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Synthesis of linear *cis-anti-cis* triquinane derivative *via* a [3+2] cycloaddition and Krapcho decarboxylation as key steps

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A short synthetic sequence to a linear triquinane is reported involving [3+2] cycloaddition, oxidative cleavage of double bond using ruthenium catalyst followed by decarboxylation. By this methodology, norbornene double bond can be easily cleaved to obtain the linear triquinane unit. This methodology is useful for the synthesis of natural and non-natural products having fused cyclopentane ring systems.

Keywords: Triquinane, Cycloaddition, Decarboxylation, Oxidative Cleavage, Cyclopentane

Three cyclopentane rings are fused together to form propellanes, linear and angular triquinanes. Linear triquinanes are the core units in sesquiterpenoids predominantly isolated from fungi, soft corals, plants, microbes and sponges. A wide range of biological activities have been noted for linear triquinane based sesquiterpenoids, including anti-inflammatory activities, microbial properties and cytotoxicity which have sustained a high-level interest of phytochemist and pharmaceutical chemist in this family of natural products[1-4]. The fascinating tricyclic skeleton of the triquinanes has been prepared in a variety of novel ways starting with hirsutene isolation, and frequently the framework itself is a testing ground to demonstrate new synthetic strategies for the creation of fused cyclopentanoids[5-8]. Selected examples of linear triquinanes are shown in Fig. 1. Most of these approaches to assemble linear triquinanes consists of a large number of steps and chemists are working continuously to improve the synthetic economy in efficient ways.

Here we are reporting a new strategy to synthesize linear triquinane by oxidative cleavage of the C–C double bond. The most common method for the oxidative cleavage of double bond to carboxylic acid is the ozonolysis but this technique involves the tedious feature that the reaction is carried out at low temperature by bubbling an excess of ozone. Despite advancements in ozone technology in terms of energy usage, handling ozonides in larger quantities as seen on a technical production scale poses safety risk. Alkenes can also be converted to carboxylic acids by using chemical reagents that combine the dihydroxylation of a double bond with the oxidative cleavage of the corresponding diol. This oxidation strategy was reported by Sharpless *et al*. and now it is widely used. Ruthenium tetroxide acts as a very powerful oxidising agent for the cleavage of olefinic bonds and also for the oxidation of alcohol, ethers and alkynes. RuO_4 is generated *in situ* by the reaction between RuO_2 and $NaIO_4$. The most widely used mixture of solvents described by Sharpless: $H_2O/MeCN/CCl_4$ in respective ratio 3:2:2. Carbon tetrachloride is necessary for the solubilization of RuO_4 and the acetonitrile is to avoid the catalytic cycle inactivation due to low-valent ruthenium carboxylate complexes[9-15]. We have utilized this oxidation strategy to synthesize linear triquinanes.

Results and Discussion

To prepare the key starting material **9**, we started with cyclopentenone **7** which was subjected to

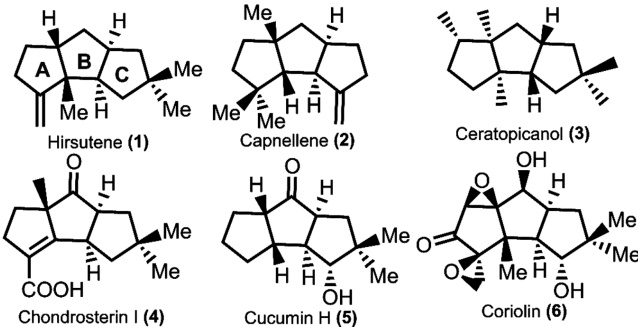
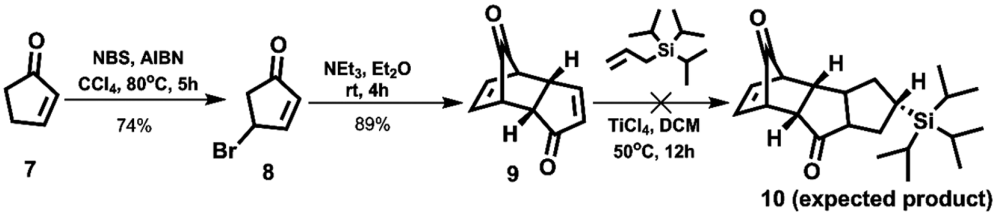


Fig. 1 — Representative examples of linear triquinanes

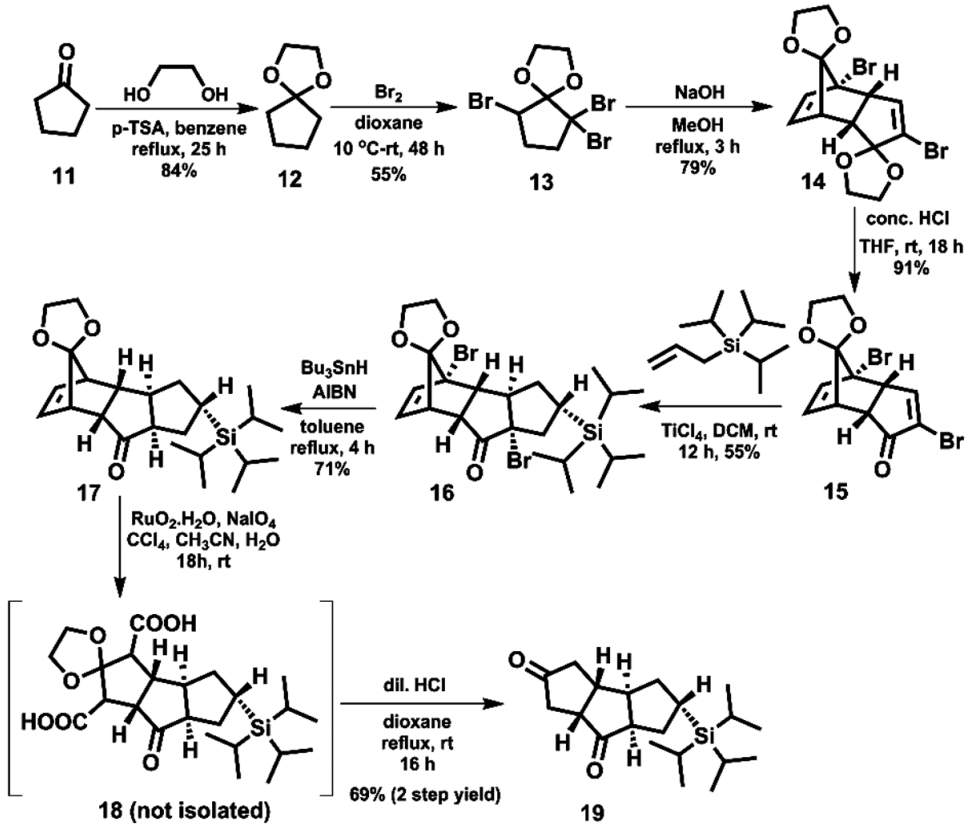
bromination using N-bromosuccinimide (NBS) followed by the [4+2] cycloaddition reaction by treating with triethylamine base to obtain dicyclopentadienone **9**[16]. Having the norbornene derivative **9**, it was treated with allyltriisopropylsilane in the presence of titanium tetrachloride to get the [3+2] addition product **10**, but unfortunately no reaction occurred as shown in Scheme 1.

In view of the above result we conceived an alternate strategy[17]. To this end, we started with the commercially available cyclopentanone **11**, which was reacted with ethylene glycol using Dean-Stark apparatus to produce the corresponding ketal derivative **12** which was then treated with bromine to give tribromo ketal **13** and the tribromo derivative **13** in the presence of base gave the diene which undergoes a [4+2] cycloaddition to produce the Diels–Alder product **14**. The cycloaddition product **14** was further heated with dilute HCl to give enone **15** (Ref. 18).

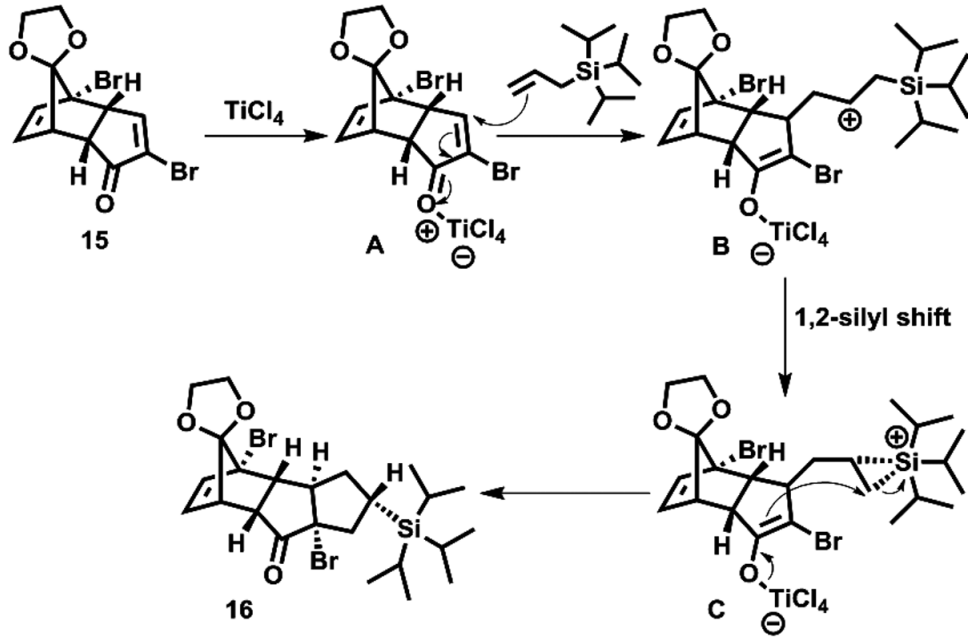
Again, we attempted [3+2] cycloaddition[19-21] reaction of compound **15** with allyltriisopropylsilane in the presence of titanium tetrachloride and obtained the desired tetracyclic product **16** which was subjected to oxidative cleavage using RuO_2 and $NaIO_4$ but gave decomposed product. To proceed further we removed the bromine atoms and the tetracyclic compound **16** was subjected to debromination in the presence of tributyltinhydride and azobisisobutyronitrile (AIBN) to get the debrominated tetracyclic compound **17** which on treatment with RuO_2 and $NaIO_4$ gave dicarboxylic acid intermediate **18** and this intermediate was decarboxylated[22] using dilute HCl to obtain the targeted linear triquinane compound **19** as shown in Scheme 2.



Scheme 1 — Attempted [3+2] cycloaddition starting from compound **7**



Scheme 2 — Synthesis of linear triquinane **19** from cyclopentanone **11**



Scheme 3 — Mechanism for the formation of compound **16**

The possible mechanism for the formation of compound **16** is shown in Scheme 3. The reaction proceeds *via* cationic 1,2-silyl shift (B to C) which generates a bridged non-classical pentavalent silicon-cation C. The intermediate C undergoes rearrangement to generate the tetracyclic compound **16**. The structure of compound **16** (CCDC: 2176916) was characterized by NMR spectral data as well as by X-ray diffraction data[17].

Experimental Section

All the reactions were monitored by thin-layer chromatography (TLC) using appropriate solvent systems. Anhydrous tetrahydrofuran (THF) was obtained by distillation from sodium and benzophenone immediately prior to use. Column chromatography was performed by using silica gel (100–200 mesh) with an appropriate mixture of EtOAc and petroleum ether. Yields refer to samples which are chromatographically isolated. All the commercial grade reagents were used as received without further purification. In general, NMR samples have been analyzed in $CDCl_3$ solvent and chemical shifts are given in δ (ppm) using tetramethylsilane (TMS) as an internal standard. The standard abbreviations for singlet, doublet, triplet, quartet, doublet of doublet and multiplet are: s, d, t, q, ddand m. The constants of coupling (*J*) are recorded in Hz. Bruker (AVANCE IIITM) 500 MHz and Bruker (AVANCE IIITM) 400 MHz spectrometers were used to record both ^1H and ^{13}C NMR spectroscopic data. The high-resolution mass measurements were carried out by using an electrospray ionization (ESI) spectrometer. Melting points were recorded on a Veego melting point apparatus.

Synthesis of cyclopentanone ethylene ketal, 12 (Ref. 18)

p-TSA (20 mol%) was added in the solution of cyclopentanone **11** (10 g, 0.12 mol), ethylene glycol (9.59 g, 0.15 mol) and benzene (100 mL). The round bottom (RB) flask containing the reaction mixture (RM) was fitted with Dean Stark Apparatus (to collect water produced during the reaction) and refluxed for 25 h. After 25 h the reaction was cooled to RT and benzene was removed carefully under vacuum. The remaining mixture was distilled under vacuum to get pure product **12** (colourless liquid, 12.78 g, 84%).

Synthesis of 2,2,5-tribromocyclopentanone ethylene ketal, 13 (Ref. 18)

In a two neck RB flask, compound **12** (15 g, 0.12 mol) was dissolved in pure dioxane (100 mL) under nitrogen atmosphere and the mixture was cooled to 10°C. Keeping the inert atmosphere, Br_2 (60 g, 0.37 mol) was added drop-wise with continuous stirring during 1 h at a temperature less than 15°C. During the reaction a continuous flow of nitrogen gas was maintained through one neck of the RB flask and a guard tube was placed at the other neck to release the fumes coming out of the reaction. The mixture was stirred for 48 h at RT. After 48 h, the RM was poured into 5% solution of sodium

bicarbonate ($NaHCO_3$) (500 mL) with continuous stirring. Thereafter, the RM was extracted three times with ethyl acetate (EtOAc). The organic layer was washed with water, filtered through anhydrous sodium sulphate (anhyd. Na_2SO_4) and concentrated to get crude product. The crude product was purified by column chromatography over silica gel, eluting with 100% pet ether (PE) to get pure product **13** (pale green solid, 23.52 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.86-4.81(m, 1H), 4.45-4.34(m, 4H), 3.07-2.98(m, 1H), 2.78-2.71(m, 1H), 2.62-2.51(m, 1H), 2.14-2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 114.9, 68.3, 68.2, 68.1, 47.5, 45.2, 30.3; DEPT135 (100 MHz, $CDCl_3$): CH, CH_3 (δ 47.5); CH_2 (δ 68.2, 68.1, 45.2, 30.3).

Synthesis of endo-2,4-dibromodicyclopentadiene-1,8-dione bisethyleneketal, 14 (Ref. 18)

NaOH (12.60 g, 0.32 mol) was added in a suspension of compound **13** (23 g, 0.06 mol) and methanol (100 mL). The mixture was refluxed for 3 h. After cooling, the RM was poured into ice and stirred for 1 h. The mixture was kept for some time and the precipitated solid was filtered, washed with water and dried in a desiccator. The crude product was recrystallized with ethanol to get pure crystals of compound **14** (white solid, 20.21 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18-6.16(m, 1H), 6.05(s, 1H), 5.83-5.81(m, 3H), 4.22-4.11(m, 4H), 4.02-3.86(m, 4H), 3.50-3.48(m, 1H), 3.07-3.05(m, 1H), 2.71(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 133.2, 132.7, 128.2, 126.2, 115.8, 67.9, 66.5, 66.4, 65.5, 65.4, 55.9, 49.7, 47.4; DEPT135 (100 MHz, $CDCl_3$): CH, CH_3 (δ 134.7, 133.2, 132.7, 55.9, 49.7, 47.4); CH_2 (δ 66.5, 66.4, 65.5, 65.4).

Synthesis of endo-2,4-dibromodicyclopentadiene-1,8-dione 8-ethylene ketal, 15 (Ref. 18)

At RT, conc. HCl (20 mL) was added drop-wise to a stirred solution of compound **15** (20 g, 0.05 mol) in THF (100 mL). The mixture was stirred for 18 h and then poured into 10% aqueous solution of $NaHCO_3$ (500 mL). The mixture was kept at RT for some time. The precipitated product was filtered off, dried and recrystallized with toluene to get pure crystals of compound **14** (creamy solid, 16.22 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.61(m, 1H), 6.01-5.98(m, 1H), 5.93-5.91(m, 1H), 4.27-4.16(m, 2H), 4.07-4.02(m, 1H), 3.97-3.92(m, 1H), 3.65-3.63(m, 1H), 3.19(t, J = 5.35 Hz, 1H), 3.08-3.05(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 158.4, 134.9, 131.1, 130.5, 126.9, 66.6, 66.5, 65.9, 52.1, 48.1, 47.4; DEPT135 (100 MHz, $CDCl_3$): CH, CH_3 (δ 158.4, 134.9, 130.5, 52.1, 48.1, 47.4); CH_2 (δ 66.6, 65.9).

Synthesis of (2'S,3a'R,3b'S,4'S,7'S,7a'R,8a'S)-4',8a'-dibromo-2'-(triisopropylsilyl)-2',3',3a',3b',4',7',7a',8a'-octahydrospiro[[1,3] dioxolane-2,9'-[4,7]methanocyclopenta[a]inden]-8'(1'*H*)-one, 16

Compound **15** (10 g, 0.03 mol) was stirred in dry DCM (100 mL). $TiCl_4$ (15.74 g, 0.08 mol) was added in the RM under inert atmosphere followed by the addition of allyltriisopropylsilane (8.22 g, 0.04 mol) at RT. The RM was stirred for 12 h and then the reaction was quenched with aqueous solution of ammonium chloride (NH_4Cl). The RM was extracted three times with DCM and the organic layer was washed with water, filtered through anhyd. Na_2SO_4 and concentrated to get the crude product. The crude product was purified by column chromatography on silica gel, eluting with 10% EtOAc in PE to get pure product **16** (white solid, 8.50 g, 55%, m.p.108-110°C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25-6.21(m, 2H), 4.25-4.15(m, 2H), 4.03-3.98(m, 1H), 3.94-3.90(m, 1H), 3.28-3.25(m, 1H), 2.99-2.96(m, 1H), 2.75(dd, J = 5.51 Hz, 3.87 Hz, 1H), 2.68-2.65(m, 1H), 2.54-2.49(m, 1H), 2.36-2.27(m, 2H), 1.97(dd, J = 7.73 Hz, 5.15 Hz, 1H), 1.584-1.581(m, 1H), 1.08-1.05(m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.4, 137.5, 134.6, 125.8, 71.4, 69.3, 66.6, 65.8, 54.6, 54.3, 53.3, 47.8, 47.4, 39.2, 24.8, 19.28, 19.25, 11.46; DEPT135 (100 MHz, $CDCl_3$): δ CH, CH_3 (δ 137.5, 134.6, 54.6, 54.3, 53.2, 47.4, 24.8, 19.28, 19.25, 11.4); CH_2 (δ 66.6, 65.8, 47.8, 39.2); HRMS (ESI): *m/z* Calcd for $C_{24}H_{36}Br_2O_3SiNa[M + Na]^+$: 581.0693. Found: 581.0691; IR (neat): 2942, 2865, 1745, 1464, 1267, 1027, 760, 675 cm^{-1}.

Synthesis of (2'S,3a'R,3b'R,4'R,7'S,7a'S,8a'R)-2'-(triisopropylsilyl)-2',3',3a',3b',4',7',7a',8a'-octa-hydrospiro[[1,3]dioxolane-2,9'-[4,7]methanocy-clopenta[a]inden]-8'(1'*H*)-one, 17

Dissolve the compound **16** (5 g, 8.9 mmol) in dry toluene followed by the addition of azobisisobutyronitrile (147 mg, 10 mol%). The whole setup was covered with aluminum foil to maintain dark conditions. Now tributyltinhydride (5.72 g, 19.6 mmol) was added drop-wise to the RM. The reaction mixture was refluxed at 110°C for 4 h. After monitoring *via* TLC, the reaction mixture was cooled down and solvent was evaporated at reduced pressure to get crude mixture. The crude mixture was purified by column chromatography on silica gel, eluting with 10% EtOAc in PE to get pure product **17** (pale green liquid, 2.54 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.29-6.27(m, 1H), 6.17-6.14(m, 1H), 3.94-3.87(m, 2H), 3.84-3.80(m, 2H), 3.02-2.99(m, 1H), 2.96-2.93(m, 1H), 2.91-2.89(m, 1H), 2.68-2.64(m, 1H), 2.36-2.29(m, 2H), 2.08-2.03(m, 1H), 1.88-1.85(m, 2H), 1.71-1.67(m, 1H),

1.60(s, 1H), 1.05-1.03(m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 226.1, 133.9, 133.7, 127.0, 65.1, 64.6, 58.6, 55.0, 51.5, 50.0, 47.0, 42.9, 40.5, 36.2, 24.4, 19.3, 11.5; DEPT135 (100 MHz, $CDCl_3$): CH, CH_3 (δ 133.9, 133.7, 58.6, 55.0, 51.5, 49.9, 47.0, 42.9, 24.4, 19.3, 11.5); CH_2 (δ 65.1, 64.6, 40.5, 36.2); HRMS (ESI): *m/z* Calcd for $C_{24}H_{39}O_3Si$ $[M + H]^+$: 403.2663. Found: 403.2660; IR (neat): 2931, 2865, 1727, 1465, 1296, 1100, 757 cm^{-1}.

Synthesis of (2S,3aR,3bR,6aR,7aR)-2-(triisopropylsilyl)octahydro-1*H*-cyclopenta[a]pentalene-5,7-dione, 19

Compound **17** (200 mg, 0.49 mmol) was dissolved in a solvent mixture consisting of carbon tetrachloride, acetonitrile and water (5:5:7) respectively. Sodium metaperiodate (426 mg, 1.99 mmol) and ruthenium dioxide hydrate (15 mg, 20 mol%) were added sequentially. The resulting mixture was stirred vigorously at RT for 18 h. After the completion of reaction, DCM and water were added and the aqueous phase was separated. The aqueous phase was extracted with EtOAc and the combined organic layers were dried over anhyd. Na_2SO_4, filtered and concentrated *in vacuo* to get crude product **18**. Then, to the crude mixture, 1N 10 mL HCl and dioxane (20 mL) was added. The reaction mixture was kept at reflux for 16 h. After this time, the reaction mixture was extracted with EtOAc and the organic layer was separated out. The organic layer was washed with brine, filtered over anhyd. Na_2SO_4, concentrated and dried to get the crude compound **19**. The crude mixture was purified by column chromatography on silica gel, eluting with 10% EtOAc in PE to get pure product **19** (yellow liquid, 115 mg, 69%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88-2.81 (m, 2H), 2.66-2.56 (m, 3H), 2.48-2.45 (m, 2H), 2.21-2.16 (m, 1H), 2.09-1.85 (m, 5H), 1.08-1.05(m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 222.5, 216.7, 52.8, 50.7, 45.9, 44.9, 43.5, 39.2, 37.7, 35.4, 23.3, 19.3, 11.5; DEPT135 (100 MHz, $CDCl_3$): δ CH, CH_3 (δ52.8, 50.7, 45.9, 43.5, 23.3, 19.3, 11.5); CH_2 (δ 44.9, 39.2, 37.7, 35.4); HRMS (ESI): *m/z* Calcd for $C_{20}H_{35}O_2Si$ $[M + H]^+$: 335.2401. Found: 335.2402; IR (neat): 2931, 2865,1727, 1720, 757 cm^{-1}.

Conclusion

A new strategy has been successfully developed to obtain linear triquinane by using [3+2] cycloaddition, ruthenium catalyzed oxidative cleavage followed by Krapcho decarboxylation. The linear triquinane thus formed is having *cis-anti-cis* configuration which was confirmed by the X-ray single crystal diffraction data of compound **16**.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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