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Synthesis of *cis-syn-cis* and *cis-anti-cis* linear triquinanes via photo-thermal metathesis

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Diverse *cis-syn-cis* and *cis-anti-cis* triquinane frameworks have been assembled by a simple synthetic protocol starting with substituted cage diones under microwave irradiation conditions. Thermal fragmentation of the cyclobutane ring play a key role in this process and milder reaction conditions have been employed in contrast to normal flash vacuum pyrolysis conditions. Here, thermal isomerization of the double bond has also been realized under the microwave irradiation conditions to afford the isomeric triquinanes at low temperature. These triquinane units are considered to be useful for the total synthesis of natural products and non-natural products containing fused cyclopentane rings.

Keywords: Cage molecules, cycloreversion, linear triquinanes, photo-thermal metathesis, Diels–Alder reaction, microwave irradiation

Cage compounds[1] serve as a useful precursors for the synthesis of a wide variety of polyquinanes. Triquinane framework is a critical unit in many natural products containing fused five-membered rings that share configuration. Moreover, *cis-anti-cis* triquinane motif is a basic skeleton in natural products[2]. Different varieties of polyquinanes (**1-4**) such as angular, linear, and propellane form of triquinanes present in various natural and non-natural products are shown in Figure 1 [3]. Hirsutic acid was the first linearly fused triquinane natural product reported by Trotter and Comer[4].

These carbocyclic frameworks are sub class of polyquinanes which are large family of sesquiterpenoids isolated from marine sources such as fungi, sponges, soft corals, plants and microbes. The majority of the linear triquinane sesquiterpenoids shown a wide range of biological activities such as anti-inflammatory, anti-microbial, and cytotoxicity[5]. Triquinanes with *cis-anti-cis* fused rings were embraced in various core frameworks of biologically active sesquiterpenoids such as coriolin and capnellanes[6]. Moreover, *cis-syn-cis* fused triquinanes are useful synthons to construct architecturally interesting targets such as dodecahedron and peristylanes[7].

Due to their intricate molecular structures and prominent biological activities, many routes have been envisaged by several groups to assemble the triquinanes starting with hirsutene discovery[8]. Some of the strategies such as Mehta's photo-thermal olefin metathesis [9], Curran's radical pathways[10], Little's 1,3-diyl cycloaddition[11], Wender's cycloaddition[12], Oppolzer's ene reaction[13], rearrangement approaches[14], diene-carbene annulations[15], ring-rearrangement metathesis[16], Rawal's photocycloaddition-fragmentation[17], metal-mediated reductive cleavage[18], oxa-di-π-methane rearrangement[19], and electro reductive cyclization[20] approaches were reported in literature during the past few decades. Literature reports indicate that, 118 linear triquinane were isolated and only 56 compounds exhibit promising biological activities. Selected structures of these compounds reported in literature with promising biological activities are shown in Figure 2 [6d]. Most of the earlier reports to assemble the triquinane framework require somewhat lengthy sequences[9-20]. To address these issues,

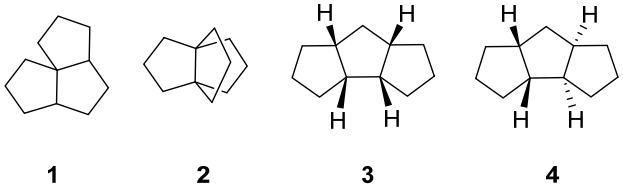


Figure 1 — Different types of carbocyclic triquinane skeletons (angular, propellane, and linear)

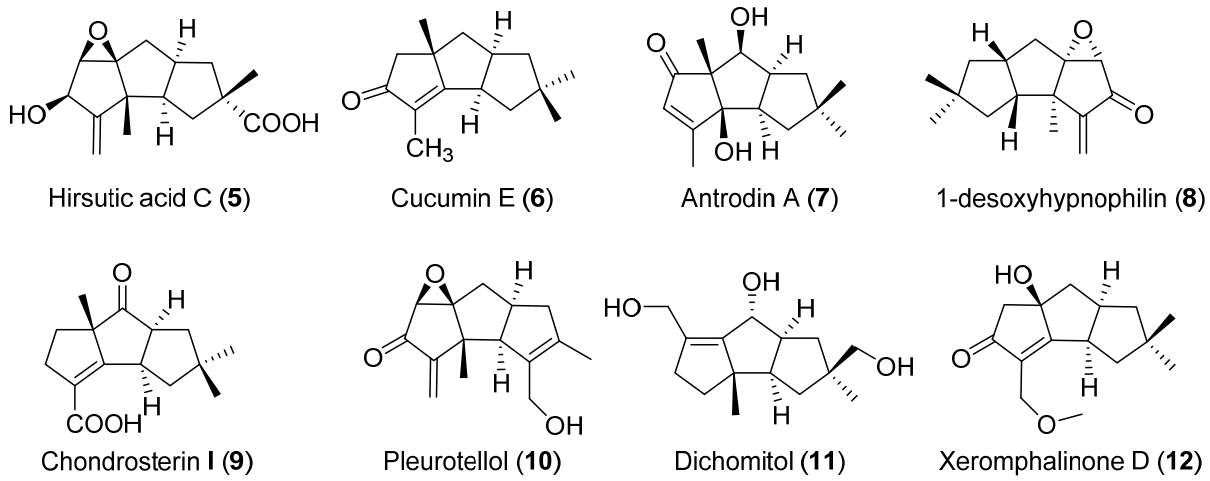


Figure 2 — Representative examples of biologically active linear triquinanes **5-12**

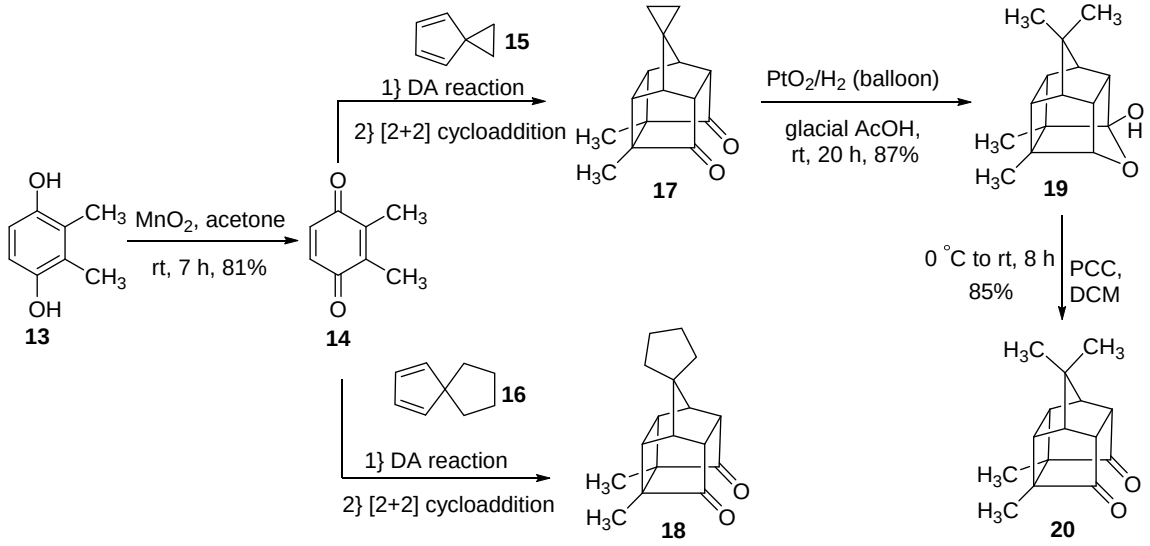
considerable efforts has been made to design efficient methods for the synthesis of triquinanes in our laboratory via olefin metathesis using Ru catalysts and also photo-thermal olefin metathesis under microwave irradiation conditions[21]. In this regard, photo-thermal metathesis plays a prominent role in the construction of the triquinane framework which is key building block for natural product synthesis. Mehta and co-workers employed flash-vacuum pyrolysis (FVP) conditions for the preparation of *cis-syn-cis* triquinane framework useful for the various natural products synthesis. These includes, hirsutene, coriolin, and $\Delta^{7(10)}$-capnellene, complicatic acid, precapnelladiene, and ikarugamycin[22-25].

Based on earlier experience, it was anticipated that the presence of vicinal methyl substituents on cyclobutane ring in the pentacycloundecane (PCUD) system facilitate the formation of *cis-syn-cis* linear triquinane via regiospecific thermal fragmentation of the strained cyclobutane ring. In view of this assumption, we used microwave irradiation conditions at lower temperature in a short period as compared with the FVP method. The electron-donating substituents located in the cyclobutane ring of Cookson's dione helps in the formation of linear triquinanes by ring-fragmentation. The C_1–C_7 bond length of methoxy substituted PCUD cage system increases due to the synergistic captodative stabilization of 1,4-diradical and push-pull mechanism. Various PCUD cage systems bearing spiro and *gem*-dimethyl substituents were subjected to the photo-thermal metathesis under microwave irradiation (MWI) conditions (150 W, 220–240°C/diphenyl ether) to offer various linear triquinane derivatives.

Results and Discussion

Towards the development of methods for the preparation of various triquinane scaffolds and expand their synthetic applications, we explored MWI conditions for the synthesis of substituted triquinanes bearing spiro and *gem*-dimethyl moieties. Recently, we also reported several triquinanes holding *cis-syn-cis* configurations along with the double bond isomerized frameworks via MWI conditions. In this context, we chosen substituted PCUD cage diones as key precursors for the preparations of *cis-syn-cis* triquinane frameworks. We observed that, the PCUD cage systems having methyl groups adjacent to carbonyl moiety provide the driving force for the formation of triquinane system via cleavage of cyclobutane ring.

The present methodology describes MWI conditions for the synthesis of triquinanes and offer an alternate way to various triquinane-based natural products. To this end, the required PCUD cage derivatives were prepared by known methods via the Diels–Alder (DA) reaction and [2+2] photocycloaddition sequence. To begin, we started with a readily available starting materials such as freshly made spirodienes **15** and **16** and 2,3-dimethyl hydroquinone **13** as key synthones. The synthesis of the required PCUD cage diones **17** and **18** commenced with the preparation of key synthone such as 2,3-dimethyl-1,4-benzoquinone **14** (Scheme I). The quinone derivative **14** [26] was prepared

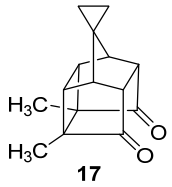
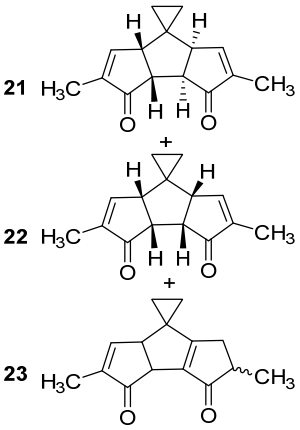
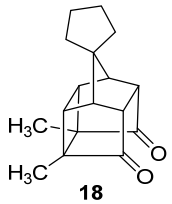
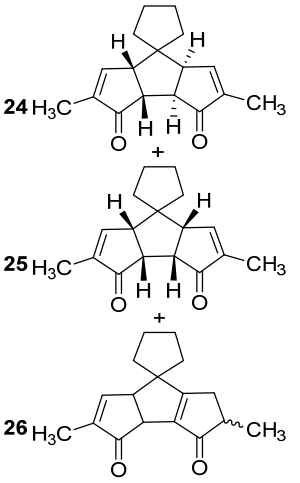
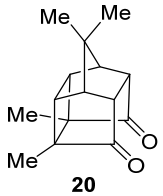
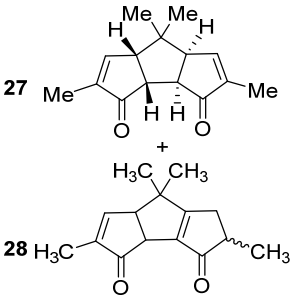


Scheme I — Synthesis of required PCUD cage diones **17**, **18**, and **20** useful for MW irradiation

by MnO_2 oxidation of the 2,3-dimethylhydroquinone **13** in acetone (81% isolated yield). The cage diones **17** and **18** were assembled from quinone derivative **14** with the aid of freshly prepared spirodienes such as **15** and **16** via DA reaction[27] and intramolecular [2+2] photocycloaddition based on reported procedures. Along similar lines, the other *gem*-dimethyl containing cage dione **20** was produced from the cage dione **17** through reductive cleavage of the cyclopropane with PtO_2 treatment followed by oxidation of the hemiketal **19** with PCC (pyridinium chlorochromate) (Scheme I)[26].Having synthesized a variety of cage diones such as **17**, **18**, and **20** suitable for photo-thermal metathesis, next, our efforts were directed towards the synthesis of different triquinane skeletons under MWI conditions in diphenyl ether (DPE) as a solvent. In this context, the substituted cage diones **17** and **18** bearing spiro linkage were subjected to MWI (150 W, 240 °C, 15 min) in DPE to produce the respective triquinane motifs having *cis-syn-cis* stereochemistry **22** and **25** along with *cis-anti-cis* stereochemistry such as **21** and **24** in good yields. We have also isolated double bond isomerized products **23** and **26** under similar conditions (Table I). Finally, we proved the stereochemistry (*cis-syn-cis* and *cis-anti-cis*) of triquinanes via intramolecular [2+2] photocycloaddition reaction. In this regard, triquinanes such as **22** and **25** was proceeded to photocycloaddition in the presence of 125 W UV lamp in a Pyrex well furnished the respective spiro cage diones **17** and **18**. Based on this observation, we found the stereochemistry of the triquinanes **22** and **25** was *cis-syn-cis* (Table I). Whereas the other triquinanes such as **21, 24** and **27** were not participated in the photocycloaddition under similar conditions. This clearly indicates that the stereochemistry of these triquinanes was *cis-anti-cis* (Table I). The structural features of these triquinane derivatives (**21-28**) were fully established on the basis of ^{1}H NMR, ^{13}C NMR, DEPT-135, APT NMR and HRMS data. Further, the stereochemistry of these triquinanes such as **21** and **22** was supported by the single-crystal X-ray diffraction studies (Figure 3)[28].

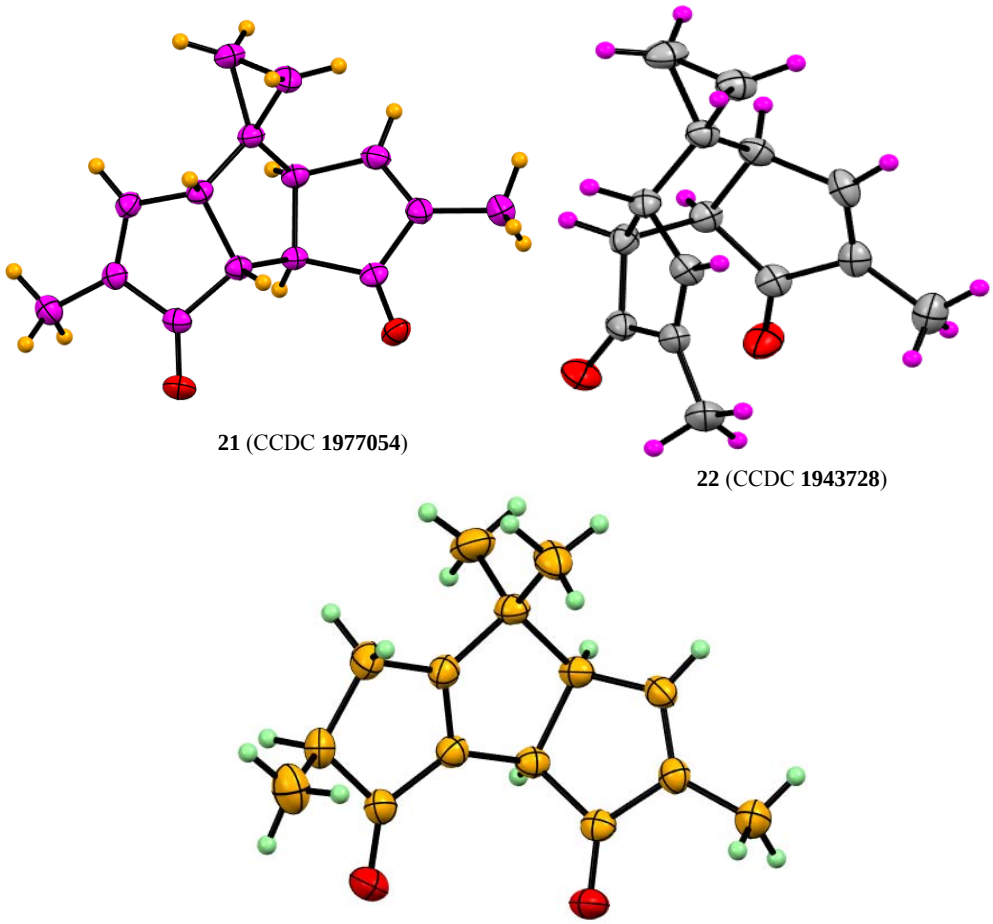
Later, the *gem*-dimethyl substituted cage dione **20** was subjected to MWI under similar conditions in DPE solvent to afford the other triquinane frameworks such as **27** and **28**. The structures of these triquinanes **27** and **28** was characterized by ^{1}H NMR, ^{13}C NMR, and DEPT-135, APT NMR, further with HRMS data. Finally, the structure of the double bond isomerized compound **28** was fully confirmed with the single-crystal X-ray diffraction studies (Figure 3)[28]. Triquinanes having *cis-anti-cis* configuration is present in numerous cyclopentanoid natural products. Triquinanes delivered here via MWI conditions and the methodology is useful because of its simplicity in operation and mild conditions which tolerate several sensitive substrates as compared with the previous methods (conventional heating and FVP conditions).

Table I — Formation of triquinane motifs under MWI conditions via photo-thermal olefin metathesis

S. No	Caged molecules	Triquinanes	Temp (°C)/ Watt	Time (min)	Yields(%)
1.	 17	 21 + 22 + 23	240°C/150 W	15 min	27, 23, 37
2.	 18	 24 + 25 + 26	240°C/150 W	15 min	29, 21, 31
3.	 20	 27 + 28	240°C/150 W	15 min	35, 48

Experimental Section

All the chemicals, reagents, and solvents reported here were purchased from the commercial suppliers and used as such 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. Reactions were monitored by TLC using a suitable solvent system and visualization was done under UV light, exposure to iodine vapor and by dipping into a solution of $KMnO_4$. Air and moisture sensitive reactions were carried out in an oven-dried glassware



21 (CCDC **1977054**)

22 (CCDC **1943728**)

28 (CCDC **1943342**)

Figure 3 — Single crystal X-ray structures of triquinanes **21, 22,** and **28**

under nitrogen atmosphere using syringe-septum techniques. Acme's silica gel (100-200 mesh size) was used for column chromatography. Dichloromethane (DCM), benzene and toluene were distilled from P_2O_5 or CaH_2. Ethyl acetate (EtOAc) was dried over powdered K_2CO_3 for [2+2] photocycloaddition reactions.

Infrared spectra (IR) were recorded on a Nicolet Impact-400 FTIR spectrometer. ^{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 on delta scale (δ, ppm) with TMS as an internal standard and values for the coupling constants (*J*) are given in Hz. The multiplicities abbreviations are reported as s, d, t, q, ABq, dd, dt, td, and m for s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, td = 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. Single crystal X-ray data were collected on diffractometer (Rigaku Saturn 724+) equipped with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) and structure was solved by direct methods shelxl-97 and refined by full-matrix least-squares against F^2 using shelxl-97 software. Microwave irradiation (MWI) was carried out with commercially available microwave reactor such as CEM Discover-sp, CEM Corporation, North Carolina, USA and the reaction temperature was maintained by an external infrared sensor.

General procedure for synthesis of triquinane frameworks under microwave irradiation (MWI) conditions

The hexacyclic cage diones **17**, **18**, and **20** (0.86-1.31 mmol) was dissolved in minimum volume of diphenyl ether (3-5 mL) and subjected to microwave irradiation (150 W) at 240°C for 15 min using CEM Sp instrument. At the conclusion of the reaction based on TLC monitoring, the crude triquinane derivatives were purified by column chromatography on 100-200 mesh silica gel using appropriate mixture of ethyl acetate in petroleum ether an eluent to obtain the respective triquinane derivatives such as *cis-syn-cis*, *cis-anti-cis* and double bond isomerized triquinanes **21**, **22**, **23**, **24**, **25**, **26**, **27**, and **28** in moderate to good yields.

Triquinane 21, **22**, and **23**

The triquinanes **21**, **22**, and **23** were prepared according to the above general procedure using cage dione **17** (300 mg, 1.31 mmol) and diphenyl ether (3 mL) under MWI for 15 min.

Triquinane 21: Eluent: 25% Petroleum ether-ethyl acetate; Colourless crystalline solid. Yield 85 mg (27%). m.p.124-126°C; IR (neat): 3050, 2989, 2952, 2908, 1717, 1698, 1635, 1440, 1373, 1330, 1224, 1076, 1003, 971, 939, 917, 885, 843, 783 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.01-6.99 (m, 2H), 3.03-2.98 (m, 4H), 1.80 (t, *J* = 1.5 Hz, 6H), 0.70-0.64 (m, 2H), 0.53-0.47 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 209.4, 157.3, 141.6, 52.7, 51.6, 29.0, 10.6, 10.5; HRMS (ESI): *m/z* Calcd for $C_{15}H_{17}O_2$ $[M+H]^+$: 229.1223. Found: 229.1225.

Triquinane 22: Eluent: 25% Petroleum ether-ethyl acetate; Colourless crystalline solid. Yield 70 mg (23%). m.p.105-107°C; IR (neat): 3000, 2888, 1717, 1327, 1215, 980, 893, 841, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 1.4 Hz, 2H), 3.45 (q, *J* = 2.1 Hz, 2H), 2.68-2.65 (m, 2H), 1.61-1.60 (m, 6H), 0.85-0.81, 0.68-0.64 (m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 207.5, 157.6, 141.7, 55.0, 53.7, 25.2, 18.2, 10.2, 4.8; HRMS (ESI): *m/z* Calcd for $C_{15}H_{16}NaO_2$ $[M+Na]^+$: 251.1043. Found: 251.1036.

Triquinane 23: Eluent: 40% Petroleum ether-ethyl acetate; Colourless crystalline solid. Yield 110 mg (37%). m.p.157-159°C; IR (neat): 2955, 2922, 1712, 1637, 1615, 1403, 1373, 1332, 1237, 1205, 1180, 1114, 1064, 1005, 961, 912, 844, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.04 (q, *J* = 1.5 Hz, 1H), 3.77-3.74 (m, 1H), 3.49-3.47 (m, 1H), 2.71-2.63 (m, 1H), 2.40-2.34 (m, 1H), 1.75 (t, *J* = 1.3 Hz, 3H), 1.71 (t, *J* = 2.9 Hz, 1H), 1.21-1.12 (m, 5H), 1.04-0.99 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 205.5, 203.3, 186.8, 155.9, 141.3, 140.6, 53.2, 50.4, 45.8, 30.9, 30.2, 16.8, 15.9, 10.5, 10.1; HRMS (ESI): *m/z* Calcd for $C_{15}H_{16}KO_2$ $[M+K]^+$: 267.0782. Found: 267.0782.

Triquinane frameworks 24, **25**, and **26**

The triquinanes **24**, **25**, and **26** were prepared according to the described general procedure using the cage dione **18** (300 mg, 1.17 mmol) and diphenyl ether (4 mL) under MWI for 15 min.

Triquinane 24: Eluent: 20% ethyl acetate in petroleum ether; Colourless liquid. Yield 87 mg (29%); IR (neat): 3020, 2955, 1710, 1215, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.15 (q, *J* = 1.3 Hz, 2H), 3.00-2.99 (m, 2H), 2.87-2.85 (m, 2H), 1.77 (t, *J* = 1.7 Hz, 6H), 1.63-1.59 (m, 4H), 1.52-1.47 (m, 2H), 1.35-1.31(m, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 209.2, 156.7, 141.9, 55.4, 54.6, 52.1, 35.6, 23.2, 10.6; HRMS (ESI/Q-TOF): *m/z* Calcd for $C_{17}H_{21}O_2$ $[M+H]^+$: 257.1536. Found: 257.15367.

Triquinane 25: Eluent: 25% Petroleum ether-ethyl acetate; Colourless crystalline solid. Yield 65 mg (21%). m.p.144-146°C; IR (neat): 2938, 2864, 1715, 1635, 1449, 1376, 1327, 1242, 1159, 1092, 990, 922, 881, 807 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 2H), 3.31 (t, *J* = 2.1 Hz, 2H), 2.91 (s, 2H), 1.76 (s, 6H), 1.60 (m, 8H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 207.8, 157.2, 142.3, 56.1, 52.5, 52.4, 42.1, 30.8, 23.9, 22.7, 10.3; HRMS (ESI/Q-TOF): *m/z* Calcd for $C_{17}H_{20}O_2$ $[M+K]^+$: 295.1095. Found: 295.1092.

Triquinane 26: Eluent: 30% Petroleum ether-ethyl acetate; Colourless solid. Yield 95 mg (31%). m.p. 93-95°C; IR (neat): 2955, 2925, 2871, 1706, 1634, 1456, 1374, 1327, 1242, 1200, 1176, 1083, 1049, 993, 958, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.15 (s, 1H), 3.59 (d, *J* = 2.0 Hz, 1H), 3.47 (s, 1H), 2.68-2.57 (m, 2H), 2.01-1.98 (m, 1H), 1.83-1.62 (m, 11H), 1.19 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 206.2, 204.8, 188.4, 156.4, 140.8, 140.4, 57.14, 57.11, 50.3, 45.7, 40.4, 32.2, 31.5, 25.1, 24.2, 16.7, 10.5; HRMS (ESI): *m/z* Calcd for $C_{17}H_{20}NaO_2$ $[M+Na]^+$: 279.1356. Found: 279.1361.

Triquinane frameworks 27 and **28**

The triquinanes **27** and **28** were prepared according to the above general procedure using cage dione **20**

(200 mg, 0.86 mmol) and diphenyl ether (3 mL) under MWI for 15 min.

Triquinane 27: Eluent: 25% Petroleum ether-ethyl acetate; Colourless solid. m.p.124-126°C. Yield 70 mg (35%); IR (neat): 2959, 2928, 1715, 1634, 1584, 1488, 1373, 1332, 1310, 1285, 1237, 1159, 1075, 1025, 990, 951, 926, 866, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 1.26 Hz, 2H), 2.92-2.86 (m, 4H), 1.79 (s, 6H), 0.94 (s, 6H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 209.2, 156.2, 142.1, 57.2, 51.9, 42.8, 26.9, 10.6; HRMS (ESI): *m/z* Calcd for $C_{15}H_{18}KO_2$ $[M+K]^+$: 269.0938. Found: 269.0942.

Triquinane 28: Eluent: 30% Petroleum ether-ethyl acetate; Colourless crystalline solid. Yield 95 mg (48%). m.p.88-90°C; IR (neat): 2959, 2928, 1715, 1639, 1461, 1447, 1366, 1325, 1271, 1178, 1114, 1046, 953 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H), 3.63 (d, *J* = 2.8 Hz, 1H), 3.47 (s, 1H), 2.72-2.62 (m, 2H), 1.92 (d, *J* = 18.3 Hz, 1H), 1.76 (s, 3H), 1.29 (s, 3H), 1.19 (d, *J* = 7.3 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 206.1, 205.3, 190.2, 156.3, 140.5, 139.7, 58.4, 50.1, 46.1, 45.4, 30.9, 29.2, 22.0, 17.1, 10.6; HRMS (ESI): *m/z* Calcd for $C_{15}H_{18}KO_2$ $[M+Na]^+$: 253.1199. Found: 253.1197.

Conclusions

In summary, we have reported a simple and a convenient route for synthesis of *cis-syn-cis* and *cis-anti-cis* triquinane frameworks via MWI conditions from PCUD cage diones bearing *gem*-dimethyl and spiro ring systems. Additionally, the double bond isomerization was observed during the microwave irradiation to afford the other triquinanes which are key precursors for natural product synthesis. These skeletons described as worthwhile scaffolds for the design and synthesis of various biological active natural products as well as architecturally interesting non-natural targets such as dodecahedron.

Supplementary Information

The supporting information file is available free of charge on the journal website. Characterization data copies of ^1H, ^{13}C, ^{13}C-APT, DEPT-135 NMR spectra of all new products (PDF) and X-ray refinement data for **21**, **22**, and **28** (ORTEP diagrams) are available in the supplementary information (SI) file.

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28 CCDC 1977054 (**21**), CCDC 1943728 (**22**), and CCDC 1943342 (**28**) such as triquinanes 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 **21**, **22**, and **28**, please see the SI file.