{16}H_{20}NaO_2$ $[M + Na]^+$ 267.1356; found: 267.1354.

Wollf-Kishner reduction of cage ketone (18)

To a round bottom flask with a reflux condenser were added diethylene glycol (10 mL) and KOH pellets and then heated at 80 °C until all of the KOH get dissolved. To this solution, cage ketone **18** (200 mg, 0.52 mmol) and hydrazine hydrate (169 mg, 5.28 mmol) were added sequentially. The resultant reaction mixture was heated at 100-110 °C for 3 h. Afterwards, the round bottom flask was fitted with a Dean-Stark apparatus, and water was removed from the reaction mixture by azeotropic distillation. The Dean-stark set up was removed and the temperature of the reaction mixture was increased to 190-200 °C. The reaction mixture was heated at the same temperature for 10 h. After completion of the reaction by TLC monitoring, the reaction mixture was allowed to room temperature, diluted with water and quenched by aqueous HCl. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were successively washed with water, brine solution and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced

pressure followed by silica gel column chromatography of the resultant crude residue using 1% ethyl acetate in petroleum ether as an eluent gave the desired cage hydrocarbon **35** as a pure colourless solid.

Yield: 77% (150 mg); mp 112-114 °C; IR (neat, cm^{-1}): 2955, 2938, 2328, 1495, 1473, 1036, 700; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32-7.34 (m, 2H), 7.23-7.30 (m, 6H), 7.12-7.16 (m, 2H), 2.22-2.30 (m, 4H), 2.05 (s, 2H), 2.03 (t, *J* = 2.2, 1H), 1.95-1.96 (m, 1H), 1.79-1.88 (m, 4H), 1.58-1.69 (m, 3H), 1.49-1.53 (m, 1H), 1.28, 1.19 (ABq, *J* = 10.2 Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.9, 149.5, 128.1, 127.8, 125.78, 125.71, 125.0, 61.0, 57.0, 55.7, 53.3, 50.7, 49.5, 47.96, 47.95, 47.4, 45.3, 40.6, 38.4, 37.3, 34.4, 33.9, 21.3 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{28}H_{28}K$ $[M + K]^+$ 403.1823; found: 403.1828.

$NaBH_4$ Reduction of Cage ketone (18)

A solution of cage ketone **18** (75 mg, 0.19 mmol) in anhydrous methanol (5 mL), $NaBH_4$ (30 mg, 0.40 mmol) was added at 0 °C in small portions over a period of 10 min. The resultant 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 the addition of water and was extracted with ethyl acetate. The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product obtained after evaporation of solvent was purified from column chromatography on silica gel using 5-7% EtOAc in petroleum ether as an eluent delivered the cage alcohol **36** as a colourless solid.

Yield: 82% (62 mg): mp 101-103 °C; IR (neat, cm^{-1}): 3461, 2952, 2861, 1427, 1357, 1266, 1224, 1085, 734, 702; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33-7.34 (m, 4H), 7.24-7.30 (m, 4H), 7.13-7.17 (m, 2H), 4.03 (s, 1H), 2.68-2.74 (m, 1H), 2.43 (t, *J* = 5.6 Hz, 1H), 2.27-2.33 (m, 2H), 2.16-2.25 (m, 4H), 2.04 (d, *J* = 6.8 Hz, 1H), 1.90-1.96 (m, 2H), 1.67-1.77 (m, 3H), 1.55-1.62 (m, 1H), 1.21, 1.29 (ABq, *J* = 10.3, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.9, 149.5, 128.29, 128.2, 127.22, 127.8, 125.79, 125.77, 125.1, 79.7, 60.7, 56.9, 56.5, 54.1, 53.6, 50.8, 48.3, 47.7, 45.3, 42.2, 38.5, 37.6, 34.2, 33.8, 21.1 ppm; HRMS (ESI, Q-ToF): m/z calcd for $C_{28}H_{28}NaO$ $[M + Na]^+$ 403.2032; found: 403.2037.

Associated content

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:

ORTEP drawings as shown by X-ray crystallography and copies of ^{1}H, ^{13}C, ^{13}C-APT, DEPT-135 NMR of all new products and GC spectra of compound 29 (PDF).

Crystal data for **18** and **30** (CIF)

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Notes

The authors declare no competing financial interest.

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22. CCDC 1590575 (**18**) and 1586116 (**30**) contains 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 **18** and **30**, please see the SI file.