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FULL PAPER

A total synthesis of (±)-ceratopicanol via palladium catalyzed reductive cyclization.

Dr. Rira Kim[a], Sanghyeon Lee[a], Jaeyeon Lee[a], and Prof. Dr. Hee-Yoon Lee*[a]

Abstract: An efficient total synthesis of ceratopicanol was achieved through successive Pd catalyzed reductive cycloaddition and cyclization reactions. The Pd mediated cyclization reaction to form a triquinane structure demonstrated that a small structural difference changed the reaction pathway either to form different structures or reduced non-cyclized product depending on the reaction conditions.

Introduction

Discovery of a novel linearly fused triquinane sesquiterpene, (+)-ceratopicanol in 1988, afforded crucial key to support the biogenetic mechanism of hirsutene and associated sesquiterpenoids synthesized through protoilludane cation rearrangement from humulene.[1] (Figure 1) In addition, it was recently reported that ceratopicanol and other terpenes might be useful for prophylaxis or the treatment of pain,[2] and also its angelate ester showed moderate antifeedant effect on *S. littoralis*.[3]

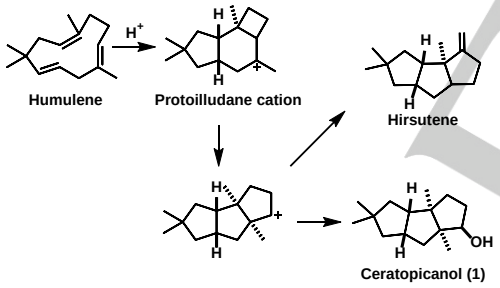

Figure 1. Biogenic origin of ceratopicanol and hirsutene.

Along with biogenetic and pharmacological significances, ceratopicanol is an intriguing and challenging synthetic target due to its highly congested structural features[4] with unusual five contiguous chiral centers including two consecutive quaternary carbons in the linearly fused *cis*, *anti*, *cis*-triquinane framework. For these reasons, there are eight reports of total synthesis and a formal synthesis.[5] Elegant synthetic strategies such as arene-olefin meta cycloaddition reaction,[5c] squaric acid mediated oxy-Cope rearrangement,[5d] free radical mediated cyclizaiton,[5b] and [3+2] cycloaddition reactions of trimethylenemethanes[5h] were explored to construct the linearly fused triquinane structure with contiguous quaternary centers. Among these total syntheses, the seemingly straightforward strategy using tinhydride mediated free radical cyclization of the enyne compound **A**, produced unanticipated product **B** without the desired triquinane compound **13**.[5b] While formation of **B** was thought to be via well-established rearrangement of initially formed desired five-membered ring,[6] further study strongly indicated that the cyclization occurred through endo-cyclic closure to form **B** directly (Figure 2).

For the construction of a five-membered ring from the 1-hexen-5-yne, palladium mediated cyclization reaction[7] is the well-known alternative to free radical mediated cyclization reaction. Thus, we envisioned that construction of the framework of ceratopicanol **1** could be feasible via palladium catalyzed reaction from **A**. The palladium mediated reductive cyclization of **A**, could serve not only as the alternative to free radical cyclization reaction but also as the test ground for influence of seemingly small structural change that would generate congested quaternary carbon centers to the cyclization reaction. Herein, we report similarities and differences of the Pd mediated cyclization reaction from the radical mediated cyclization reaction as well as a total synthesis of ceratopicanol.

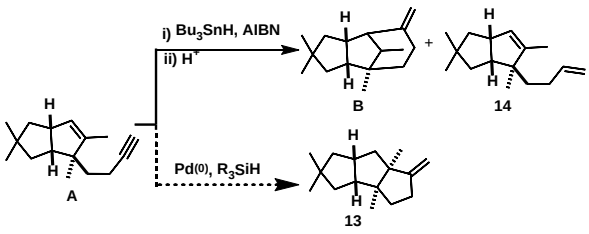

Figure 2. Two complimentary cyclization reactions toward ceratopicanol.

For the synthesis of the substrate **A**, rather than following the reported synthetic route[5b] we adopted Pd catalyzed cycloaddition reaction route that eliminated protection-deprotection steps from the previous synthetic route to **A**, since compound **A** could readily be prepared from bicyclic ketone **C** that was the known compound synthesized from commercially available **D** via Pd mediated cycloaddition reaction.[8] (Scheme 1)

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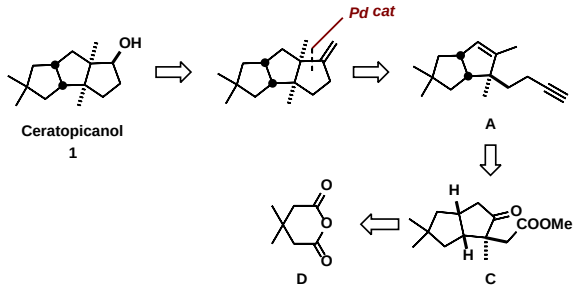
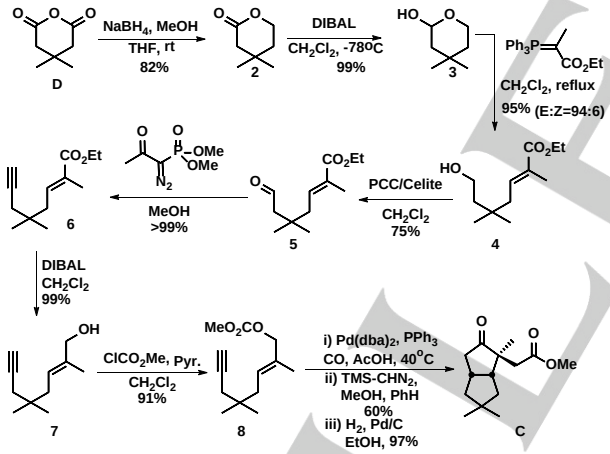


Scheme 1. Retrosynthesic analysis of ceratopicanol.

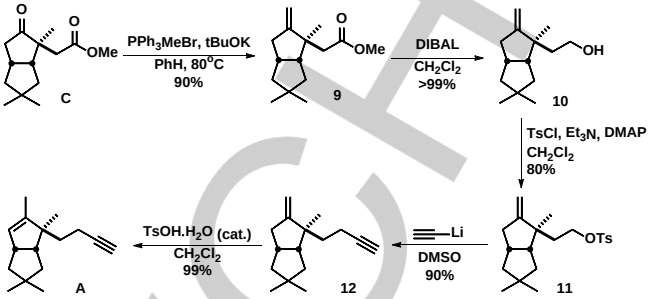
Results and Discussion

The total synthesis started with preparation of the intermediate **C** from commercially available 3,3-dimethylglutaric anhydride **D** using modified procedures from the literature preparation.[8] (Scheme 2) 3,3-Dimethylglutaric anhydride was reduced twice to the lactol **3**, and Wittig olefination of the lactol **3** produced the conjugate ester **4**. After oxidation of the alcohol of **4** into the corresponding aldehyde **5**, alkynylation using Ohira-Bestmann reagent[9] produced the alkyne **6**. Reduction of the ester followed by the carbonate formation produced **8**, the precursor for the palladium catalyzed cycloaddition reaction. Palladium catalyzed tandem ene-cyclization-carbonylation reaction[7b] produced, after esterification followed by olefin reduction, **C**.



Scheme 2. Stereoselective synthesis of diquinane intermediate **C**.

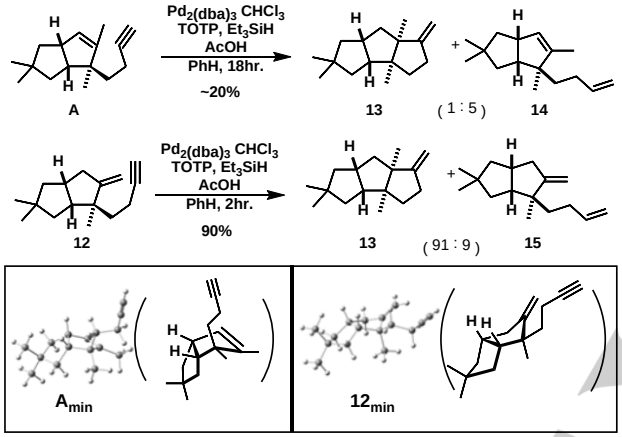
With the diquinane intermediate **C** in hand, the enyne **A**, precursor for the Pd catalyzed reductive cyclization was obtained in five step sequence. (Scheme 3) The ketone of **C** was transformed into the corresponding exocyclic olefin using the Wittig reagent at an elevated temperature to circumvent the steric hindrance to form **9**. The ester group was reduced and was activated as a sulfonate for the acetylide addition reaction, and the final olefin isomerization was successfully carried out using catalytic amount of TsOH to afford enyne intermediate **A**, the precursor for reductive cyclization reaction.



Scheme 3. Preparation of the cyclization precursor.

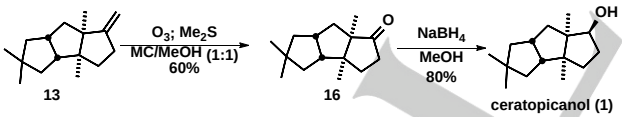
When the key cyclization reaction was carried out using $Pd_2(dba)_3$•$CHCl_3$ as the catalyst in the presence of triethylsilane, acetic acid and tri(*o*-tolyl) phosphine (TOTP) as the ligand following the conditions reported by Trost, disappointingly, the reaction was so sluggish that, even after 12 hours, the starting material **A** remained and a simple reduction product, terminal alkene **14** was observed as the major product along with the desired cyclization product **13** as a minor product and a mixture of other nonpolar side products which appeared to be β-elimination products during cyclization reaction judged by GM/MS. In the Clive's radical cyclization of **A**, formation of the 6-endo cyclized product **B** was rationalized by direct 6-endo cyclization rather than the initial 5-exo cyclic radical product that rapidly rearranged into the 6-endo product via homoallylic radical rearrangement[10], since the desired 5-exo cyclization product was not observed at all. The current result also supports the Clive's observation in the free radical cyclization reaction that a structural uniqueness of diquinane precursor **A** suppressed the usual exo-cyclic closure of the vinyl radical generated from **A**. This bias appeared to be reflected in the Pd mediated hydrogenative cycloaddition reaction as well. To understand this abnormal reactivity of **A**, a simple computational analysis with Gaussian 09 software package, using B3LYP density functional and the 6-31G(d) basis set, was run to find a unique structural feature of **A** that might prevent 5-exo cyclization reaction. (Scheme 4) The optimized conformation of **A** showed that the butynyl chain was located in a pseudo axial position and thus placed either vinyl radical or vinyl-Pd complex away from the desired reaction center for five-membered ring formation. This could explain the preference of 6-endo cyclization over 5-exo cyclization in the free radical cyclization and low reactivity of Pd mediated cyclization toward the five-membered ring formation. When we ran the same analysis on **12** for comparison, the butynyl chain was positioned at a pseudo-equatorial position that would not block the 5-exo cyclization. While free radical mediated cyclization reaction of **12** would still form 6-endo cyclization product through rapid isomerization of initially formed 5-exo cyclization product through homoallylic radical rearrangement,[11] Pd mediated cyclization could produce the desired 5-exo cyclization product. (Scheme 4)

Thus, we turned our attention to the intermediate **12**, olefinic isomer and precursor of **A**. When the Pd mediated reductive cyclization was carried out under the same reaction conditions, as we anticipated, the reaction produced the desired product **13** along with **15** (91:9 by GC/MS) in 90% yield and the reaction was much faster compared to the reaction of **A**. The two isomeric substrates **A** and **12** with only difference in positions of olefins provided completely different environment for the cyclization reactions of butenyl radical and Pd complex with the olefins. The successful cyclization of **12** into the ceratopicane structure through 5-exo cyclization was quite noteworthy as the corresponding free radical cyclization formed six-membered ring exclusively just like in the case of **A**.



Scheme 4. Pd mediated cyclization reactions of two isomers.

Finally, **13** was converted into (±)-ceratopicanol **1** through ozonolysis followed by the known ketone reduction[5h]. (Scheme 5)



Scheme 5. Completion of the synthesis of ceratopicanol.

Conclusions

We accomplished a total synthesis of ceratopicanol in 7 steps from the known compound **C** with overall yield 25.8% (10% from the commercially available starting material). The current total synthesis demonstrated not only the efficiency of successive Pd catalyzed cycloaddition and cyclization reactions in the total synthesis of natural products but also the importance of conformation of the substrate for cyclization of 1,5-hexenyne systems as seemingly minor change in substrate structure could alter the reactivity of the substrate toward Pd mediated enyne cyclization reaction as well as free radical cyclization of enynes. Furthermore, Pd mediated cyclization and free radical mediated cyclization of 1,5-hexenyne system are complimentary to each other to form the same products or alternate products as the major product.

Experimental Section

General procedures. All oxygen or moisture sensitive reactions were carried out in oven dried glassware under a positive pressure of argon. Sensitive liquids and solutions were transferred by syringe or cannula and were introduced through rubber septa through which a high flow of inert gas was maintained. Unless otherwise stated, reactions were carried out at room temperature. Concentration of solutions was accomplished using a Büchi rotary evaporator with a water aspirator. This was generally followed by removal of residual solvents on a vacuum line held at 0.1-1 torr.

Reagents and solvents. Unless otherwise noted, all reagents and solvents were used without additional purification. Exceptions include: chromatography grade hexane and ethyl acetate were technical grade and distilled before use; Et_2O and THF were distilled from sodium benzophenone ketyl under nitrogen; triethylamine were distilled from sodium; dichloromethane was distilled from P_2O_5. Benzene and toluene were washed with concentrated sulfuric acid, water and saturated $NaHCO_3$ solution, and then dried over sodium for more than 12 h before distillation. Concentration of alkyllithium solutions was determined by titration against diphenylacetic acid.

Chromatography. Analytical thin layer chromatography (TLC) was performed on Merck precoated Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel 60 F254 plates. Visualization on TLC was achieved by use of UV light (254 nm), exposure to iodine vapor, or treatment with acidic anisaldehyde or ceric ammonium molydate stain followed by heating. Flash column chromatography was carried out using Merck 60, 230-400 mesh ASTM.

Physical and spectroscopic measurements. Proton-1 nuclear magnetic resonance spectroscopy (^{1}H NMR) was recorded on Bruker Avance 400 (400 MHz), Bruker Ascend 400 (400 MHz), or Agilent Technologies DD2 (600 MHz). Chemical shifts were reported in δ units, parts per million (ppm) relative to the singlet as 7.24 ppm for chloroform-*d* or 7.15 ppm for benzene-*d*. The following abbreviations were used to describe peak patterns when appropriate: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constant, J, was reported in Hertz unit (Hz). Carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR) was recorded on Bruker Avance 400 (100 MHz), Bruker Ascend 400 (100 MHz), or Agilent Technologies DD2 (150 MHz) and was fully decoupled by broad-band decoupling. Chemical shifts were reported in ppm with the centerline of the triplet for chloroform-*d* set at 77.00 ppm or benzene-*d* set at

128.00 ppm. Mass spectra were obtained on Bruker Daltonik micrOTOF-Q Ⅱ high resolution mass spectrometer using electrospray ionization (ESI) method.

4,4-Dimethyltetrahydro-2H-pyran-2-one (2). To the solvent of THF (70 mL) and MeOH (5.9 mL, 140.7 mmol, 2 equiv) was added sodium borohydride (5.32 g, 140.7 mmol, 2 equiv) at 0 °C very carefully. The mixture was stirred for 20 min, and 3,3-dimethyl glutaric anhydride (10 g, 70.3 mmol, 1 equiv.) in THF(30 mL) was carefully moved dropwise into the mixture by cannula at same temperature. The resulting mixture was allowed to warm to room temperature and stirred for 3h. After the 3,3-dimethyl glutaric anhydride disappeared on TLC plate(stained by PMA), the 1N HCl (68 mL, 210 mmol, 3 equiv) was added very slowly to the mixture cooled to 0 °C. The reaction mixture was stirred for 3 h at room temperature, again. Then, it was quenched by saturated sodium bicarbonate and distilled water, and the aqueous layer was extracted three times with diethyl ether after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, Et_2O/ Hx 1:1) to give lactone **2** (7.38 g, 82%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.32 (t, J = 6.1 Hz, 1H), 2.27 (s, 1H), 1.65 (t, J = 6.1 Hz, 1H), 1.04 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.5, 66.5, 44.1, 35.9, 29.7, 28.8. **High Resolution MS (ESI)**: Calculated for $C_7H_{12}O_2$ $[M+Na]^+$: 151.0730, Found: 151.0727

4,4-Dimethyltetrahydro-2H-pyran-2-ol (3). To a evacuated lactone **2** (6.6 g, 51.6 mmol, 1 equiv) in DCM(20 mL) was added diiosbutylaluminum hydride (DIBAL 1M in DCM, 103 mL, 103 mmol, 2 equiv) at -78°C over 1 h. The resulting mixture was stirred for 2 h at -78°C. To quench the reaction mixture, Rochell salt and distilled water was added at -78°C and stirred until the cloudy solution became clear at 0°C. After then, and the aqueous layer was extracted with diethyl ether and also, ethyl acetate, two times. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, Et_2O/ pentane 2:3) to give lactol **3** (6.7 g, >99%) as oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.87 (dd, J = 8.4, 2.6 Hz, 1H), 4.11 (s, 1H), 3.87 (dt, J = 11.9, 4.2 Hz, 1H), 3.60 (td, J = 11.4, 2.8 Hz, 1H), 1.54 (dt, J = 13.2, 2.1 Hz, 1H), 1.41 (ddd, J = 13.3, 10.8, 4.6 Hz, 1H), 1.28 – 1.15 (m, 2H), 0.97 (s, 3H), 0.95 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 93.1 , 61.3, 44.9, 37.8, 31.6, 29.6, 26.0.

Ethyl (*E*)-7-hydroxy-2,5,5-trimethylhept-2-enoate (4). To a solution of lactol **3** (6.7 g, 51.6 mmol, 1 equiv) in DCM (150 mL) was added 1-Carboethoxy-ethylidenetriphenylphosphorane (23 g, 63 mmol, 1.2 eqiuv). The reaction mixture was stirred for 20 h under the reflux condition (40°C). After then, water was poured into the mixture, and the aqueous layer was extracted three times with dimethylchloride (DCM) after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, Et_2O/ pentane 2:3) to give stereoisomeric mixture alcohol **4** (10.5 g, 95%) as oil in ratio of 94:6(E:Z). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.82 (tq, J = 7.8, 1.5 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.70 (t, J = 7.5 Hz, 3H), 2.09 (dd, J = 7.8, 1.1 Hz, 2H), 1.81 (d, J = 1.2 Hz, 3H), 1.56 (dd, J = 15.5, 7.7 Hz, 4H), 1.28 (t, J = 7.1 Hz, 3H), 0.94 (s, 6H). Distinctive proton peak of Z isomer: 5.94 (tq, J = 7.8, 1.5 Hz, 1H), 2.39 (dd, J = 7.7, 1.5 Hz, 2H), 1.90 (d, J = 1.4 Hz, 3H), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.2 , 138.9, 129.1, 60.4, 59.4, 44.2, 41.2, 27.2, 14.2, 12.5. **High Resolution MS (ESI)**: Calculated for $C_7H_{14}O_2$ $[M+Na]^+$: 237.1461, Found: 237.1444

Ethyl (*E*)-2,5,5-trimethyl-7-oxohept-2-enoate (5). To the solution of alcohol **4** (10 g, 46.6 mmol, 1 equiv) in DCM (100 mL) was added pyridinium chlorochromate(PCC, 20.9 g, 97 mmol, 2 equiv) and celite (20.9 g) at 0°C. The mixture was warmed to room temperature and stirred for 2 h. The crude mixture was filtered with DCM and diethyl ether, and the filtrate was concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hexane 1:10) to give aldehyde **5** (7.41 g, 75%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.81 (t, J = 2.8 Hz, 1H), 6.79 (tq, J = 8.1, 1.6 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.29 (d, J = 2.8 Hz, 2H), 2.20 (dd, J = 7.8, 1.0 Hz, 2H), 1.81 (dd, J = 1.6, 0.9 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.09 (s, 6H).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.6, 167.9, 137.2, 130.1, 60.5, 54.5, 41.1, 34.5, 27.4, 14.2, 12.6. **High Resolution MS (ESI)**: Calculated for $C_{12}H_{20}O_3$ $[M+Na]^+$: 235.1305, Found: 235.1302

Ethyl (E)-2,5,5-trimethyloct-2-en-7-ynoate (6). To the solution of aldehyde **4** (3 g, 13.7 mmol, 1equiv) and dimethyl(1-diazo-2-oxopropyl)-phosphonate(Bestmann reagent, 2.9mL, 19.2 mmol, 1.4 equiv) in MeOH (7 mL) was added potassium carbonate(4.54 g, 32.9 mmol, 2.4 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 4 h. Then, it was quenched by saturated sodium bicarbonate and distilled water, and the aqueous layer was extracted three times with diethyl ether after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hx 1:10) to give alkyne **6** including esterificated byproduct (ethylester(a) : methylester(b) = 2 : 1, >99%, 2.2 g) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.79 – 6.71 (m, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.18 – 2.12 (m, 2H), 2.05 (d, J = 2.7 Hz, 2H), 1.96 (t, J = 2.7 Hz, 1H), 1.79 (dq, J = 1.6, 0.8 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 0.96 (s, 6H). Distinctive methyl ester peak: 3.68 (s, 1H), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.0, 138.2, 129.6, 81.9, 70.3, 60.3, 39.6, 34.5, 31.6, 26.6, 14.2, 12.5. Methyl ester : δ 168.4, 138.6, 129.3, 81.9, 70.3, 51.6, 39.6, 34.5, 30.2, 26.6, 12.5. **High Resolution MS (ESI)**: Calculated for $C_{13}H_{20}O_2$ $[M+Na]^+$: 231.1356, Found: 231.1331n

(*E*)-2,5,5-Trimethyloct-2-en-7-yn-1-ol (7). To the solution of alkyne **6** (a and b) (1.23 g, 6.1 mmol, 1 equiv) in diethylether(12 mL) was added DIBAL (1M in DCM, 17 mL, 17 mmol, 2.8 equiv) at -78 °C carefully. The resulting mixture was stirred for 2 h at room temperature. To quench the reaction mixture, Rochell salt and distilled water was added at 0 °C and stirred until the cloudy

solution became clear. After then, and the aqueous layer was extracted with diethyl ether (Et_2O) three times. The extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ hexane 1:10 to 1:5) to give alcohol **7** (1.04 g, >99%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.43 (tq, J = 7.7, 1.4 Hz, 1H), 3.99 (s, 2H), 2.07 – 1.99 (m, 4H), 1.96 (t, J = 2.7 Hz, 1H), 1.67 – 1.61 (m, 3H), 0.94 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.9, 122.0, 82.6, 69.9, 69.0, 38.7, 34.3, 31.3, 26.5, 13.8. **High Resolution MS (ESI)**: Calculated for $C_{11}H_{18}O$ $[M+Na]^+$: 189.1250, Found: 189.1226

(*E*)-Methyl (2,5,5-trimethyloct-2-en-7-yn-1-yl) carbonate (8). To a solution of primary alcohol **7** (907 mg, 5.4 mmol, 1 equiv) in DCM (27 mL) was added pyridine (0.87 mL, 10.8 mmol, 2 equiv) and methyl choloroformate (0.84 mL, 10.8 mmol, 2 equiv) at 0°C. The reaction mixture was warmed to temperature and stirred for 2h. The crude mixture was concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hexane 1:10) to give allylchloroformate **8** (1.1 g, 91%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.53 (tq, J = 7.8, 1.3 Hz, 1H), 4.52 (s, 2H), 3.76 (s, 3H), 2.08 – 2.01 (m, 4H), 1.96 (t, J = 2.6 Hz, 1H), 1.67 (s, 3H), 0.95 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.7, 131.7, 126.6, 82.4, 73.9, 70.00, 54.7, 38.8, 34.4, 31.4, 26.5, 14.0. **High Resolution MS (ESI)**: Calculated for $C_{13}H_{20}O_3$ $[M+Na]^+$: 247.1305, Found: 247.1272

Methyl 2-(1,5,5-trimethyl-2-oxo-1,2,4,5,6,6a- hexahydropentalen-1-yl)acetate (S1). A flask, containing (E)-carbonate **8** (451.6 mg, 2.03 mmol, 1 equiv), $Pd(dba)_2$ (116.7 mg, 0.2 mmol, 0.1 equiv.) and triphenylphosphine (106.5 mg, 0.41 mmol, 0.2 equiv) was evacuated and then filled with CO gas. After addition of degassed acetic acid (10 mL), carbon monoxide was bubbled through the mixture. The reaction mixture was stirred for 21 h under CO (1 atm) at 40°C. Then, acetic acid was removed under reduced pressure, and the residue was filtered with ethyl acetate through celite. The solution was concentrated in vacuo to afford diastereoisomeric carboxylic acids, followed by treated with TMS-diazomethane (2 M in ether, 2 mL, 2 equiv) in MeOH (5 mL) and benzene (5 mL), and stirred for 1 h. The crude mixture was concentrated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hexane 1:10) to **S1** (288 mg, 60%) as oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 5.68 (s, 1H), 3.25 (s, 3H), 3.18 – 3.10 (m, 1H), 2.63 (d, J = 16.2 Hz, 1H), 2.47 (d, J = 16.2 Hz, 1H), 1.95 (d, J = 18.5 Hz, 1H), 1.83 (d, J = 18.5 Hz, 1H), 1.50 (dd, J = 12.2, 8.2 Hz, 1H), 1.03 (t, J = 12.2 Hz, 1H), 0.91 (s, 3H), 0.87 (s, 3H), 0.81 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 211.4, 186.2, 171.8, 121.7, 55.0, 50.9, 49.2, 42.1, 40.8, 40.4, 40.1, 30.3, 29.9, 20.4. **High Resolution MS (ESI)**: Calculated for $C_{14}H_{20}O_3$ $[M+Na]^+$: 259.1305, Found: 259.1286

Methyl 2-(1,5,5-trimethyl-2-oxooctahydropentalen-1-yl) acetate (C). To a solution of **S1** (153.8 mg, 0.65 mmol, 1 equiv) in ethanol (3.25 mL) was added Pd /C (10%, 76.9 mg). The reaction mixture was stirred for overnight at room temperature under H_2 gas (1 atm). The resulting mixture was filtered through celite with ether, and the filtrate was evacuated in vacuo. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hexane 1:20) to afford **C** (141 mg, 91%) as oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 3.25 (s, 3H), 2.63 (m, 1H), 2.52 (dd, J = 18.4, 10.2 Hz, 1H), 2.43 (m, 1H), 2.33 – 2.17 (m, 2H), 1.74 (dd, J = 18.4, 6.6 Hz, 1H), 1.57 (ddd, J = 13.0, 8.1, 1.7 Hz, 1H), 1.24 (ddd, J = 12.7, 7.4, 1.7 Hz, 1H), 1.00 (s, 4H), 0.91 – 0.83 (m, 7H), 0.79 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 219.4, 171.1, 51.0, 49.7, 49.4, 49.0, 43.7, 43.6, 42.9, 40.3, 35.1, 29.8, 28.3, 19.6. **High Resolution MS (ESI)**: Calculated for $C_{14}H_{22}O_3$ $[M+Na]^+$: 261.1461, Found: 261.1447

Methyl 2-(-1,5,5-trimethyl-2-methyleneoctahydropentalen-1-yl)acetate (9). To a solution of methyltriphenylphosphonium bromide (525.1 mg, 1.47 mmol, 2.5 equiv), flame dried, in distilled toluene (3.5 mL) was added potassium *tert*-butoxide (141.4 mg, 1.26 mmol, 2 equiv). To generate ylide, the mixture was stirred for 30 min under reflux condition (80˚C) for about 30 min, appearing yellow color. After then, the solution was allowed to cool to room temperature, and a solution of ketone **C** (147 mg, 0.6 mmol, 1 equiv) in distilled toluene (3.5 mL) was moved into the solution via cannula. The reaction mixture was stirred for 1h under reflux condition (at 80˚C). Then, it was quenched by saturated ammonium chloride and distilled water, and the aqueous layer was extracted three times with ethyl acetate after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hx 1:30 to 1 : 20) to give methylene diquinane **9** (128.6 mg, 90%) as oil. **^{1}H NMR** (600 MHz, C_6D_6) δ 4.87 – 4.85 (m, 1H), 4.81 – 4.79 (m, 1H), 3.33 (s, 3H), 2.75 (ddt, *J* = 15.8, 10.1, 2.6 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.26 (d, *J* = 13.3 Hz, 1H), 2.18 (d, *J* = 13.3 Hz, 1H), 1.86 – 1.81 (m, 1H), 1.67 (ddd, *J* = 12.7, 8.4, 2.3 Hz, 1H), 1.23 (s, 3H), 1.02 – 0.92 (m, 6H), 0.84 (s, 3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 171.3, 157.1, 106.2, 53.7, 50.7, 49.6, 47.1, 46.0, 43.4, 40.18 , 40.16 , 37.7, 29.4, 27.4, 19.9. **High Resolution MS (ESI)**: Calculated for $C_{15}H_{24}O_2$ $[M+Na]^+$: 259.1669, Found: 259.1638.

2-(1,5,5-Trimethyl-2-methyleneoctahydropentalen-1-yl)ethan-1-ol (10). To the solution of methyl acetate **9** (128 mg, 0.54 mmol, 1 equiv) in DCM (5 mL) was added DIBAL (1M in DCM, 1.5 mL, 1.5 mmol, 3 equiv) at -78 ˚C carefully. The resulting mixture was stirred for 2 h at room temperature. To quench the reaction mixture, Rochell salt and distilled water was added at 0 ˚C and stirred until the cloudy solution became clear. After then, and the aqueous layer was extracted with ethyl acetate three times. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ hexane 1:5) to give alcohol **10** (106.8 mg, 95%) as oil. **^{1}H NMR** (300 MHz, C_6D_6) δ 4.82 (d, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 1.8 Hz, 1H), 3.46 (t, *J* = 7.0 Hz, 2H), 2.69 (ddt, *J* = 15.7, 10.4, 2.6 Hz, 1H), 2.52 – 2.32 (m, 1H), 2.18 (dt, *J* = 11.6, 7.9 Hz, 1H), 1.78 (dd, *J* = 15.9, 2.4 Hz, 1H), 1.68 (ddd, *J* = 12.6, 8.7, 2.3 Hz, 1H), 1.67 – 1.54 (m, 1H), 1.35 (dt, *J* = 13.6, 6.7 Hz, 2H), 1.17 (ddd, *J* = 12.2, 7.2, 2.3 Hz, 1H), 0.98 (s, 3H), 0.95 (d, *J* = 3.8 Hz, 1H), 0.91 (s, 4H), 0.84 (s,

3H). **^{13}C NMR** (100 MHz, C_6D_6) δ 158.3, 105.7, 59.9, 54.9, 49.7, 46.6, 44.1, 43.2, 40.5, 40.0, 37.5, 29.3, 27.3, 19.4 **High Resolution MS (ESI)**: Calculated for $C_{14}H_{25}O$ $[M+H]^+$: 209.1900, Found: 209.1900.

2-(1,5,5-Trimethyl-2-methyleneoctahydropentalen-1-yl)ethyl-4-methylbenzenesulfonate (11). To a stirred solution of alcohol **10** (104.17 mg, 0.5 mmol, 1 equiv) in DCM (5 mL) was added p-toluenesulfonyl chloride (114.4 mg, 0.5 mmol, 1.2 equiv), triethylamine (83.7 µL, 0.6 mmol, 1.2 equiv) and 4-dimethyl-aminopyridine (DMAP, 18.3 mg, 0.15 mmol, 0.3 equiv). The resulting mixture was stirred for 15 h at room temperature. Then, it was quenched by saturated ammonium chloride (sat.NH_4Cl) and distilled water, and the aqueous layer was extracted three times with ethyl acetate (EtOAc) after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was purified by flash column chromatography on silica gel (eluent, EtOAc/ Hx 1:15) to give tosylated product **11** (145.07mg, 80%) as oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.9 Hz, 2H), 4.80 – 4.69 (m, 1H), 4.60 – 4.49 (m, 1H), 3.96 (dddd, *J* = 26.7, 9.9, 8.9, 6.1 Hz, 2H), 2.60 – 2.44 (m, 2H), 2.43 (s, 3H), 2.22 (dt, *J* = 11.5, 7.8 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.75 – 1.67 (m, 2H), 1.66 – 1.58 (m, 1H), 1.58 – 1.55 (m, 1H), 1.20 (ddd, *J* = 12.1, 7.2, 2.3 Hz, 1H), 0.95 (s, 3H), 0.92 – 0.88 (m, 1H), 0.87 (s, 3H), 0.83 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 144.6, 133.3, 129.7, 127.8, 106.5, 68.3, 54.3, 49.3, 46.1, 42.9, 40.0, 39.8, 38.9, 37.1, 29.1, 27.1, 21.6, 19.1. **High Resolution MS (ESI)**: Calculated for $C_{21}H_{30}O_3S$ $[M+Na]^+$: 385.1808, Found: 385.1850.

1-(But-3-yn-1-yl)-1,5,5-trimethyl-2-methylene octahydropentalene (12). To a stirred solution of compound **11** (80 mg, 0.22 mmol, 1 equiv) in DMSO (2.2 mL) was added lithium acetylide (stabilized with ethylenediamine, 90 wt%, 101.3 mg, 1.1 mmol, 5 equiv). The reaction mixture was stirred for 3.5 h at room temperature. Then, it was quenched by distilled water, and the aqueous layer was extracted three times with hexane after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was purified by flash column chromatography on silica gel (eluent, pentane) to give alkyne **12** (42.8 mg, 90%) as oil. **^{1}H NMR** (400 MHz, C_6D_6) δ 4.76 – 4.70 (m, 1H), 4.54 – 4.49 (m, 1H), 2.56 (ddt, *J* = 15.5, 10.3, 2.6 Hz, 1H), 2.46 (dddd, *J* = 15.9, 10.6, 7.5, 2.5 Hz, 1H), 2.26 – 2.14 (m, 1H), 2.03 – 1.80 (m, 2H), 1.80 (t, *J* = 2.7 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.64 (ddd, *J* = 12.6, 8.5, 2.3 Hz, 1H), 1.50 (ddd, *J* = 13.5, 11.2, 5.3 Hz, 1H), 1.45 – 1.32 (m, 1H), 1.16 (ddd, *J* = 12.0, 7.2, 2.4 Hz, 1H), 0.87 (s, 3H), 0.88 – 0.80 (m, 2H), 0.80 (s, 3H), 0.77 (s, 3H). **^{13}C NMR** (150 MHz, CD_2Cl_2) δ 156.3, 105.5, 85.0, 67.0, 53.9, 49.0, 47.1, 42.8, 39.6, 39.6, 39.5, 36.9, 28.5, 26.5, 17.9, 13.5 . **High Resolution MS (ESI)**: Calculated for $C_{16}H_{25}$ $[M+H]^+$: 217.1951, Found: 217.1944.

3a,5,5,7a-Tetramethyl-1-methylenedecahydro-1H-cyclopenta[a]pentalene (13). To a solution of diquinane **12** (25.5 mg, 0.12 mmol, 1 equiv), $Pd_2(dba)_3$•$CHCl_3$ (5.4 mg, 0.006 mmol, 0.05 equiv) and tri(*o*-tolyl)phosphine (3.5 6mg, 0.012 mmol, 0.1 equiv) in benzene (5.9 mL) was added acetic acid (6.7 µL, 0.117 mmol, 1 equiv) at room temperature. The resulting mixture was stirred until the solution color changed from purple to yellow. (Generally, it takes about 10 min) After then, to the solution was added triethylsilane (47 µL, 0.29 mmol, 2.5 equiv) slowly, and the reaction mixture was stirred till purple color appeared again. The resulting mixture was filtered with pentane through silica pad and concentrated under reduced pressure. The organic residue was purified by flash column chromatography on silica gel (eluent, pentane) to give triquinane **13** (22.9 mg, 90%) as oil.**^{1}H NMR** (400 MHz, CD_2Cl_2) 4.66 (td, *J* = 2.1, 1.1 Hz, 1H), 4.61 (td, *J* = 2.4, 1.0 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.38 – 2.29 (m, 2H), 2.29 – 2.19 (m, 1H), 1.84 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.55 – 1.42 (m, 2H), 1.37 – 1.30 (m, 1H), 1.30 – 1.26 (m, 1H), 1.22 (dd, *J* = 8.0, 2.0 Hz, 1H), 1.20 – 1.13 (m, 1H), 1.00 (dd, *J* = 12.5, 8.2 Hz, 1H), 0.93 (s, 3H), 0.89 (s, 3H), 0.87 – 0.80 (m, 2H), 0.78 (s, 3H), 0.74 (s, 3H). **^{13}C NMR** (100MHz, CD_2Cl_2) δ 162.9, 102.6, 57.4, 54.1, 52.2, 48.3, 47.0, 42.4, 41.7, 41.0, 38.4, 29.8, 28.9, 26.6, 22.4, 18.6. **High Resolution MS (ESI)**: Calculated for $C_{16}H_{27}$ $[M+H]^+$: 219.2107, Found: 219.2106.

3a,5,5,7a-Tetramethyldecahydro-1H-cyclopenta[a]pentalen-1-one (16). A stirred solution of triquinane **13** (21 mg, 0.096 mmol) in DCM/MeOH (1 mL/1 mL) was saturated with ozone for 5 min at -78˚C. The resulting mixture was quenched with dimethylsulfide (0.2 mL) and allowed to warm to room temperature for 2 h. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent, EtOAc/Hx 1 : 20) to give ketone **16** (12.7 mg, 60%) as oil. **^{1}H NMR** (600 MHz, CD_2Cl_2) δ 2.50 (pd, *J* = 8.9, 5.0 Hz, 1H), 2.46 – 2.40 (m, 1H), 2.22 (ddd, *J* = 19.1, 9.0, 4.8 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.93 (dd, *J* = 13.6, 9.3 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.54 (ddd, *J* = 13.4, 9.4, 4.8 Hz, 1H), 1.31 – 1.27 (m, 2H), 1.11 (dd, *J* = 13.6, 5.0 Hz, 1H), 1.03 (dd, *J* = 12.6, 8.4 Hz, 1H), 0.94 (s, 3H), 0.89 (s, 3H), 0.82 (s, 3H), 0.78 (s, 3H).**^{13}C NMR** (150 MHz, $CDCl_3$) δ 223.6, 61.1, 55.8, 51.5, 49.5, 43.3, 43.2, 42.2, 41.8, 35.1, 34.5, 29.4, 26.8, 18.8, 17.9. **High Resolution MS (ESI)**: Calculated for $C_{15}H_{24}O$ $[M+Na]^+$: 243.1719, Found: 243.1687

(±)-Ceratopicanol (1). A stirred solution of ketone **95** (10 mg, 0.045 mmol, 1 equiv) in MeOH (1mL) was added sodium borohydride (5.1 mg, 0.135, 3 equiv) at 0 ˚C. The solution was allowed to warm to room temperature and stirred for 2 h. Then, the reaction mixture was quenched with 1N hydrochloric acid and distilled water at 0˚C, and the aqueous layer was extracted three times with diethyl ether (Et_2O) after addition of brine. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The organic residue was purified by flash column chromatography on silica gel (eluent, Et_2O/ Hx 1:20) to give ceratopicanol (**1**) (8.1 mg, 80%) as amorphous solid. **^{1}H NMR** (600MHz, $CDCl_3$) δ 3.70 (t, *J* = 7.9 Hz, 1H), 2.49 (dq, *J* = 15.6, 8.4 Hz, 1H), 2.34 (dt, *J* = 11.7, 8.2 Hz, 1H), 2.16 (dd, *J* = 13.8, 9.6 Hz, 1H), 1.89 (dtd, *J* = 11.8, 7.5, 4.0 Hz, 1H), 1.67 (ddd, *J* = 12.9, 8.5, 1.5 Hz, 1H), 1.56 (ddd, *J* = 13.2, 9.2, 4.3 Hz, 1H), 1.45 – 1.28 (m, 5H), 1.21 (dd, *J* = 12.9, 5.6 Hz, 1H), 1.07 (d, *J* = 7.0 Hz, 1H), 1.04 (s, 6H), 0.88 (s, 3H), 0.87 (s, 3H). **^{13}C NMR** (150 MHz,$CDCl_3$) δ 82.6, 58.8, 55.0, 51.2,

48.8, 44.2, 42.0, 41.7, 40.9, 39.6, 31.6, 30.6, 28.6, 23.9, 21.3. **High Resolution MS (ESI)**: Calculated for $C_{15}H_{26}O$ $[M+Na]^+$: 245.1876, Found: 245.1850

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Keywords: triquinane • cyclization • free radical • Pd catalysis • total synthesis

[1] a) K. Hayano, Y. Ohfune, H. Shirahama, T. Matsumoto, *Helv. Chim. Acta* **1981**, *64*, 1347-1364; b) F. W. Comer, F. McCapra, I. H. Qureshi, A. I. Scott *Tetrahedron* **1967**, *23*, 4761-4768.

[2] a) J. M. McPartland, *J. Am. Osteopath. Assoc.* **2004**, *104*, 244-249; b) T. T. Bothma, J. H. Rossouw, A.-M. Richard, J. P. Cronfe, WO/2007/066305 A1.

[3] B. M. Fragaa, C. E. Díaza, L. J. Amadora, M. Reinaa, O. Santana, A. G.-Colomad, *Phytochemistry* **2014**, *108*, 220-228.

[4] P. Hu, H. M. Chi, K. C. Debacker, X. Gong, J. H. Keim, I. T. Hsu, S. A. Snyder, *Nature*, **2019**, *569*, 703-707.

[5] a) G. Mehta, S. R. Karra, *J. Chem. Soc. Chem. Commun.* **1991**, 1367-1368; b) D. L. J. Clive, S. R. Magnuson, *Tetrahedron Lett.* **1995**, *36*, 15-18; c) C. Baralotto, M. Chanon, M. Julliard, *J. Org. Chem.* **1996**, *61*, 3576-3577; d) L. A. Paquette, F. Geng, *J. Am. Chem. Soc.* **2002**, *124*, 9199-9203; e) T. Anger, O. Graalmann, H. Schçder, R. Gerke, U. Kaiser, L. Fitjer, M. Noltemeyer, *Tetrahedron* **1998**, *54*, 10713-10720; f) C. Mukai, M. Kobayashi, I. J. Kim, M. Hanaoka, *Tetrahedron* **2002**, 58, 5225-5230; g) C. H. Oh, C. Y. Rhim, M. Kim, D. I. Park, A. K. Gupta, *Synlett* **2005**, 2694-2696; h) H.-Y. Lee, S. S. Lee, W. Y. Kim, *Chem. Asian J.* **2012**, *7*, 2450-2456.

[6] D. L. J. Clive, S. R. Magnuson, H. W. Manning, D. L. Mayhew, *J. Org. Chem*. **1996**, *61*, 2095-2108.

[7] a) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34-42; b) K. Kong, J. A. Enquist, M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz, J. L. Wood, *J. Am. Chem. Soc.* **2013**, *135*, 10890-10893.

[8] W. Oppolzer, C. Robyr, *Tetrahedron* **1994**, 50, 415-424.

[9] S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett* **1996**, 521-522.

[10] G. Stork, R. Mook, *Tetrahedron lett.* **1986**, *27*, 4529-4532.

[11] H.-Y. Lee, D. K. Moon, J. S. Bahn, *Tetrahedron Lett*. **2005**, *46*, 1455-1458.

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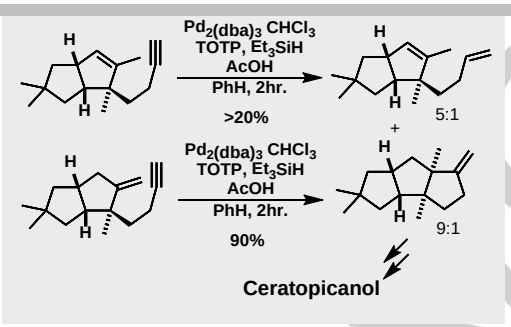
Layout 1:

FULL PAPER

An efficient total synthesis of ceratopicanol was achieved through successive Pd catalyzed reductive cycloaddition and cyclization reactions. The Pd mediated cyclization reaction to form a triquinane structure demonstrated that a small structural difference changed the reaction pathway either to form different structures or reduced non-cyclized product depending on the reaction conditions.



Total Synthesis

Rira Kim[a], Sanghyeon Lee[a], Jaeyeon Lee[a], and Hee-Yoon Lee[a]*

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A total synthesis of (±)-ceratopicanol via palladium catalyzed reductive cyclization