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Total Synthesis of Ceratopicanol through Tandem Cycloaddition Reaction of a Linear Substrate

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Abstract: Total synthesis of ceratopicanol (**1**) was achieved with a tandem cycloaddition reaction of allenyl diazo compound **6** via a trimethylenemethane (TMM) diyl intermediate. The TMM diyl mediated [2+3] cycloaddition reaction furnished the consecutive quaternary carbon centers and showed an unusual diastereoselectivity.

Keywords: diradical · cycladdition reaction · stereoselectivity · total synthesis · triquinane

Introduction

Fungi are a source of various natural products that possess unique structural features. The majority of these natural products are secondary metabolites that include volatile hydrocarbons with diverse structural features. These compounds have been found to be produced as part of a protection mechanism and communication with other organisms.[1] Hanssen and Abraham reported the first isolation of the ceratopicane sesquiterpene natural product, ceratopicanol, from the fungus *Ceratosystis Piceae* Ha 4/82.[2] Ceratopicane possesses a linearly fused triquinane structure, which is different to that of the hirsutane or capnellane skeleton (Figure 1). Ceratopicane is biogenetically related to hirsutane as one of the proposed intermediate structures in between humulene to hirsutane is ceratopicane. Recently, another ceratopicane natural product, cucumin H, was isolated from *Macrocystidia cucumis*.[3] While the pharmacological and clinical aspects of ceratopicanol were not fully explored as sesquiterpene hydrocarbons had not shown typical biological activities, recent reports have indicated that terpenes including ceratopicanol could be useful as prophylaxis or the treatment of pain.[4a,b]

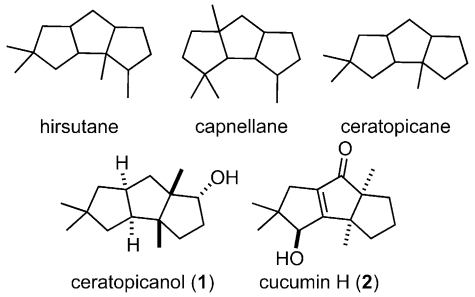
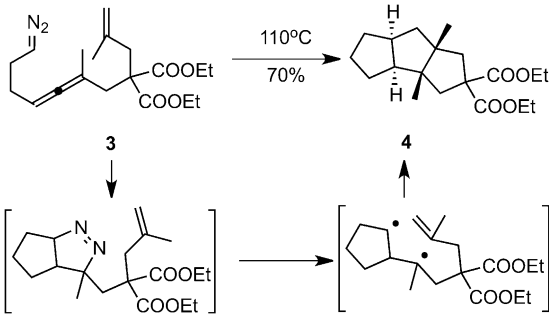


Figure 1. Structure of (+)-ceratopicanol and other sesquiterpene compounds.

Along with its biological activities, the highly congested structural feature of ceratopicanol with the *cis/anti/cis*-linearly fused triquinane structure that has five contiguous chiral carbon atoms, with two consecutive quaternary carbon centers, has challenged the synthetic chemistry community. As a result, there have been several reports on the total synthesis of ceratopicanol. In all the reported total syntheses, the consecutive quaternary centers of ceratopicanol were assembled in a stepwise fashion.[5] We were intrigued by the structural features of ceratopicanol and became interested in an efficient total synthesis of ceratopicanol by introducing the two consecutive quaternary centers simultaneously.

Recently, we reported a tandem cycloaddition reaction strategy to triquinanes from linear substrates through a trimethylenemethane (TMM) diyl [2+3] cycloaddition reaction.[6a,b, 7a–i] Among the reported examples, the tandem cycloaddition reaction of **3** produced the complete structure of ceratopicanol **4** with two consecutive quaternary centers (Scheme 1). This outcome was a good model system for the total synthesis of ceratopicanol using the tandem cycloaddition reaction strategy from a linear substrate (Scheme 2).



Scheme 1. Tandem cycloaddition reaction of allenyl diazo compound **3**.

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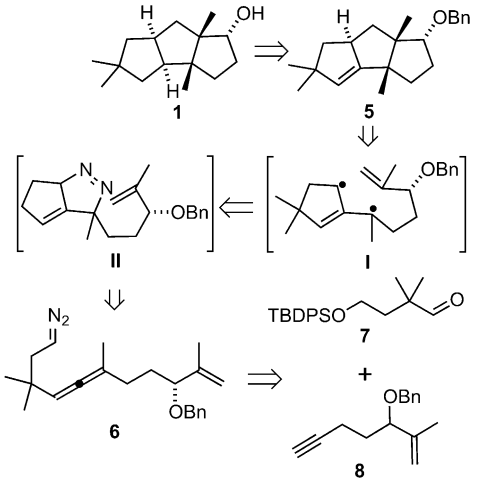
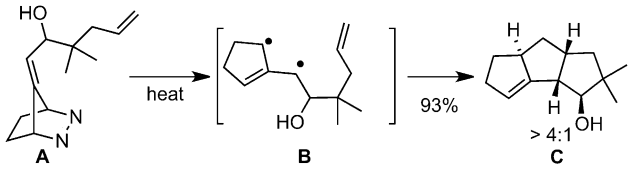


Scheme 2. Synthetic analysis of the total synthesis of ceratopicanol.

While this tandem cycloaddition reaction strategy can construct the ceratopicanol skeleton in a single operation, the stereoselectivity of the cycloaddition reaction of the TMM intermediate **I** has not been explored so far. To the best of our knowledge, the only report of a diastereoselectivity study on the TMM cycloaddition reaction to form linearly fused triquinanes was with substrates bearing the substituents at different positions in the tether (Scheme 3).[8] Thus, the total synthesis of ceratopicanol would also provide an opportunity to understand the stereoselectivity of the cycloaddition reaction.

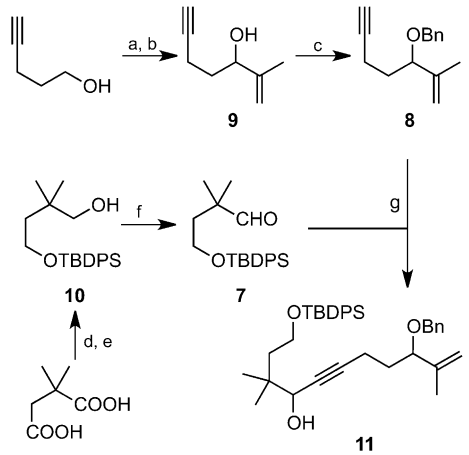


Scheme 3. Diastereoselective cycloaddition reaction of the TMM intermediate.

Ceratopicanol could be synthesized from **5**, which could be obtained from diazo compound **6** through the tandem cycloaddition reaction (Scheme 2). The first step of the tandem cycloaddition reaction sequence would be the formation of the thermally labile pyrazole intermediate **II** through a 1,3-dipolar cycloaddition reaction. Then, intermediate **II** would lose N_2 to generate the TMM diyl intermediate **I**, which would undergo a [2+3] cycloaddition reaction with the olefin to produce the triquinane **5**. The diazo group of **6** could be generated from the corresponding aldehyde. The allenyl compound could be obtained through the coupling of aldehyde **7** and alkyne **8**. The coupling partners, **7** and **8** can be readily prepared from 2,2-dimethylsuccinic acid and pentynol, respectively.

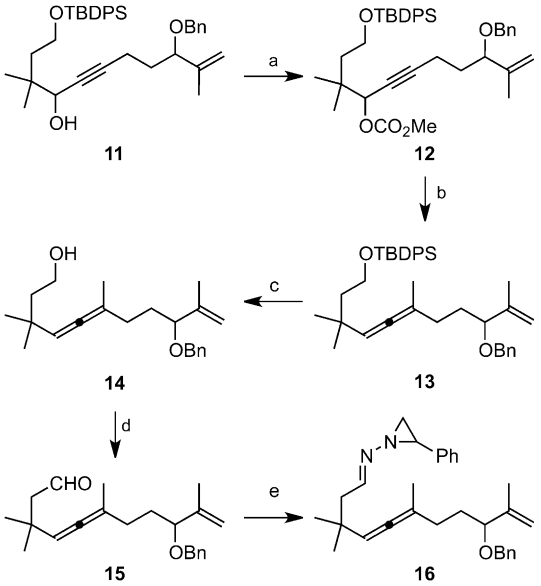
Results and Discussion

The total synthesis of ceratopicanol started with the preparation of alkyne **8** and aldehyde **7** (Scheme 4). Swern oxidation of pentynol produced volatile pentynal, which was treated with an excess amount of isopropenyl Grignard reagent to afford the alcohol **9** in 78% yield over two steps. The alcohol **9** was protected as the benzyl ether to form **8**. The other coupling partner, aldehyde **7**, was prepared in a three-step sequence from 2,2-dimethylsuccinic acid. Reduction of the diacid functional groups to the diols and selective monoprotection of the less hindered alcohol with bulky *tert*-butyldiphenylsilyl group produced **10**. The alcohol **10** was oxidized into aldehyde **7**. An addition reaction of the acetylide anion of **8** with aldehyde **7** furnished the propargylic alcohol **11**.



Scheme 4. Preparation of the intermediate **11**. a) $(COCl)_2$ (1.2 equiv), DMSO (1.5 equiv), THF, −78 °C; Et_3N (3 equiv), then rt for 4 h; b) isopropenyl magnesium bromide (11 equiv), THF, −20 °C, 1 h, 78% (over 2 steps); c) benzyl bromide (1.05 equiv), sodium hydride (1.3 equiv), TBAI (0.05 equiv), THF, rt, 12 h, 95%; d) LAH (3.2 equiv), diethylether, 0 °C, then rt for 24 h, 99%; e) TBDPSCl (1 equiv), imidazole (1.5 equiv), THF, 0 °C, then rt for 12 h, 81%; f) $(COCl)_2$ (1.5 equiv), DMSO (2.5 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (5 equiv), then rt for 4 h, 98%; g) **7** (1.1 equiv), LiHMDS (1.5 equiv), −78 °C, 1 h, then rt for 2 h, 98%.

Preparation of the precursor **16** for the tandem cycloaddition reaction from **11** required the introduction of the methyl group to form the trisubstituted allene moiety from the propargyl alcohol of **11** (Scheme 5). To introduce the methyl group and the allene functionality, alcohol **11** was transformed into methyl carbonate **12**. The propargylic carbonate of **12** was treated with Gilman's reagent[9] to produce the trisubstituted allene **13.**[10] The allene compound **13** was treated with tetrabutylammonium fluoride to give the primary alcohol **14**. Swern oxidation of the alcohol afforded the aldehyde **15**. The aldehyde moiety of **15** could be converted into the diazo functionality with several methods.[11a–e] Among these methods, the phenylaziridinyl imine was selected as the precursor of the diazo group because it would generate the diazo functionality under neutral reaction con-

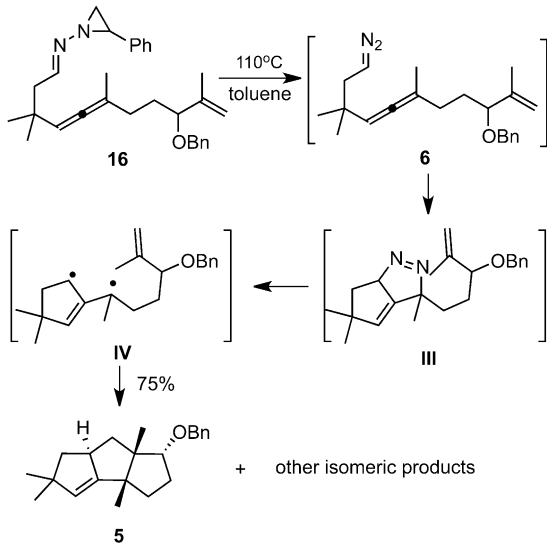


Scheme 5. Preparation of the substrate for the tandem cycloaddition reaction. a) $ClCO_2Me$ (3 equiv), pyridine (5 equiv), CH_2Cl_2, 0 °C, 2 h, then rt for 2 h, 99 %; b) MeMgBr (12 equiv), CuI (12 equiv), LiBr (12 equiv), 0 °C, 0.5 h, then rt for 1 h, 97 %; c) TBAF (5 equiv), THF, rt for 10 h, 98 %; d) $(COCl)_2$ (1.5 equiv), DMSO (2.5 equiv), CH_2Cl_2, −78 °C, 1 h; Et_3N (5 equiv),then rt for 4 h, 93 %; e) *N*-amino-2-phenylaziridine (1.5 equiv), MeOH, 0 °C, 0.5 h, then rt for 16 h, 90 %

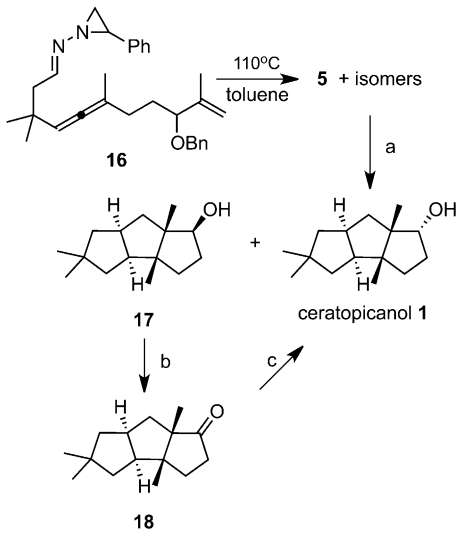
ditions.[12a–c] The aldehyde of **15** underwent condensation with *N*-amino-2-phenylaziridine[13] in MeOH to produce allenyl aziridinylimine **16** in good yield.

With the precursor **16** in hand, we were ready to explore the tandem cycloaddition reaction and the diastereoselectivity of the TMM diyl [2+3] cycloaddition reaction (Scheme 6).

Contrary to the model case in Scheme 2, the tandem cycloaddition reaction produced an inseparable mixture of at least four isomeric cycloaddition products in a ratio of 9:5:2:1, as judged by GC-MS analysis because all compounds showed similar fragmentation patterns with the same molecular ion peak of the tandem cycloaddition reaction product. As the isomers were not separable by column chromatography, separation of the isomers was deferred until after deprotection of the benzyl ether (Scheme 7).



Scheme 6. Tandem cycloaddition reaction of **16**.



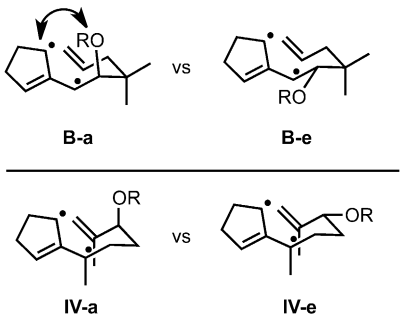
Scheme 7. Completion of the total synthesis of ceratopicanol. a) Pd/C (240 mg, 10 wt. % activated carbon), H_2 (60 psi) in a Parr shaker, 36 % + 21 % of other isomers; b) TPAP (0.1 equiv), NMO (2 equiv), CH_2Cl_2, rt, 1.5 h, 82 %; c) $NaBH_4$ (1.3 equiv), MeOH, −15 °C, 1 h, 95 %. NMO = 4-methylmorpholine *N*-oxide; TPAP = tetra-*n*-propylammonium perruthenate.

When the tandem cycloaddition reaction product mixture was subjected directly to the hydrogenation/hydrogenolysis reaction conditions, two fractions were separated in a 1.7:1 ratio. The major fraction contained ceratopicanol along with its alcohol epimer **17** (3.7:1 ratio). The ratio of the two isomers was determined by NMR spectroscopy. The structure of the synthesized ceratopicanol was confirmed by comparison of its spectroscopic data with the reported data.[2] The structure of **17** was confirmed through an oxidation–reduction sequence that produced ceratopicanol by inversion of the alcohol stereochemistry of **17**.

The minor fraction also contained a mixture of two epimeric alcohols with a ratio of 5:1. The epimeric nature of the alcohol mixture was confirmed through the oxidation of the alcohol mixture to a single isomeric ketone. Unfortunately, the exact structure of the minor fraction could not be deduced firmly owing to the instability of the ketone product. The structure of the ketone was tentatively assigned as the regioisomeric cycloaddition product of **5**. This result was quite different from the result of the cycloaddition reaction of **3** or **A**. It was presumed that the efficiency and the selectivity of the cycloaddition reaction were affected by the substitution patterns, as **3** and **A** contained quaternary centers in the tether. A Thorpe–Ingold effect[14] must have influ-

enced the selectivity as well as the efficiency of the cycloaddition reaction.

The diastereoselectivity of the TMM cycloaddition reaction of **IV** was opposite to that of the cycloaddition reaction of **B** (Scheme 3). The stereoselectivity of the cycloaddition reaction of **B** was clearly explained by the 1,3-diaxial interaction between the pseudo-axial substituent and the cyclopentene ring in **B-a** (Scheme 8).[8] However, the preference



Scheme 8. Comparison of transition states leading to cycloaddition reaction products.

between the two plausible transition states of **IV** was not obvious. When energies for two plausible transition states, which led to the formation of **5** and its epimer, were calculated by using HF/6-31G* level of theory,[15a,b] the pseudo-axial transition state, **IV-a** was calculated to be more stable than the pseudo-equatorial transition state **IV-e** by 1.7 kcal mol^{-1}. Presumably, the lack of the 1,3-diaxial interaction of the pseudo-axial orientation and the gauche interaction of the pseudo-equatorial orientation in the allylic conformation made the pseudo-axial orientation more stable than the pseudo-equatorial orientation.[16] Interestingly, the similar reversal in the selectivity was also observed in the TMM cycloaddition reaction for the formation of angularly fused triquinanes.[17]

Conclusions

In summary, a total synthesis of ceratopicanol has been accomplished in 11 steps for the longest linear sequence with simultaneous construction of consecutive quaternary centers. The total synthesis also revealed an unexpected diastereoselectivity in the cycloaddition reaction and the influence of the substitution patterns for the efficiency of the cycloaddition reaction. The favorable diastereoselectivity for the formation of ceratopicanol could be applied to the asymmetric total synthesis of ceratopicanol if intermediate **8** is prepared enantioselectively.

Experimental Section

General Information

NMR spectra were obtained on Bruker DPX400 (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) or Bruker AM300 spectrometers (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR) in $CDCl_3$. Chemical shifts were recorded in ppm relative to internal standard $CDCl_3$ and coupling constants were reported in Hz. The high-resolution mass spectra were recorded on VG Autospec Ultima and JMS-700 spectrometers. All reactions were carried out in oven-dried glassware under a N_2 atmosphere, and were monitored by TLC analysis using Merck precoated silica gel 60 F_{254} plates. All solvents were distilled from the indicated drying reagents straight before use: Et_2O and THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), and MeCN, 1,4-dioxane, and *N*,*N*-dimethylformamide (DMF; CaH_2). The normal work-up procedure involved extraction, drying over $MgSO_4$, and evaporation of volatile materials in vacuo. Purification by column chromatography was perfomed using Merck (Darmstadt, Germany) silica gel 60 (230~400 mesh).

*2-Methyl-hept-1-en-6-yn-3-ol (**9**)*

A solution of oxalyl chloride (1.87 mL, 21.40 mmol) in THF (80 mL) was cooled to −78 °C, and a solution of dimethyl sulfoxide (DMSO; 1.90 mL, 26.75 mmol) in THF (40 mL) was added dropwise over 45 min. A white precipitate formed as the resulting mixture was stirred at −78 °C for 45 min. A solution of 4-pentyn-1-ol (1.5 g, 17.83 mmol) in THF (40 mL) was then introduced dropwise over 1 h. After an additional 1 h at −78 °C, triethylamine (7.50 mL, 53.50 mmol) was added dropwise over 30 min. The reaction was stirred at −78 °C for 1 h, warmed to room temperature, and stirred for an additional 1 h. Finally, the mixture was filtered, the filter cake was washed with THF (30 mL), and the aldehyde was used directly in the subsequent reaction. To this solution cooled to −20 °C, was added isopropenyl magnesium bromide (200 mmol) in diethyl ether (178 mL), prepared from Mg turnings (1.3 g, 53.50 mmol) and 2-bromopropene (3.20 mL, 35.66 mmol) by standard techniques using dibromoethane (50 μL) in THF (40 mL), and the resulting reaction mixture was stirred for 1 h at that temperature, then warmed to room temperature. After 1 h, the reaction was quenched with saturated NH_4Cl solution, and the solution was extracted with diethyl ether (2×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (Et_2O/*n*-pentane = 1:5) to give 1.72 g (13.85 mmol, 78 % over 2 steps) of the alcohol as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 4.92 (d, J = 0.68 Hz, 1H), 4.80 (d, J = 1.41 Hz, 1H), 4.12 (t, J = 7.20 Hz, 1H), 2.23–2.18 (m, 3H), 1.92 (t, J = 2.65 Hz, 1H), 1.72–1.69 (m, 2H), 1.67 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 146.8, 111.2, 84.0, 74.3, 68.6, 33.4, 17.5, 14.7 ppm. IR (neat): $\tilde{\nu}$ = 3302, 3075, 2952, 2117, 1814, 1435, 1374, 1283, 1057, 904 cm^{-1}.

*[(1-Isopropenyl-pent-4-ynyl)oxymethyl)benzene (**8**)*

A solution of alcohol **9** (400 mg, 3.22 mmol) in THF (10 mL) containing a catalytic amount of tetrabutylammonium iodide was added to a stirred suspension of NaH (167 mg of 60 % dispersion in mineral oil, 4.19 mmol) in THF (20 mL). The mixture was stirred for 45 min, and then benzyl bromide (402 μL, 3.38 mmol) was added dropwise. The resulting suspension was stirred at room temperature; 12 h later, TLC showed that the alcohol had almost disappeared and then EtOAc and H_2O were added to the reaction mixture. The organic layer was separated and washed with brine. After drying over $MgSO_4$, the solvent was evaporated in vacuo and the crude product was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:20) to afford 658 mg (3.07 mmol, 95 %) of the benzylated product as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.34–7.27 (m, 5H), 4.99 (d, J = 1.69 Hz, 2H), 4.50 (d, J = 11.66 Hz, 1H), 4.70 (d, J = 11.66 Hz, 1H), 3.88 (dd, J = 8.28, 2.98 Hz, 1H), 2.29–2.24 (m, 2H), 1.92–1.86 (m, 2H), 1.73 (s, 3H), 1.71 ppm (m, 1H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 144.0, 138.6, 128.3, 127.8, 127.4, 114.0, 84.0, 81.7, 70.2, 68.4, 32.6, 16.7, 15.0 ppm. IR (neat): $\tilde{\nu}$ = 3303, 3030, 2943, 2863, 1649, 1453, 1374, 1071, 905 cm^{-1}.

*4-(tert-Butyldiphenylsilanyloxy)-2,2-dimethylbutan-1-ol (**10**)*

A solution of 2,2-dimethylsuccinic acid (5.0 g, 34.62 mmol) in dry diethyl ether (50 mL) was added dropwise to a stirred slurry of lithium aluminium hydride (LAH; 4.15 g, 0.11 mol) in dry diethyl ether (150 mL) at 0 °C. The mixture was stirred at room temperature for 24 h and quenched sequentially with addition of water (4.20 mL), 10% NaOH solution (8.40 mL), and water (12.60 mL). The slurry was filtered and the inorganic salts were washed with diethyl ether (2×50 mL). The combined ethereal extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude diol product (4.06 g, 34.36 mmol, 99%) was used directly without further purification: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 4.02 (s, 2H), 3.62 (t, J = 5.90 Hz, 2H), 3.26 (s, 2H), 1.48 (t, J = 5.90 Hz, 2H), 0.85 ppm (s, 6H) ^{13}C NMR (100 Hz, $CDCl_3$): δ = 71.3, 58.7, 42.6, 34.8, 24.8 ppm. IR (neat): $\tilde{\nu}$ = 3359, 2925, 1652, 1469, 1365, 1159, 1053, 985, 903 cm^{-1}. Imidazole (1.96 g, 28.84 mmol) and TBDPSCl (5.0 mL, 19.23 mmol) were added to a solution of the diol (2.27 g, 19.23 mmol) in THF (45 mL). After 24 h, the reaction was quenched with sat. $NaHCO_3$. The solution was extracted with diethyl ether (3×50 mL), dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to give 5.54 g (15.54 mmol, 81%) of the protected alcohol as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.69 (dd, J = 7.44, 1.50 Hz, 4H), 7.46–7.38 (m, 6H), 3.72 (t, J = 5.70 Hz, 2H), 3.37 (d, J = 6.51 Hz, 2H), 3.25 (brs, 1H), 1.55 (t, J = 5.75 Hz, 2H), 1.07 (s, 9H), 0.90 ppm (s, 6H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 135.5, 133.0, 129.8, 127.7, 71.6, 61.0, 41.9, 35.0, 26.7, 25.0, 19.0 ppm. IR (neat): $\tilde{\nu}$ = 3443, 3071, 2957, 1959, 1890, 1823, 1589, 1471, 1427, 1391, 1362, 1308, 1264, 1188, 1111, 939, 890, 822 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{22}H_{32}NaO_2Si$: 379.2069; found: 379.2096.

*4-(tert-Butyldiphenysilanyloxy)-2,2-dimethylbutyraldehyde (**7**)*

To a solution of oxalyl chloride (1.65 mL, 18.86 mmol) in CH_2Cl_2 (40 mL) cooled at −78 °C was added DMSO (2.23 mL, 31.43 mmol) in CH_2Cl_2 (10 mL) dropwise. The reaction mixture was stirred for 15 min and the solution of alcohol **10** (4.48 g, 12.57 mmol) in CH_2Cl_2 (10 mL) was added by cannula over 5 min. After the solution was stirred for 30 min, triethylamine (8.80 mL, 62.86 mmol) was added, and the reaction mixture was stirred for 1 h, then allowed to warm to room temperature for 4 h. Water (50 mL) was added, and the aqueous layer was extracted with additional CH_2Cl_2 (60 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:10) to give the aldehyde (4.35 g, 12.27 mmol, 98%) as a white solid: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 9.54 (s, 1H), 7.63 (dd, J = 7.65, 1.49 Hz, 4H), 7.42–7.35 (m, 6H), 3.63 (t, J = 6.16 Hz, 2H), 1.78 (t, J = 6.11 Hz, 2H), 1.05 (s, 6H), 1.02 ppm (s, 9H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 205.4, 135.6, 133.4, 129.7, 127.7, 60.2, 44.5, 40.6, 26.7, 21.6, 19.0 ppm. IR (neat): $\tilde{\nu}$ = 2961, 2928, 2855, 2360, 2341, 1734, 1711, 1459, 1428, 1109, 1085, 1056, 990, 824 cm^{-1}.

*9-Benzyloxy-1-(tert-butyldiphenylsilanyloxy)-3,3,10-trimethylundec-10-en-5-yn-4-ol (**11**)*

To a solution of alkyne **8** (845 mg, 3.94 mmol) in THF (30 mL) cooled to −78 °C was added LiHMDS (5.90 mL of 1.0 M solution in THF, 5.92 mmol). After stirring for 30 min, a solution of aldehyde **7** (1.54 g, 4.34 mmol) in THF (10 mL) was added. The mixture was stirred for 1 h at −78 °C and slowly warmed to room temperature. After stirring for 2 h, saturated ammonium chloride solution was added, and the mixture was extracted with diethyl ether (2×40 mL). The combined ethereal extracts were dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified using flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:10) to yield 2.23 g (3.91 mmol, 99%) of the alkynol as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.70–7.66 (m, 4H), 7.42–7.38 (m, 6H), 7.38–7.24 (m, 5H), 4.97 (d, J = 6.46 Hz, 2H), 4.49 (d, J = 11.73 Hz, 1H), 4.23 (d, J = 11.73 Hz, 1H), 4.07 (s, 1H), 3.85 (dd, J = 8.09, 5.41 Hz, 1H), 3.72–3.66 (m, 2H), 2.29 (t, J = 7.30 Hz, 2H), 1.90–1.85 (m, 2H), 1.72 (s, 3H), 1.70–1.67 (m, 1H), 1.45–1.39 (m, 1H), 1.04 (s, 9H), 0.95 ppm (s, 6H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 144.12, 144.07, 138.6, 135.58, 135.56, 133.03, 132.95, 129.78, 129.76, 128.31, 127.78, 127.74, 127.74, 127.72, 127.4, 113.99, 113.97, 85.4, 81.94, 81.90, 80.1, 70.5, 70.1, 60.9, 40.7, 38.3, 33.0, 26.7, 24.7, 23.8, 19.0, 16.7, 15.5 ppm. IR (neat): $\tilde{\nu}$ = 3396, 3070, 2957, 2858, 1822, 1650, 1589, 1472, 1428, 1390, 1362, 1319, 1188, 1111, 1028, 904, 823 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{37}H_{48}NaO_3Si$: 591.3270; found: 591.3323.

*9-(benzyloxy)-1-(tert-butyldiphenylsilyloxy)-3,3,10-trimethylundec-10-en-5-yn-4-yl-methyl carbonate (**12**)*

To a solution of alkynol **11** (2.18 g, 3.84 mmol) in CH_2Cl_2 (25 mL) cooled to 0 °C was added pyridine (1.55 mL, 19.18 mmol) and methyl chloroformate (890 μL, 11.51 mmol). After stirring for 2 h, the reaction mixture was warmed to room temperature, and further stirred for 2 h. The reaction mixture was diluted with CH_2Cl_2 and washed with 1N HCl, H_2O, and brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified using flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:20 to 1:10) to give 2.40 g (3.83 mmol, 99%) of the carbonate product as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.68–7.66 (m, 4H), 7.41–7.24 (m, 11H), 5.00–4.97 (m, 1H), 4.48 (d, J = 11.65 Hz, 1H), 4.23 (dd, J = 11.60, 2.20 Hz, 1H), 3.86–3.84 (m, 1H), 3.76 (s, 3H), 3.73 (t, J = 6.12 Hz, 2H), 2.29 (t, J = 7.32 Hz, 2H), 1.87–1.83 (m, 1H), 1.75–1.73 (m, 1H), 1.73 (s, 3H), 1.70–1.64 (m, 2H), 1.05 (s, 9H), 0.96 ppm (s, 6H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 155.3, 144.0, 138.6, 135.5, 133.81, 133.79, 129.5, 128.3, 127.74, 127.60, 127.44, 113.9, 87.4, 82.00, 81.88, 76.2, 75.8, 70.22, 70.19, 60.5, 54.7, 40.34, 40.30, 37.21, 37.20, 32.7, 26.8, 23.3, 23.0, 19.1, 16.7, 15.4 ppm. IR (neat): $\tilde{\nu}$ = 3070, 2957, 2857, 1754, 1441, 1428, 1390, 1341, 1264, 1190, 1145, 1110, 1029, 998, 952, 904, 823 cm^{-1}. HRMS (EI): *m*/*z* calcd for $C_{39}H_{50}NaO_5Si$: 649.3325; found: 649.3352.

*(9-benzyloxy-3,3,6,10-tetramethylundeca-4,5,10-trienyloxy)(tert-butyl)diphenylsilane (**13**)*

To a well stirred mixture of lithium bromide (2.35 g, 26.99 mmol) and copper iodide (5.14 g, 26.99 mmol) in THF (135 mL) at 0 °C was added methyl magnesium bromide (9.0 mL of 3 M ethereal solution, 26.99 mmol), and the solution was stirred for 30 min. The carbonate **12** (1.41 g, 2.25 mmol) in THF (10 mL) was added dropwise. The progress of the reaction was followed by TLC until completion (5 min to 1 h). The mixture was then poured into a saturated aqueous solution of ammonium chloride, extracted with ether, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified using flash chromatography on silica gel (EtOAc/*n*-hexane = 1:20) to afford 1.24 g (2.19 mmol, 97%) of the substituted allene product as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.67–7.63 (m, 4H), 7.40–7.24 (m, 11H), 4.95–4.89 (m, 1H), 4.89 (s, 1H), 4.87–4.85 (m, 1H), 4.48 (d, J = 11.80 Hz, 1H), 4.23 (d, J = 11.80 Hz, 1H), 3.71 (t, J = 7.13 Hz, 3H), 2.10–1.92 (m, 1H), 1.88–1.84 (m, 1H), 1.75–1.72 (m, 1H), 1.67 (d, J = 3.99 Hz, 3H), 1.63 (m, 2H), 1.57 (s, 3H), 1.55–1.54 (m, 1H), 1.03 (s, 9H), 0.92 (d, J = 2.32, 3H), 0.90 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ = 198.64, 198.60, 144.60, 144.56, 138.8, 135.5, 134.1, 129.5, 128.3, 127.78, 127.75, 127.55, 127.4, 113.74, 113.69, 101.28, 101.22, 100.88, 100.78, 82.86, 82.81, 69.9, 61.4, 45.2, 34.03, 34.00, 31.8, 31.6, 30.1, 28.76, 28.70, 28.05, 27.97, 26.9, 19.6, 19.1, 16.62, 16.60 ppm. IR (neat): $\tilde{\nu}$ = 3070, 3030, 2957, 2857, 1960, 1650, 1496, 1455, 1428, 1390, 1362, 1308, 1188, 1153, 1110, 997, 939, 902, 823 cm^{-1}.

*9-benzyloxy-3,3,6,10-tetramethylundeca-4,5,10-trien-1-ol (**14**)*

To a stirred solution of silyl-protected alcohol **13** (1.24 g, 2.19 mmol) in THF (30 mL) was added TBAF (11 mL of 1 M solution in THF, 10.94 mmol) at room temperature. After stirring for 10 h at room temperature, the reaction mixture was diluted with diethyl ether (30 mL), and water was added (30 mL). The organic layer was washed with 1N HCl, H_2O, and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane = 1:4) to give 705 mg (2.15 mmol, 98%) of the free alcohol as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ = 7.32–7.23 (m, 5H), 4.97–4.95 (m, 2H), 4.92 (s, 1H), 4.48 (d, J = 11.81 Hz, 1H), 4.23 (d, J = 11.81 Hz, 1H), 3.74 (t, J = 6.90 Hz, 1H), 3.66 (t, J = 7.19 Hz, 2H), 2.03–1.99 (m, 1H), 1.89–1.87 (m, 1H), 1.78–1.74 (m, 1H), 1.70 (s, 3H), 1.66 (d,

J=1.65, 3H), 1.64–1.1.56 (m, 4H), 0.99 (s, 3H), 0.98 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ=198.75, 198.69, 144.56, 144.50, 138.7, 128.3, 127.80, 127.77, 127.4, 113.88, 113.84, 101.29, 101.27, 101.16, 101.13, 82.89, 82.80, 69.94, 69.92, 60.2, 45.46, 45.43, 34.11, 34.09, 31.81, 31.69, 30.14, 30.10, 28.63, 28.60, 28.2, 19.68, 19.62, 16.59, 16.56 ppm. IR (neat): $\tilde{\nu}$=3385, 3068, 3031, 2956, 2864, 2361, 2340, 1961, 1497, 1454, 1372, 1151, 1068, 1027, 987, 902, 817 cm^{-1}.

*9-benzyloxy-3,3,6,10-tetramethylundeca-4,5,10-trienal (**15**)*

To a solution of oxalyl chloride (105 μL, 1.21 mmol) in CH_2Cl_2 (10 mL) cooled at −78 °C was added DMSO (143 μL, 2.01 mmol) dropwise. The reaction mixture was stirred for 10 min and the solution of alcohol **14** (264 mg, 0.80 mmol) in CH_2Cl_2 (3 mL) was added by cannula over 5 min. After the solution was stirred for 15 min, triethylamine (560 μL, 4.02 mmol) was added, and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (10 mL). The organic layers were combined, washed with saturated brine (10 mL), and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane=1:10) to give 244 mg (0.75 mmol, 93%) of the aldehyde as a colorless liquid: ^{1}H NMR (400 Hz, $CDCl_3$): δ=9.75 (t, J=3.03 Hz, 1H), 7.32–7.24 (m, 5H), 5.08–5.05 (m, 1H), 4.97 (d, J=1.40 Hz, 1H), 4.97 (s, 1H), 4.48 (d, J=11.81 Hz, 1H), 4.22 (d, J=11.81 Hz, 1H), 3.74 (t, J=6.51 Hz, 1H), 2.30–2.28 (m, 2H), 2.03–2.00 (m, 1H), 1.93–1.90 (m, 1H), 1.77–1.74 (m, 1H), 1.70 (s, 3H), 1.65 (d, J=1.06 Hz, 3H), 1.61–1.57 (m, 1H), 1.12(s, 3H), 1.11 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ= 203.3, 198.72, 198.68, 144.45, 144.38, 138.68, 128.2, 127.73, 127.70, 127.3, 113.86, 113.81, 102.44, 102.32, 100.26, 100.17, 82.72, 82.62, 69.9, 54.8, 34.35, 34.33, 31.69, 31.53, 30.0, 28.70, 28.68, 28.66, 19.52, 19.49, 16.5 ppm. IR (neat): $\tilde{\nu}$=3068, 3031, 2959, 2865, 2731, 2360, 1963, 1721, 1649, 1497, 1454, 1371, 1323, 1070, 1028, 903, 815 cm^{-1}.

*N-(9-benzyloxy-3,3,6,10-tetramethylundeca-4,5,10-trienylidene)-2-phenylaziridin-1-amine (**16**)*

To the solution of aldehyde **15** (220 mg, 0.67 mmol) in MeOH (3 mL) cooled to 0 °C with an ice-bath was added *N*-amino-2-phenylaziridine (1.0 mL of 1.0 M solution in MeOH, 1.00 mmol). After stirring for 16 h, the mixture was concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (EtOAc/*n*-hexane=1:5) to afford 267 mg (0.61 mmol, 90%) of the aziridinylimine as a pale yellow oil: ^{1}H NMR (400 Hz, $CDCl_3$): δ=7.97 (t, J=6.23 Hz, 1H), 7.33–7.24 (m, 10H), 5.00 (d, J=2.26 Hz, 1H), 5.00–4.97 (m, 1H), 4.93–4.91 (m, 1H), 4.48 (d, J=11.85 Hz, 1H), 4.23 (d, J=11.80, 1H), 3.73 (t, J=7.12 Hz, 1H), 3.00 (m, 1H), 2.40 (d, J=7.79 Hz, 1H), 2.29 (d, J=4.79 Hz, 1H), 2.21 (d, J=6.24 Hz, 2H), 2.15–1.95 (m, 1H), 1.88–1.86 (m, 1H), 1.78–1.76 (m, 1H), 1.70 (s, 3H), 1.66 (s, 3H), 1.60 (m, 1H), 1.04 (s, 3H), 1.03 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ=198.76, 198.74, 198.71, 161.80, 161.76, 144.52, 144.46, 138.73, 138.62, 128.28, 128.24, 127.74, 127.72, 127.33, 127.1, 126.4, 113.82, 113.76, 101.76, 101.64, 100.72, 100.71, 100.63, 100.59, 82.79, 82.77, 82.72, 77.3, 77.0, 76.7, 69.9, 44.9, 43.61, 43.59, 40.1, 34.90, 34.89, 31.73, 31.57, 30.0, 28.48, 28.46, 28.42, 27.98, 27.94, 27.92, 19.61, 19.57, 16.58, 16.57 ppm. IR (neat): $\tilde{\nu}$=3065, 3031, 2958, 2361, 1963, 1807, 1648, 1606, 1497, 1455, 1372, 1311, 1186, 1070, 1028, 990, 904, 813 cm^{-1}.

*Cycloaddition reaction of **16** and synthesis of (±)-Ceratopicanol (**1**)*

A solution of aziridinylimine **16** (235 mg, 0.53 mmol) in toluene (53 mL, 10 mM) was heated in an oil bath (ca. 125 °C) for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/*n*-hexane=1:10) to give the cyclized product (123 mg, 0.40 mmol, 75%) as a colorless oil. The cyclized product (120 mg, 0.39 mmol) underwent hydrogenolysis with a shaker-type Parr Hydrogenator under H_2 (60 psi), Pd/C (240 mg of 10 wt.% activated carbon), in EtOH (5 mL) for 12 h. The mixture was filtered over a Celite pad, and evaporated in vacuo. The crude product was purified by flash column chromatography to give 30.7 mg (0.14 mmol, 36%) of the alcohol as an oil (3:1 diastereomeric mixture).

The crude product was purified with flash column chromatography (*n*-hexane/EtOAc=10:1) to give 15.5 mg of ceratopicanol (32%): ^{1}H NMR (400 Hz, $CDCl_3$): δ=3.72–3.68 (m, 1H), 2.50–2.48 (m, 1H), 2.35–2.32 (m, 1H), 2.16 (dd, J=13.79, 9.52 Hz, 1H), 1.90–1.86 (m, 1H), 1.67 (ddd, J= 13.0, 8.4, 1.3 Hz, 1H), 1.60–1.50 (m, 1H), 1.50–1.32 (m, 5H), 1.23 (dd, J= 13.0, 4.8 Hz, 1H), 1.08 (dd, J=13.8, 6.8 Hz, 1H), 1.04 (s, 6H), 0.88 (s, 3H), 0.87 ppm (s, 3H). ^{13}C NMR (100 Hz, $CDCl_3$): δ=82.6, 58.8, 54.9, 51.2, 48.8, 44.2, 41.9, 41.7, 40.8, 39.5, 31.5, 30.6, 28.5, 23.9, 21.2 ppm. IR (neat): $\tilde{\nu}$=3364, 2948, 2866, 1460, 1374, 1312, 1065, 1032, 989 cm^{-1}. HRMS (EI): m/z calcd for $C_{15}H_{26}NaO$: 245.1881; found: 245.1876.

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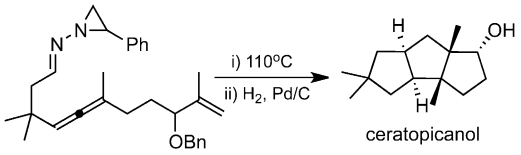
FULL PAPER

Total Synthesis

*Sang-Shin Lee, Won-Yeob Kim, Hee-Yoon Lee** ———— ▮▮▮▮–▮▮▮▮

Total Synthesis of Ceratopicanol through Tandem Cycloaddition Reaction of a Linear Substrate



When they all add up: Total synthesis of ceratopicanol was achieved by using a tandem cycloaddition reaction of allenyl diazo compound **6** via a trimethylenemethane (TMM) diyl intermediate. The TMM diyl mediated [2+3] cycloaddition reaction furnished the consecutive quaternary carbon centers and showed an unusual diastereoselectivity.

