

## Synthetic studies towards pteridanone, a novel protoilludane-type tricyclic sesquiterpenoid

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Dedicated with respect and affection to Professor Sukh Dev on his 80<sup>th</sup> birthday

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### Abstract

A synthetic approach directed towards the total synthesis of the novel protoilludane sesquiterpene pteridanone, the aglycon of the glucoside pteridanoside from a bioactive hot-water extract of the neotropical braken fern *Pteridium aquilinum* var. *caudatum* (Dennstaedtiaceae), has been delineated. This endeavour has delivered an advanced pre-target having the complete protoilludane skeleton with strategic placement of the functionalities and set the stage for the total synthesis of the natural product. The key features of our approach are the ready availability of the starting material (1,5-cyclooctadiene), an interesting photochemical [2+2]-cycloaddition and a thallium(III) mediated ring expansion reaction.

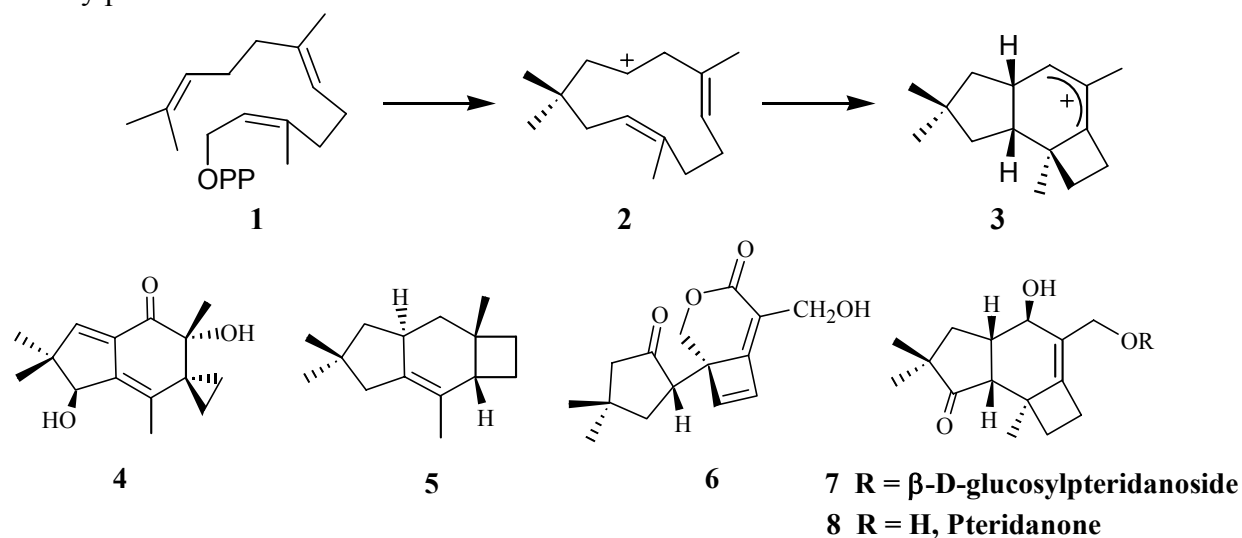
**Keywords:** Sesquiterpenes; [2+2]-photocycloaddition; ring expansion; Wittig reaction.

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Nature exhibits special flair for creating a vast array of carbocyclic skeleta with different concatenation of rings, replete with multitude of functionalities and stereochemical intricacies, among sesquiterpenoids.<sup>1</sup> Quite remarkably, this breathtaking diversity emanates from a single biosynthetic precursor in farnesyl pyrophosphate **1**. This skeletal mosaic has always fascinated generations of synthetic chemists and even today sesquiterpenoids continue to be a fertile ground for the exploration of new tactics and strategies in synthesis.<sup>2</sup> The isolation of sesquiterpenes from many diverse and exotic sources in recent years and observation of wide ranging biological activity in many of them has further added to their synthetic appeal.

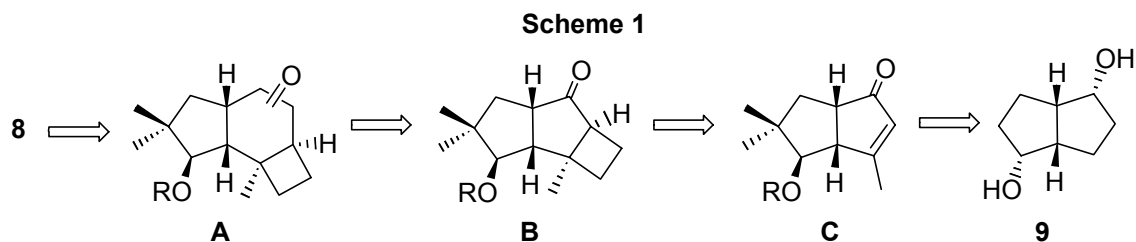
Protoilludyl cation **3**, derived from farnesyl pyrophosphate **1** via the humulenyl cation **2** is a common precursor of a diverse range of sesquiterpene skeleta bearing a variegated union of 3, 4, 5 and 6-membered rings. Examples of some of the different carbocyclic frameworks originating from the protoilludyl cation **2** are represented by illudol **4**, sterpurene **5** and fomannosin **6**.<sup>1</sup> Among these, natural products bearing illudane and sterpurane skeleta are fairly

widespread and the derivatives of the former in particular, exhibit wide-ranging biological activity profile. It is

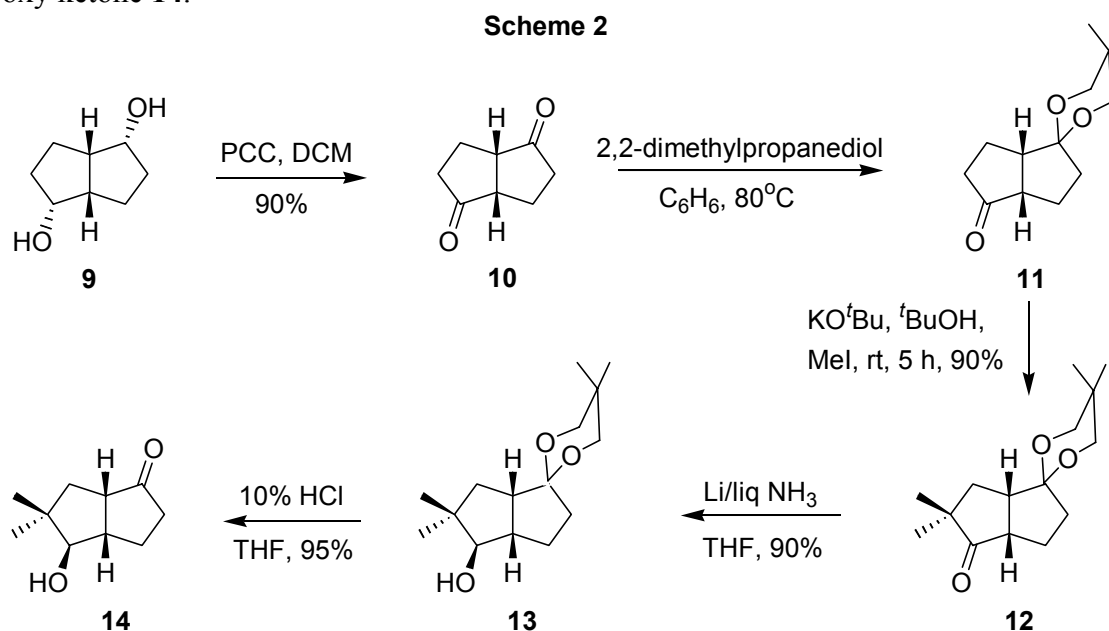


hardly surprising that the protoilludyl cation **2**, itself is captured in nature and many oxygenated derivatives based on this system have been isolated and characterized.<sup>1</sup> Recently, a protoilludane-type sesquiterpene glucoside, pteridanoside **7**, from a bioactive hot-water extract of the neotropical bracken fern *Pteridium aquilinum* var. *caudatum* (Dennstaedtiaceae) has been isolated.<sup>3</sup> The enzymatic hydrolysis of **7** led to its aglycon, pteridanone **8**, bearing an interesting oxygen functionalisation and to our knowledge this is the first protoilludane with a cyclopentanone moiety.<sup>3</sup> In view of our ongoing interest in the synthesis of cyclobutane fused polycyclic sesquiterpenoids,<sup>4</sup> structure of **8** aroused our interest and herein we report our synthetic studies in pursuit of this natural product. Our efforts have led to the acquisition of the complete protoilludyl framework with functionality in the five-membered ring, necessary for the synthesis of the natural product.

Our synthetic approach to pteridanone **8** was delineated through the retrosynthetic analysis depicted in the Scheme 1, which identified the key steps as well as the main starting material. Thus, tricyclic ketone A, embodying the entire skeleton of the natural product **8** and bearing functionalities in the five and the six-membered rings emerged as the advanced pre-target, which in turn could be accessed through the ring expansion of the tricyclic ketone B. The tricyclic ketone B could be derived from the diquinane enone C through stereoselective [2+2]-photocycloaddition. The diquinane enone C was sought to emanate from the bicyclic *cis*-diol **9** of  $C_2$ -symmetry, which is available from the commercially available 1,5-cyclooctadiene.<sup>4a,5</sup> In delineating this synthetic plan, we were influenced by the ongoing efforts in our research group<sup>4</sup> and promising leads in the literature along similar lines.<sup>6</sup>



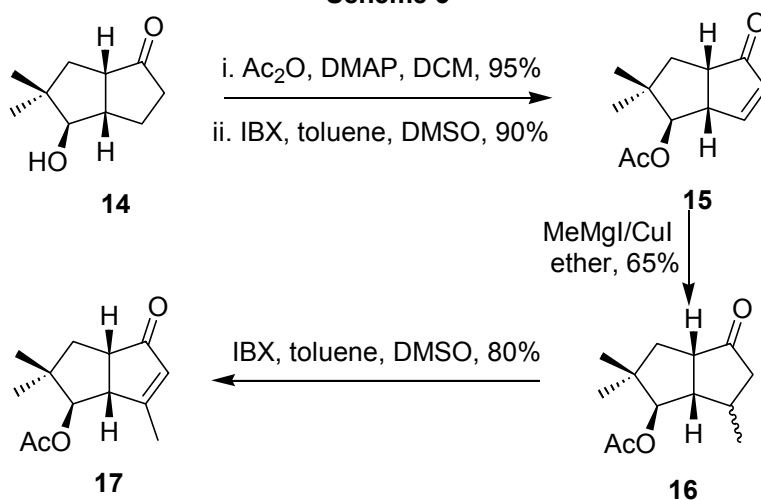
Readily available *cis*-diol **9**, prepared from commercial 1,5-cyclooctadiene *via* Pd(II) catalysed transannular cyclization,<sup>5</sup> was oxidised with PCC to the dione **10**, Scheme 2.<sup>4b</sup> At this stage, it was important to differentiate between the two carbonyl groups of **10**. Selective monocarbonyl protection in **10** with 2,2-dimethylpropanediol furnished the mono-ketal **11**. Protected ketone **11** was now subjected to  $\alpha$ -*gem*-dimethylation to furnish **12** and further reduced with lithium metal in liq. NH<sub>3</sub> to furnish the thermodynamically more stable *exo*-hydroxy compound **13** in a stereoselective manner. Deprotection of the ketal moiety in **13** was smooth and led to the hydroxy ketone **14**.



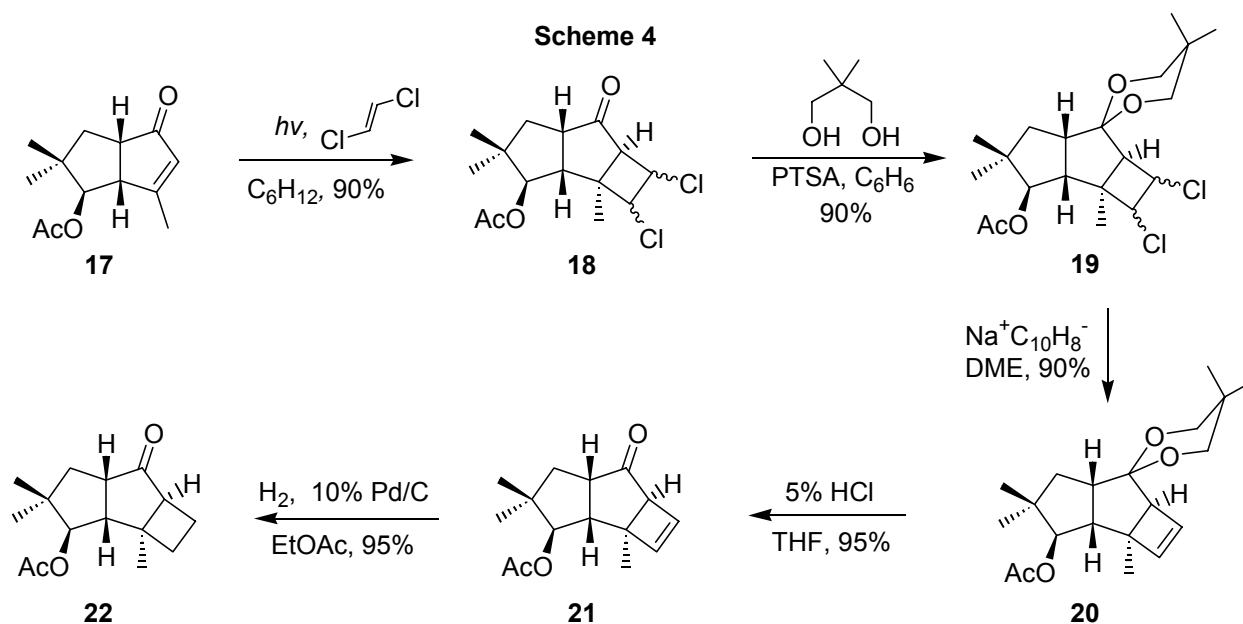
Stage was now set to elaborate the bicyclic ketone **14** for the projected [2+2]-photocycloaddition protocol (Scheme 1). Towards this end, the hydroxy group in **14** was protected and the derived acetate was treated with IBX to effect one step dehydrogenation as described recently by Nicolaou et al.<sup>7</sup> to furnish the enone **15** in excellent yield, Scheme 3. Copper(I) mediated addition of methylmagnesium iodide to **15** delivered **16** as a mixture of diastereomers through 1,4-conjugate addition. The trimethylated ketone **16** was again subjected to IBX oxidation<sup>7</sup> to deliver the bicyclic enone **17**, corresponding to the intermediate C identified in the retrosynthetic theme shown in Scheme 1.

Irradiation of **17** from a 450W medium pressure Hg-lamp, in the presence of an excess of *trans*-1,2-dichloroethylene, furnished tricyclic ketones **18** in excellent yield, as a mixture of diastereomers, Scheme 4.<sup>4</sup> The halogen functionality in **18** now needed to be dispensed with. Attempts towards direct reductive dehalogenation in **18** were not productive and therefore a more circuitous approach involving protective group manoeuvre was resorted to. Thus, the carbonyl group in the tricyclic ketones **18** was protected as the 2,2-dimethyl-1,3-propylene ketal **19** and further eliminative dehalogenation<sup>8</sup> furnished the cyclobutene compound **20** in good yield. Deprotection of the ketal moiety in **20** delivered the unsaturated ketone **21** and was hydrogenated to furnish the saturated tricyclic ketone **22**, corresponding to the advanced intermediate B identified in the retrosynthetic formulation.

Scheme 3

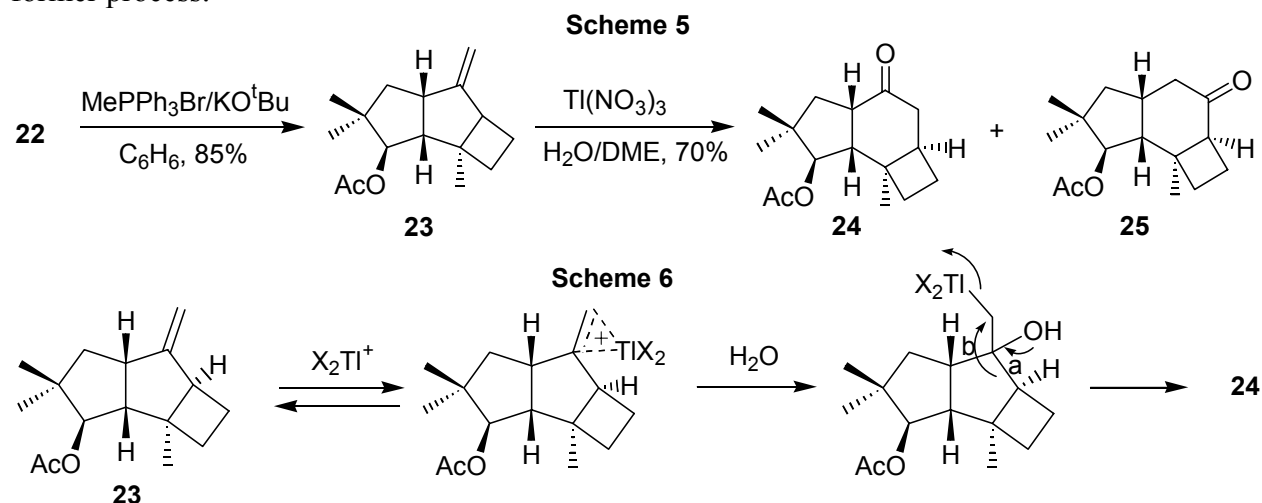


Scheme 4



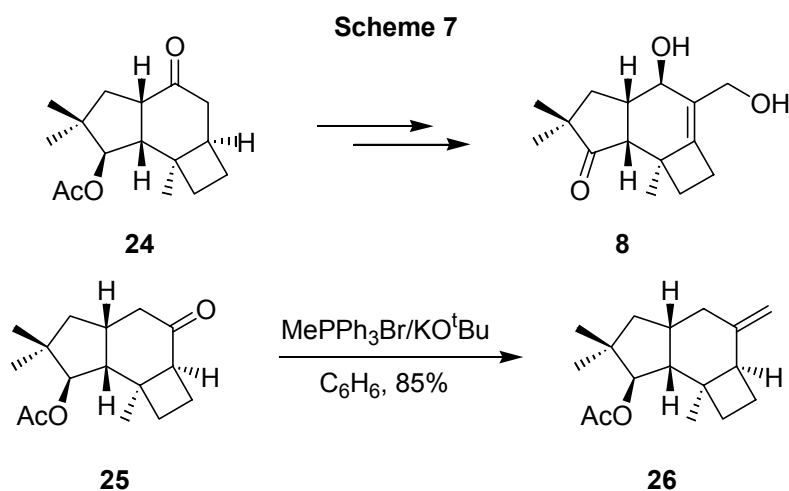
The next target was to transform the central five-membered ring in the tricyclic ketone **22** to a six-membered ring through one carbon ring expansion methodology. In this regard, several efforts using conventional protocols with diazomethane or diazoesters in the presence of various catalysts proved to be singularly unsuccessful. An alternate approach was thus devised in which one carbon ring expansion was sought to be effected through thallium(III) oxidation of the terminal olefin derived from **22**.<sup>9</sup> To implement this protocol, tricyclic ketone **22** was subjected to Wittig olefination to furnish the exocyclic olefin **23**, Scheme 5. On exposing **23** to oxidation with thallium trinitrate (TTN)<sup>9</sup> in aqueous DME, two regioisomeric ketones **24** and **25** in a 2:1 ratio were obtained. While the structures of **24** and **25** were revealed through the incisive analysis of their spectroscopic data (*vide experimental*), a distinction between them beyond the realm of ambiguity was not possible. Therefore, the crystalline tricyclic cyclohexanone **24** was subjected to X-ray crystal structure determination and an ORTEP projection is shown in the Figure.

The regioselectivity observed in the preferential formation of **24** during the ring expansion is interesting. If one considers the mechanism of the thallium(III) mediated ring expansion, as depicted in Scheme 6, it reveals that the regiochemistry emerges through the preferential migration of the cyclobutylcarbinyl C-C (bond 'a') vs cyclopentylcarbinyl C-C bond ('b') migration. The product ratio of **24** and **25** observed here indicates the dominance of the former process.



With the arrival of **24** and **25**, we had reached the pre-target stage A indicated in Scheme 1. What remained to be done en route was to effect strategic functional group adjustments in these substrates to reach the target. Our initial efforts in this direction employing the limited amounts of tricyclic ketones **24** and **25** available to us have not been successful. In particular,  $\alpha$ -carbomethoxylation and  $\alpha$ -hydroxymethylation on **24** proved to be quite capricious. We therefore decided to first accomplish the synthesis of the full framework of the protoilludane system with appropriate functionalisation in the five-membered ring. This was accomplished simply by subjecting **25** to a Wittig olefination to furnish the C<sub>15</sub>-tricycle **26** having the complete

protoilludane framework, Scheme 7. Access to **26** was a satisfying accomplishment and sets the stage for further evolution towards the target structure **8**.



In summary, a new synthetic approach to the protoilludane system has been executed, from the commercially available 1,5-cyclooctadiene, en route the newly isolated sesquiterpene natural product pteridanone **8**.

## Experimental

All compounds reported here are racemic and the relative configuration shown here is for convenience only. All reactions were monitored by employing tlc technique using appropriate solvent systems for development. Moisture sensitive reactions were carried out using standard syringe-septa techniques under nitrogen or argon atmosphere. Dichloromethane and chloroform were distilled over  $\text{P}_2\text{O}_5$ . Benzene and DME were distilled over sodium and stored over pressed sodium wire. Dry tetrahydrofuran was distilled freshly over sodium-benzophenone ketyl prior to use. DMSO and TMSCl were dried over calcium hydride. All solvent extracts were washed with water, brine and dried over anhydrous sodium sulphate, and then concentrated under reduced pressure. Yields reported are of isolated material and the homogeneity was judged by tlc and NMR.

Analytical thin layer chromatography (tlc) was performed on (10×5 cm) glass plates coated with Acme's silica gel G or GF<sub>254</sub> (250 mm), containing 13% of calcium sulphate as binder. Column chromatography was performed using Acme's silica gel (100-200 mesh size). The columns were usually eluted with ethyl acetate-hexane (60-80 °C). Infrared spectra were recorded on JASCO FT-IR 410 spectrometer. <sup>1</sup>H (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were recorded on a JEOL JNM-λ 300 spectrometer in chloroform-d ( $\text{CDCl}_3$ ) and chemical shifts are reported in  $\delta$  scale with reference to internal tetramethylsilane (for <sup>1</sup>H NMR) or central line (77.1 ppm) of  $\text{CDCl}_3$  (for <sup>13</sup>C NMR) as standard unless stated otherwise. The standard

abbreviations s, d, t, q, m and b refer to singlet, doublet, triplet, quartet, multiplet and broad, respectively. Mass spectral measurements were carried out on either a JEOL, JMS DX-303 or on VG-Autospec spectrometers.

**(3aS\*,6aS\*)-5',5'-Dimethylperhydropentalene-[1,2']-spiro-1',3'-dioxan-4-one [11].** A solution of the diketone **10** (5 g, 36.2 mmol),<sup>4a</sup> 2,2 dimethyl-1, 3 propanediol (5.6 g, 53.8 mmol) and camphorsulphonic acid (20 mg) in benzene (50 ml) was refluxed. After 3 h the reaction mixture was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product, which was charged on a silica gel column. Elution with 10% ethyl acetate–hexane furnished the ketal **11** (5.7 g, 70%) as an oil. IR: 2953, 1736, 1479 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$  3.55-3.36 (m, 4H), 2.90-2.82 (m, 1H), 2.68-2.60 (m, 1H), 2.38-2.20 (m, 2H), 2.07-1.93 (m, 4H), 1.85-1.69 (m, 2H), 1.09 (s, 3H), 0.85 (s, 3H); <sup>13</sup>C NMR:  $\delta$  222.7, 109.1, 72.1, 71.9, 49.0, 47.6, 38.2, 30.3, 30.0, 24.5, 22.6, 22.2, 20.8; MS: *m/z* 224(M<sup>+</sup>).

**(3aS\*,6aS\*)-5,5,5',5'-Tetramethylperhydropentalene-[1,2']-spiro-1',3'-dioxan-4-one [12].** To a solution of ketone **11** (5.5 g, 24.5 mmol) in dry <sup>t</sup>BuOH (50 ml) at 0°C was added KO<sup>t</sup>Bu (6 g, 53.6 mmol). After 2 minutes, MeI (10 ml) was added and stirring was continued for 0.5 h. The reaction mixture was filtered through a cotton plug and the filtrate was concentrated to afford a viscous liquid, which was charged on a silica gel column. Elution with 8% ethyl acetate–hexane furnished the *gem*-dimethylated compound **12** as a viscous liquid (5g, 81%). IR: 1736 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$  3.53 (s, 2H), 3.43 (q, J= 10.6 Hz, 2H), 3.01-2.85 (m, 2H), 2.05-1.90 (m, 3H), 1.86-1.77 (m, 1H), 1.65-1.52 (m, 2H), 1.07 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H), 0.96 (s, 3H); <sup>13</sup>C NMR:  $\delta$  224.3, 109.7, 72.9, 71.2, 47.6, 46.8, 41.6, 38.1, 31.0, 30.0, 25.4, 24.3, 22.8, 22.5, 22.3; MS: *m/z* 252(M<sup>+</sup>).

**(3aS\*, 4R\*, 6aS\*)-4-Hydroxy-5, 5-dimethylperhydro-1-pentalenone [14].** A solution of the ketone **12** (5 g, 19.6 mmol) in dry THF (20 ml) was added dropwise to a blue colored solution of lithium-NH<sub>3</sub> (generated by adding lithium metal 200 mg, 28.6 mmol in liq. NH<sub>3</sub> 400 ml) at –33°C. After 1 h, excess of lithium was quenched by the slow addition of solid ammonium chloride and the ammonia was allowed to evaporate. The residue was extracted with ethyl acetate (150 mlx2) and the combined organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product, which was charged on a silica gel column. Elution with 15% ethyl acetate–hexane furnished the alcohol **13** (4.5 g, 90%) as oil.

To a solution of alcohol **13** (4.5 g, 17.7 mmol) in THF (30 ml) was added 20% HCl (0.3 ml). After 2 h, the reaction mixture was diluted with water (50 ml) and extracted with ethyl acetate (30 mlx2) and the organic extract was washed with water, saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product, which was charged on a silica gel column. Elution with 20% ethyl acetate–hexane furnished the ketone **14** (2.8 g, 94%) as oil. IR: 3440, 2954, 2870, 1733 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$  3.38-3.33 (m, 1H),

2.71-2.53 (m, 2H), 2.48-2.24 (m, 2H), 2.18-1.90 (m, 3H), 1.40 (dd,  $J = 13.5, 6.9$  Hz), 1.01 (s, 3H), 0.92 (s, 3H).

**(1R\*, 3aS\*, 6aS\*)-2,2-Dimethyl-4-oxo-1,2,3,3a,4,6a-hexahydro-1-pentalenylacetate [15].** A solution of alcohol **14** (2.8 g, 16.7 mmol), acetic anhydride (2.02 g, 19.8 mmol) and DMAP (20 mg) in dry DCM (25 ml) was stirred at rt. After 1 h, the reaction mixture was washed with water, saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave a crude product, which was charged on silica gel column. Elution with 15% ethyl acetate–hexane furnished the corresponding acetate (3.4 g, 97%) as oil. IR:  $1735\text{cm}^{-1}$ .

To the above keto-acetate (2 g, 9.5 mmol) in dry toluene and DMSO (2:1, 15 ml) was added IBX (4 g, 14.3 mmol) and stirred the mixture for 4 h at  $75^{\circ}\text{C}$ . The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic extract was washed with water, saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product, which was charged on a silica gel column. Elution with 15% ethyl acetate–hexane furnished the enone **15** (1.75 g, 88%) as oil. IR: 3080, 1738,  $1713\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  7.87 (dd,  $J = 5.6, 2.6$  Hz, 1H), 6.03 (dd,  $J = 5.5, 1.8$  Hz, 1H), 4.43 (d,  $J = 6$  Hz, 1H), 3.26 (t,  $J = 6.3$  Hz, 1H), 2.96-2.89 (m, 1H), 2.13 (s, 3H), 1.98 (dd,  $J = 13.2, 9.6$  Hz, 1H), 1.50 (dd,  $J = 13, 8.5$  Hz), 1.05 (s, 3H), 0.97 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  211.6, 171.1, 165.2, 132.8, 82.9, 53.7, 46.8, 45.8, 39.6, 26.4, 21.9, 21.0; HRMS:  $m/z$  Calcd for  $\text{C}_{12}\text{H}_{16}\text{O}_3 + \text{Na}$ : 231.1099; Found 231.1015.

**(1R\*, 3aS\*, 6aR\*)-2,2,6-Trimethyl-4-oxo-1,2,3,3a,4,6a-hexahydro-1-pentalenylacetate [17].** To a suspension of magnesium turnings (242 mg, 10.1 mmol) in dry ether (10 ml) in a two necked (25 ml) round bottomed flask, equipped with a condenser with cold water circulation and nitrogen inlet, was added MeI (1.43 g, 10.1 mmol) so that a gentle reflux could be maintained. After all the metal had reacted, the contents were cooled and added to a suspension of CuI (96 mg, 0.5 mmol) in dry ether (5 ml) at  $-10^{\circ}\text{C}$ . To the resulting yellow colored suspension, the enone **15** (0.7 g, 3.36 mmol) in dry ether (5 ml) was added dropwise. After 1 h, the reaction mixture was quenched with water and extracted with ether. The ether extract was washed with 2% HCl, water and brine. Removal of solvent furnished a pale pink color liquid, which was charged on a silica gel column and elution with 10% ethyl acetate-hexane furnished the compound **16** (0.48 g, 64%) as oil. Spectral data for the major isomer is as follows: IR:  $1738\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.74 (d,  $J = 7.2$  Hz, 1H), 2.76 (m, 1H), 2.63 (dd,  $J = 18, 7.5$  Hz, 1H), 2.41-2.29 (m, 1H), 2.29 (bs, 1H), 2.01 (s, 3H), 2.0-1.86 (m, 2H), 1.49 (dd,  $J = 13.5, 7.5$  Hz, 1H), 1.06 (d,  $J = 6.7$  Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H).

To the ketone **16** (450 mg, 2 mmol) in dry toluene and DMSO (2:1, 10 ml) was added IBX (1 g, 3.57 mmol) and stirred for 4 h at  $75^{\circ}\text{C}$ . The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic extract was washed with saturated sodium bicarbonate, brine and dried over anhydrous sodium sulfate. Evaporation of the solvent gave the crude product, which was charged on a silica gel column. Elution with 20% ethyl acetate–hexane



furnished the enone **17** (370 mg, 83%) as oil. IR: 1738, 1700, 1620  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  5.80 (s, 1H), 4.79 (d,  $J=4.2$  Hz), 3.16 (t,  $J=6.3$  Hz, 1H), 3.01-2.93 (m, 1H), 2.13 (s, 3H), 2.11 (s, 3H), 2.00-1.92 (m, 1H), 1.68 (dd,  $J=13.5, 6.3$  Hz, 1H), 0.91 (s, 3H), 0.90 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  211.5, 178.3, 170.5, 130.1, 81.6, 56.4, 48.8, 45.6, 39.5, 26.6, 22.5, 21.1, 17.9; HRMS:  $m/z$  Calcd for  $\text{C}_{13}\text{H}_{20}\text{O}_3+\text{Na}$ : 247.1310; Found 247.1309.

**(1R\*,2S\*,2aR\*,2bR\*,3R\*,5aS\*)-1,2-Dichloro-2a,4,4-trimethyl-6-oxoperhydrocyclobuta[a]-pentalen-3-yl acetate [18]**. A solution of enone **18** (30 mg, 0.168 mmol) and *trans* 1,2-dichloroethylene (2 ml) in dry cyclohexane (4 ml) was purged with argon and irradiated with a 450 W medium pressure Hanovia mercury vapour lamp, using Pyrex filter at rt. After 10 h of irradiation, the solvent was removed and the crude product was charged on a silica gel column. Elution with 8% ethyl acetate–hexane furnished the [2+2]-addition products as 1,2-dichloroisomers **18** as a white solid (39 mg, 91%). Spectral data for the major isomer, IR: 1736  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.82 (d,  $J=7.8$  Hz, 1H), 4.43 (d,  $J=5.7$  Hz, 1H), 4.07 (t,  $J=5.1$  Hz, 1H), 3.26-3.31 (m, 2H), 2.78 (d,  $J=4.2$  Hz, 1H), 2.09 (s, 3H), 1.98-1.88 (m, 1H), 1.69 (dd,  $J=13.5, 4.5$  Hz, 1H), 1.00 (s, 3H), 0.95 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  214.9, 170.2, 80.0, 69.9, 61.2, 57.1, 48.6, 47.2, 45.1, 43.1, 38.4, 26.5, 22.9, 22.1, 21.1.

**(2aR\*,2bR\*,3R\*,5aS\*)-2a,4,4-Trimethyl-6-oxo-2a,2b,3,4,5,5a,6,6a-octahydrocyclobuta[a]-pentalen-3-yl acetate [21]**. The ketone **18** (500 mg, 1.57 mmol) was subjected to the carbonyl protection using 2,2-dimethyl-1,3-propanediol (210 mg, 2 mmol) and catalytic amount of camphorsulphonic acid (20 mg) in benzene with Dean-Stark water separator for 8 h. The reaction was quenched with bicarbonate, extracted with ether, washed and dried over anhydrous sodium sulfate. Removal of the solvent furnished a crude product, which was purified by a small silica gel pad to afford the ketal **19** as a white solid (590 mg, 93%), which was used as such for the next step.

To a solution of **19** (580 mg, 1.43 mmol) in dry DME (10 ml) at rt, sodium naphthalenide reagent (prepared from 0.313 g, 13.6 mmol of sodium and 3.84 g, 30 mmol of naphthalene in DME, 25 ml at rt for about 12 h) was added until the deep bluish-green color persisted. After 0.5 h, the reaction was quenched with dry methanol (1 ml) and saturated  $\text{NH}_4\text{Cl}$  solution and extracted with ether (30 ml). The organic phase was washed with saturated  $\text{NH}_4\text{Cl}$  solution, brine and dried over anhydrous sodium sulfate. Removal of the solvent gave a crude product, which was charged on a silica gel column and elution with hexane removed naphthalene and less polar impurities. Further elution with 5% ethyl acetate-hexane furnished the *cis*, *anti*, *cis* tricyclic ketal **20** as a clear liquid (460 mg, 96%).

A solution of the above ketal **20** (450 mg, 1.34 mmol) in THF (15 ml) was treated with 10% HCl at rt for 2 h. The reaction mixture was extracted with ethyl acetate and the organic phase was washed with saturated sodium bicarbonate solution, brine and dried over anhydrous sodium sulfate. Removal of the solvent furnished the crude product, which was purified by a small silica gel pad to furnish the tricyclic ketone **21** as a clear liquid (325 mg, 98%).  $^1\text{H}$  NMR:  $\delta$

6.45 (d,  $J=2.1$  Hz, 1H), 6.10 (d,  $J=1.2$  Hz, 1H), 4.76 (d,  $J=9$  Hz, 1H), 3.33-3.24 (m, 1H), 3.01 (s, 1H), 2.70 (t,  $J=10.8$  Hz, 1H), 2.08 (s, 3H), 1.91-1.83 (m, 1H), 1.69 (dd,  $J=13.8, 5.1$  Hz), 1.29 (s, 3H), 0.93 (s, 6H);  $^{13}\text{C}$  NMR:  $\delta$  218.6, 170.4, 149.3, 134.0, 80.4, 61.5, 51.2, 47.6, 46.5, 42.6, 38.6, 26.8, 22.5, 21.2, 18.2. MS:  $m/z$  248 ( $\text{M}^+$ )

**(2aR\*,2bR\*,3R\*,5aS\*)-2a,4,4-Trimethyl-6-oxoperhydrocyclobuta[a]pentalen-3-yl acetate [22].** The cyclobutene ketone **21** (320 mg, 1.29 mmol) was hydrogenated using 10% Pd/C catalyst (5 mg) at 1 atm pressure in ethyl acetate (2 ml). After 2 h, the catalyst was removed and the solvent was evaporated. The crude product was charged on a silica gel column and elution with 10% ethyl acetate-hexane furnished the cyclobutane ketone **22** (290 mg, 90%) as oil. IR: 1738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.64 (d,  $J=9.6$  Hz, 1H), 3.20-3.12 (m, 1H), 2.57 (t,  $J=9.3$  Hz, 1H), 2.46-2.34 (m, 2H), 2.06 (s, 3H), 2.04-1.90 (m, 3H), 1.77-1.72 (m, 1H), 1.61 (d,  $J=13.8, 5.4$  Hz, 1H), 1.23 (s, 3H), 0.92 (s, 6H);  $^{13}\text{C}$  NMR:  $\delta$  224.8, 170.3, 80.2, 54.1, 50.6, 48.5, 42.7, 42.5, 39.1, 33.1, 26.6, 22.3, 21.2, 20.7, 19.1. MS:  $m/z$  273.1 ( $\text{M}^+\text{+Na}$ ).

**(2aS\*,2bR\*,3R\*,5aS\*)-2a,4,4-Trimethyl-6-methyleneperhydrocyclobuta[a]pentalen-3-yl acetate [23].** To a solution of ketone **22** (100 mg, 0.4 mmol) in dry THF (2 ml) was added the ylide (0.6 mmol, 1.5 eq, prepared from  $\text{CH}_3\text{PPh}_3^+\text{Br}^-$  and  $\text{K}^+\text{O}^t\text{Bu}$  in 3 ml of dry THF) dropwise at rt. After 1 h, the reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was charged on a silica gel column. Elution with 2% ethyl acetate-hexane furnished the olefin **23** (90 mg, 90%) as oil. IR: 3080, 1738  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.82 (s, 1H), 4.76 (s, 1H), 4.78 (d,  $J=9.6$  Hz, 1H), 3.36 (m, 1H), 2.73 (bs, 1H), 2.39-2.31 (m, 2H), 2.04 (s, 3H), 2.01-1.91 (m, 1H), 1.84 (t,  $J=9.3$  Hz, 1H), 1.74-1.70 (m, 1H), 1.52 (dd,  $J=13.5, 4.6$  Hz, 2H), 1.14 (s, 3H), 0.96 (s, 3H), 0.92 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  170.6, 163.1, 106.0, 81.0, 57.6, 50.2, 45.8, 44.4, 44.0, 43.3, 32.8, 27.8, 23.4, 23.1, 21.3, 21.0; MS:  $m/z$  271 ( $\text{M}^+\text{+Na}$ ).

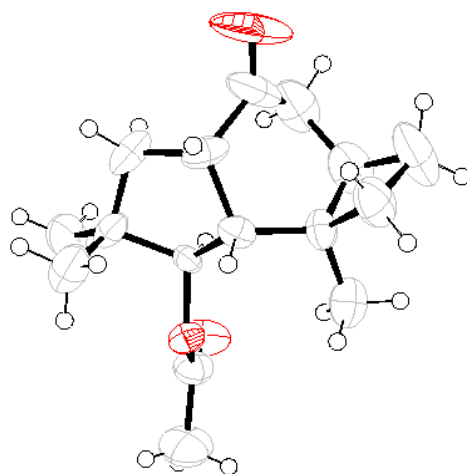
**(4aS\*,7R\*,7aR\*,7bS\*)-6,6,7b-Trimethyl-4-oxoperhydrocyclobuta[e]inden-7-yl acetate [24] and (4aR\*,7R\*,7aR\*,7bR\*)-6,6,7b-trimethyl-3-oxoperhydrocyclobuta[e]inden-7-yl acetate [25].** To a solution of olefin **23** (36 mg, 0.145 mmol) in DME (2 ml) was added dropwise a solution of  $\text{Tl}(\text{NO}_3)_3$  in 1% HCl (2 ml). After 15 min, the reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with ether. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. Evaporation of solvent gave a crude product, which was charged on a silica gel column. Elution with 8% ethyl acetate-hexane furnished ketone **24** as a solid (18 mg, 47%), continued elution with 10% ethyl acetate-hexane furnished the minor ketone **25** as a clear liquid (8 mg, 21%). Structure of **24** was determined by X-Ray crystallographic analysis (*vide infra*). Spectral data for **24**, IR: 1737, 1711  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  5.06 (d,  $J=10.8$  Hz, 1H), 3.06-2.95 (m, 2H), 2.53 (bs, 1H), 2.35 (t,  $J=10.8$  Hz, 1H), 2.32-2.24 (m, 1H), 2.08 (s, 3H), 1.95-1.77 (m, 2H), 1.68-1.46 (m, 4H), 1.16 (s, 3H), 1.02 (s, 3H), 0.92 (s,

3H);  $^{13}\text{C}$  NMR:  $\delta$  215.4, 170.6, 81.2, 51.7, 46.2, 42.7, 41.3, 41.2, 40.4, 36.6, 30.8, 27.0, 25.3, 21.8, 21.3, 20.9. Spectral data for **25**, IR: 1738, 1702  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.83 (d,  $J=9$  Hz, 1H), 2.85-2.79 (m, 2H), 2.52 (bs, 1H), 2.44-2.31 (m, 1H), 2.19-2.01 (m, 2H), 2.05 (s, 3H), 1.95-1.88 (m, 1H), 1.76 (dd,  $J=12.6, 6.6$  Hz, 2H), 1.24 (s, 3H), 1.00 (s, 3H), 0.90 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  215, 170.5, 81.5, 51.5, 47.1, 45.6, 43.1, 41.8, 40.7, 35.6, 32.8, 27.5, 25.8, 22.3, 21.2, 19.2.

**(4a*S*\*,7*R*\*,7a*R*\*,7b*S*\*)-6,6,7b-Trimethyl-3-methyleneperhydrocyclobuta[*e*]inden-7-yl**

**acetate [26].** To a solution of ketone **25** (6 mg, 0.023 mmol) in dry THF (2 ml) was added the ylide (0.03 mmol, 1.3 eq, derived from  $\text{CH}_3\text{PPh}_3^+\text{Br}^-$  and  $\text{K}^+\text{O}^t\text{Bu}$  in 3 ml of dry THF) dropwise at rt. After 1 h, the reaction mixture was quenched with water and extracted with ether. The organic extract was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was charged on silica gel column. Elution with 2% ethyl acetate-hexane furnished the olefin **26** (5 mg, 84%) as oil. IR: 3070, 1740  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  4.69 (s, 1H), 4.60 (d,  $J=9$  Hz, 1H), 4.59 (s, 1H), 2.79 (dd,  $J=12.5, 7.5$  Hz, 1H), 2.67 (dd,  $J=18.1, 9.7$  Hz, 1H), 2.52 (d,  $J=9$  Hz, 1H), 2.4-2.28 (m, 1H), 2.2-1.96 (m, 3H), 2.02 (s, 3H), 1.75-1.50 (m, 3H), 1.33-1.26 (m, 2H), 1.09 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H);  $^{13}\text{C}$  NMR:  $\delta$  170.6, 148.5, 109.1, 82.1, 46.9, 46.3, 44.2, 40.7, 39.6, 33.9, 33.0, 32.3, 26.6, 26.5, 21.5, 21.4, 21.1; MS: 220 ( $\text{M}^+-42$ ).

**Crystal Data for 24:** X-ray data were collected at 293K on a SMART CCD-BRUKER diffractometer with graphite monochromated  $\text{MoK}\alpha$  radiation ( $\lambda=0.7103\text{\AA}$ ). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on  $F^2$  using SHELXL-97. Compound **24**:  $\text{C}_{16}\text{H}_{24}\text{O}_3$  MW=264, Crystal system: monoclinic, space group: Pn, cell parameters:  $a=7.836$  (2)  $\text{\AA}$ ,  $b=10.818$  (3)  $\text{\AA}$ ,  $c=17.885$  (5)  $\text{\AA}$ ,  $\beta=91.611$  (5) $^\circ$ ,  $V=1515.71$   $\text{\AA}^3$ ,  $Z=4$ ,  $D_c=1.158$   $\text{gcm}^{-3}$ ,  $F(000)=576.0$ ,  $\mu=0.08$   $\text{mm}^{-1}$ . Total number of l.s. parameters = 351,  $R1=0.0729$  for 3095  $F_o > 4\text{sig}(F_o)$  and 0.1024 for all 4794 data. GOF = 0.933, Restrained GOF = 0.933 for all data. There are two independent molecules in asymmetric unit.



**Figure.**

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre. The CCDC depository number is CCDC 199848. This data can be obtained by free of charge via [www.ccdc.cam.ac.uk/conts/retrieving.html](http://www.ccdc.cam.ac.uk/conts/retrieving.html). An ORTEP diagram of **24** with 50% ellipsoidal probability is shown in the Figure (excluding 2<sup>nd</sup> molecule for clarity).

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