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Total synthesis of (±)-ceratopicanol

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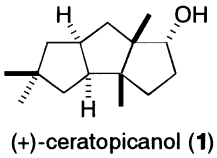
Abstract—Total synthesis of (±)-ceratopicanol (**1**) from commercially available 2-allyl-2-methylcyclopenta-1,3-dione (**6**) was completed. By taking advantage of the two carbonyl functionalities, **6** was transformed into the enyne **14** having an alkyne moiety, methyl substituent, and the hydroxy functionality with proper stereochemistry. The Pauson–Khand reaction of **14** was followed by chemical modifications resulting in the alternative total synthesis of (±)-ceratopicanol (**1**).

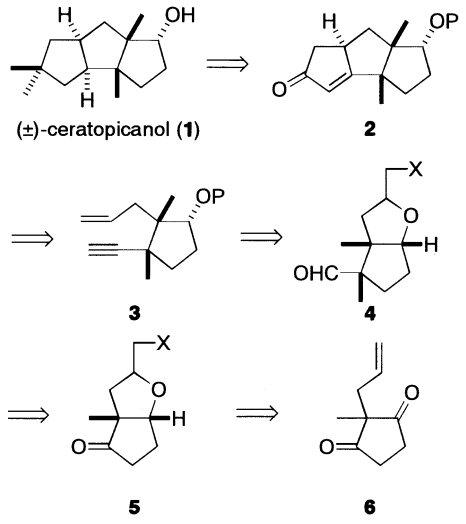
In 1988, a novel triquinane sesquiterpene, (+)-ceratopicanol (**1**), was isolated from the fungus *Ceratocystis piceae* Ha 4/82.[1] The relative stereochemistry of **1** was mainly determined based on its NMR analysis to be (1*R**,2*S**,6*S**,8*S**,9*R**)-1,4,4,8-tetramethyltricyclo[6.3.0.0^{2,6}]-undecan-9-ol.[1] The absolute configuration of (+)-ceratopicanol (**1**) was unambiguously established by the first total synthesis as its unnatural (−)-form.[2] Isolation of **1** provided the missing link in the biogenetic pathway of related sesquiterpenes from humulene.[3] In combination with these intriguing biogenetic considerations, ceratopicanol (**1**) has the interesting and unique structural feature consisting of five chiral carbon centers involving two contiguous bridgehead quaternary carbon centers. Based on these characteristics, the total synthesis of ceratopicanol (**1**) has so far been recorded by four groups.[2,4] In this paper, we describe an alternative total synthesis of (±)-ceratopicanol (**1**) based on the intramolecular Pauson–Khand reaction (Fig. 1).



(+)-ceratopicanol (**1**)

Figure 1.

Our retrosynthesis of **1** is outlined in Scheme 1. The target natural product **1** would be derived from **2** by simple chemical modifications. Construction of the tricyclic core carbon framework of **2** should be realized by the intramolecular Pauson–Khand reaction of the enyne compound **3**, which would be obtained from commercially available 2-allyl-2-methylcyclopenta-1,3-dione (**6**) via oxabicyclo[3.3.0]-octane derivatives **4** and **5** by some conventional means such as reduction, halo-etherization, and introduction of both alkyne and methyl moieties. This simple analysis prompted us to examine the total synthesis of (±)-ceratopicanol (**1**) in line with the retrosynthetic format.



Scheme 1.

At the inception of this study, we investigated the stereoselective reduction of the 1,3-dicarbonyl compound **6** leading to a compound possessing a *cis*-relationship between the hydroxy functionality and the allyl appendage. After screening several reducing agents, K-Selectride® was found to have the highest stereoselectivity for our purpose. Thus, the treatment of **6** with K-Selectride® in CH_2Cl_2 at −78°C afforded a mixture of two stereoisomers (ca. 85:15 based on ^1H NMR analysis). In order to get rid of the undesired *trans*-hydroxy compound, this mixture was subsequently exposed to *N*-bromosuccinimide (NBS) in CCl_4 to furnish a mixture consisting of two stereoisomers of the 2-oxabicyclo[3.3.0]octa-6-one derivative **7**[5] due to the C-3

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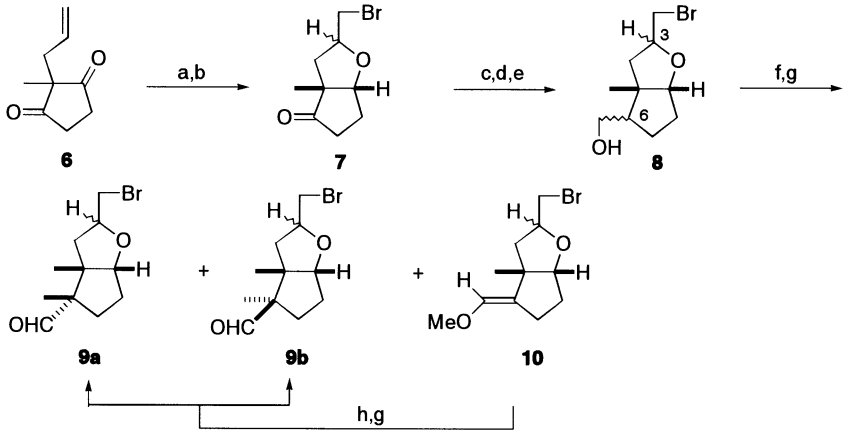
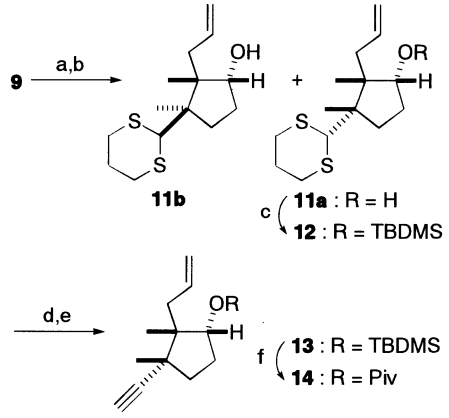


Scheme 2. *Reagents and conditions*: (a) K-Selectride®, CH_2Cl_2, −78°C; (b) NBS, CCl_4, rt, 77%; (c) Ph_3PCH_3Br, ^tBuOK, toluene reflux; (d) BH_3·THF, THF, 0°C; (e) 30% H_2O_2, 1N NaOH 0°C to rt, 65%; (f) PCC, 4 Å MS, CH_2Cl_2, rt; (g) MeI, ^tBuOK, benzene–^tBuOH, rt, **9** (39%, **a/b**=80:20) and **10** (33%); (h) 10% HCl, acetone, rt.

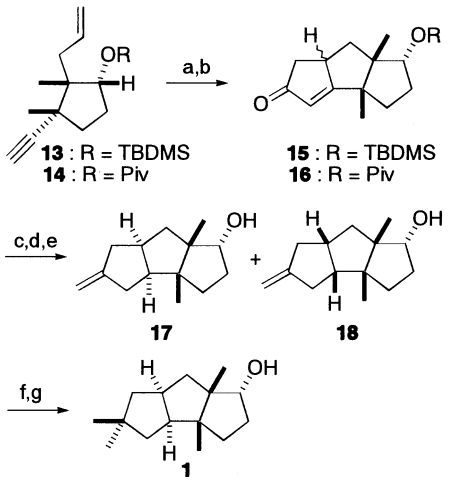
stereochemical center (ca. 67:33 based on ^1H NMR analysis) in 77% overall yield. The production of two stereoisomers due to the C-3 stereochemical center is not a serious problem because the C-3 stereochemical center would disappear in the latter step concluding with the regeneration of the allyl moiety. The Wittig reaction of **7** was followed by successive hydroboration and oxidation to provide **8** in 65% yield. The compound **8** (a mixture of possible four isomers) was then oxidized with pyridinium chlorochromate (PCC) to afford the corresponding aldehyde. Since this aldehyde was labile, we directly employed the freshly prepared crude aldehyde for the next methylation. The crude aldehyde was first exposed to various kinds of bases like LDA, NaH, and ^tBuOK to generate the enolate, which was quenched by treatment with methyl iodide or MeOTf under several conditions. However, the stereoselective methylation at the C-6 position with a satisfactory chemical yield could not be observed. The best result was recorded when the newly prepared aldehyde was treated with ^tBuOK in a solution of ^tBuOH and benzene (1:1) at room temperature in the presence of methyl iodide to produce a mixture of **9a** and **b** in 39% yield in a ratio of 80 to 20 (based on ^1H NMR analysis)[6] along with the *O*-methylated compound **10** in 33% yield. It was shown that **10** could be used as a precursor of **9**. Thus, the acidic hydrolysis of **10** with 10% HCl afforded the aldehyde, which, upon exposure to the same methylation conditions described above, provided a mixture of **9a** and **9b** (based on ^1H NMR analysis) in 37% yield together with the reformation of **10** in 37% yield. The stereochemistry of **10** was unambiguously confirmed to be (*E*) by an NOE experiment in which a 6.0% enhancement of the ring juncture methyl protons was observed by irradiation of the vinyl proton (Scheme 2).

The next phase of this research was to transform **9** into a compound having the alkyne functionality as well as the allyl group, both of which are mandatory for the intramolecular Pauson–Khand reaction. Upon treatment with 1,3-propanedithiol in the presence of BF_3·OEt_2, **9** (a mixture of **9a** and **b**) underwent thioketalization[7] to afford the corresponding dithiane derivative, exposure of which to zinc[8] in refluxing EtOH effected regeneration of the allyl group producing, after chromatographic separation, **11a** (79%) with the required stereochemistry along with its stereoisomer **11b** (19%) in a pure form. The secondary hydroxy group of **11a** was then protected with a silyl group to leave **12** in 93% yield. Dethioketalization of **12** with *N*-chlorosuccinimide (NCS)[9] was followed by treatment with lithiotrimethylsilyldiazomethane,[10] derived from trimethylsilyldiazomethane and ^nBuLi, at −78°C produced the alkyne derivative **13** also having the allyl moiety in 70% yield. Adjustment of the protecting group on the secondary hydroxy group of **13** was realized by simple treatment with pivaloyl chloride in the presence of scandium triflate to directly give the pivaloyloxy derivative **14** in 96% yield (Scheme 3).

With the required enynes in hand, we preliminarily examined the intramolecular Pauson–Khand reaction of **13**. According to the standard procedure, **13** was treated with dicobaltoctacarbonyl [$Co_2(CO)_8$] in Et_2O to give the corresponding alkyne–cobalt complex. This complex was then heated at 70°C in CH_3CN[11] to produce **15** in 97% as a mixture of two stereoisomers in the ratio of 56 to 44 (based on ^1H NMR analysis). Unexpectedly, no stereoselectivity



Scheme 3. *Reagents and conditions*: (a) 1,3-Propanedithiol, BF_3·OEt_2, CH_2Cl_2, 0°C; (b) Zn, EtOH, reflux, **11a** (79%), **11b** (19%); (c) TBDMSCl, Imid., DMF, rt, 93%; (d) NCS, $NaHCO_3$, acetone, 0°C; (e) TMSC(Li)N_2, THF, −78 to 0°C, 70%; (f) PivCl, $Sc(OTf)_3$, CH_3CN, 0°C to rt 96%.



Scheme 4. *Reagents and conditions*: (a) $Co_2(CO)_8$, Et_2O; (b) CH_3CN, 70°C, 96% (α/β=62:38); (c) 5% Pd–C, H_2, AcOEt, rt; (d) Ph_3PCH_3Br ^tBuOK, toluene, rt.; (e) DIBAL-H, CH_2Cl_2, −78°C. **17** (58%), **18** (36%); (f) $ZnEt_2$, CH_2I_2, benzene, rt; (g) PtO_2, 17 atm H_2, 10% HCl, MeOH, rt, 81%.

could be observed. Several derivatives of **13** having TBDPS, benzoyl, acetyl, and MOM groups instead of a TBDMS group on a secondary hydroxy group were prepared. The Pauson–Khand reaction of these compounds under various known conditions were examined without improvement of the stereoselectivity in the formation of tricyclo[6.3.0.0^{2,6}]undecane skeleton, although the chemical yields were constantly high in all cases. We finally introduced a pivaloyl group on the secondary hydroxy group of **13** to provide **14**,[12] which was converted to the corresponding cobalt-complex by treatment with $Co_2(CO)_8$. The resulting complex was then heated at 70°C in CH_3CN to afford **16** in 96% yield as a mixture of two stereoisomers in a ratio of 62 to 38 (based on ^1H NMR analysis). Since it was found that the isolation of each isomer was difficult at this stage, we used **16** as a mixture for further chemical elaboration. The hydrogenation of **16** in the presence of 5% Pd–C afforded the hydrogenated products, the Wittig reaction of which was followed by removal of the pivaloyl group leading to isolation of the desired **17** in 58% overall yield together with **18** (36%) (Scheme 4).

The final step in this synthesis was the transformation of the *exo*-methylene moiety of **17** into the dimethyl functionality. The Simmons–Smith reaction of **17** with diethylzinc and diiodomethane effected the formation of cyclopropane derivative, which was hydrogenated in the presence of PtO_2 under 17 atm of hydrogen pressure to give (±)-ceratopicanol (**1**) in 81% yield. The synthetic (±)-ceratopicanol was identical to the natural one by comparison of their spectral data.[1,2] Thus we have completed the alternative total synthesis of (±)-**1** from commercially available 2-allyl-2-methylcyclopenta-1,3-dione through the intramolecular Pauson–Khand reaction of the enyne **16**.

1. Experimental

1.1. General

Infrared spectra were measured with a Shimazu IR-460 spectrometer in $CHCl_3$, mass spectra with a Hitachi M-80 and JEOL GC mate mass spectrometers, ^1H NMR spectra with JEOL JNM-EX270 and JNM-GSX500 spectrometers for samples in $CDCl_3$, using either tetramethylsilane (for compounds without a silyl group) or $CHCl_3$ (7.26 ppm) (for compounds with a silyl group) as an internal standard, and ^{13}C NMR spectra with JEOL JNM-EX270 and JNM-GSX500 spectrometers in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal reference. All reactions were carried out under a nitrogen atmosphere otherwise stated. Silica gel (Silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

1.1.1. (1*R,5*R**)-3-Bromomethyl-5-methyl-2-oxabicyclo-[3.3.0]oct-6-one (7).** To a solution of **6** (60.9 mg, 0.40 mmol) in CH_2Cl_2 (2.0 mL) was added K-Selectride® (1.00 M THF solution, 0.44 mL, 0.44 mmol) at −78°C. The solution was stirred for 30 min, quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (3:1) to give the crude alcohol. To a solution of the crude alcohol in CCl_4 (2.0 mL) was added 4 Å MS (300 mg) and the mixture was stirred for 30 min at room temperature. NBS (107 mg, 0.60 mmol) was added to the reaction mixture, and stirring was continued for 12 h. MS were filtered off, and the filtrate was concentrated to dryness. The residue was chromatographed with hexane–AcOEt (7:1) to give **7** (71.8 mg, 77%) as a yellow oil: IR 1738 cm^{-1}; selected data for ^1H NMR δ 4.42 (0.67×1H, d, J=3.9 Hz), 4.25 (0.33×1H, d, J=4.4 Hz), 4.20–4.14 (1H, m), 3.44–3.31 (2H, m), 1.15 (0.67×3H, s), 1.14 (0.33×3H, s); MS *m/z* 234 (M^+, 35), 232 (M^+, 36); Anal. Calcd for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.04; H, 5.71.

1.1.2. (1*R,5*S**)-3-Bromomethyl-6-hydroxymethyl-2-oxabicyclo[3.3.0]octane (8).** To a suspension of ^{t}BuOK (168 mg, 1.50 mmol) in toluene (1.0 mL) was added methyltriphenylphosphonium bromide (536 mg, 1.50 mmol) at room temperature and the toluene solution was stirred for 2 h. A solution of **7** (117 mg, 0.50 mmol) in toluene (0.3 mL) was added to a solution of methylenetriphenylphosphorane, thus prepared, at room temperature. The reaction mixture was refluxed for 5 h, and hexane was added to reaction mixture. The resulting solids were filtered off and the filtrate was concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (30:1) to give the crude methylene derivative. To a solution of this crude methylene derivative in THF (1.0 mL) was added BH_3·THF (1.08 M THF solution, 0.51 mL, 0.55 mmol) at 0°C. The reaction mixture was stirred for 1 h, and then 30% aqueous H_2O_2 (0.3 mL) and 1.0N aqueous NaOH (0.3 mL) was successively added to the reaction mixture. After being stirred for 12 h at room temperature, the reaction mixture was diluted with water, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (3:1) to give **8** (81.3 mg, 65%) as a mixture of diastereoisomers. Compound **8** was a colorless oil: IR 3622, 3454 cm^{-1}; selected data for ^1H NMR δ 4.36 (0.39×1H, ddt, J=5.4, 9.3, 5.4 Hz), 4.21–4.16 (0.61×1H, m), 4.17 (0.61×1H, d, J=4.4 Hz), 4.10 (0.39×1H, dd, J=2.9, 6.4 Hz), 3.73–3.61

(2H, m), 3.48–3.33 (2H, m), 1.27 (0.61×3H, s), 1.02 (0.39×3H, s); FABMS *m/z* 251 (M^++1, 30), 249 (M^++1, 44); Anal. Calcd for $C_{10}H_{17}BrO_2$: C, 48.21; H, 6.88. Found: C, 48.17; H, 7.08.

1.1.3. Conversion of 8 to 9 and 10. To a solution of **8** (1.85 g, 7.42 mmol) and 4 Å MS (7.40 g) in CH_2Cl_2 (25 mL) was added PCC (2.40 g, 11.1 mmol) at room temperature and the mixture was stirred for 30 min. MS were filtered off, and the filtrate was concentrated to leave the crude aldehyde. To a solution of the crude aldehyde in benzene (19 mL) and ^{t}BuOH (19 mL) was added MeI (4.62 mL, 74.2 mmol) and ^{t}BuOK (3.33 g, 29.7 mmol) at room temperature, and the reaction mixture was stirred for 4 h. The resulting solids were filtered off and the filtrate was concentrated to dryness. The residue was chromatographed with hexane–AcOEt (30:1) to give a mixture of (1*R**,5*S**,6*S**)-3-bromomethyl-6-formyl-5,6-dimethyl-2-oxabicyclo[3.3.0]octane (**9a**) and (1*R**,5*S**,6*R**)-3-bromomethyl-6-formyl-5,6-dimethyl-2-oxabicyclo[3.3.0]octane (**9b**) (748 mg, 39%; **9a**:**b**=80:20), and (1*R**,5*S**,6*E*)-3-bromomethyl-6-methoxymethylene-2-oxabicyclo[3.3.0]-octane (**10**) (635 mg, 33%). Compound **9** (a mixture of **9a** and **b**) was a colorless oil: IR 1719 cm^{-1}; selected data for ^{1}H NMR δ 9.69 (0.80×1H, s), 9.59 (0.20×1H, s), 4.53–4.29 (2H, m), 3.64–3.48 (2H, m), 1.23 (0.80×3H, s), 1.19 (0.20×3H, s), 1.18 (0.20×3H, s), 1.06 (0.80×3H, s); MS *m/z* 262 (M^+, 0.2), 260 (M^+, 0.1); Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.25; H, 6.57. Compound **10** was a colorless oil: IR 1688 cm^{-1}; ^{1}H NMR δ 5.89 (1H, t, *J*=2.4 Hz), 4.18 (1H, dddd, *J*=4.9, 5.4, 5.8, 9.3 Hz), 4.13 (1H, d, *J*=3.9 Hz), 3.56 (3H, s), 3.41 (1H, dd, *J*=4.9, 10.3 Hz), 3.37 (1H, dd, *J*=5.8, 10.3 Hz), 2.49 (1H, ddt, *J*=9.3, 16.6, 2.0 Hz), 2.47–2.38 (1H, m), 2.16 (1H, dd, *J*=5.4, 12.2 Hz), 1.91 (1H, dd, *J*=7.3, 13.7 Hz), 1.82 (1H, dd, *J*=9.3, 12.2 Hz), 1.71–1.63 (1H, m), 1.18 (3H, s); ^{13}C NMR δ 141.0, 126.4, 92.2, 78.2, 59.5, 52.7, 47.2, 36.2, 30.3, 26.3, 25.4; MS *m/z* 262 (M^+, 2.1), 260 (M^+, 2.1); Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.59; H, 6.56. Found: C, 50.41; H, 6.61.

1.1.4. Conversion of 10 to 9a and 9b. To a solution of **10** (52.2 mg, 0.20 mmol) in acetone (1.0 mL) was added 10% HCl (1.0 mL) at room temperature. After being stirred for 15 h, the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to leave the crude aldehyde. According to the procedure described for conversion of **8** to **9**, the crude aldehyde, thus prepared, was methylated to give **9** (19.4 mg, 37%) as a mixture of **9a** and **b** (80:20) along with **10** (19.1 mg, 37%).

1.1.5. (1*R,2*S**,3*S**)- and (1*R**,2*S**,3*R**)-2-Allyl-2,3-dimethyl-3-(1,3-dithian-2-yl)cyclopentan-1-ol (11a and 11b).** To a solution of **9** (316 mg, 1.21 mmol, **a/b**=80:20) in CH_2Cl_2 (6.0 mL) was successively added 1,3-propanedithiol (0.18 mL, 1.75 mmol) and $BF_3{\cdot}Et_2O$ (1.00 M CH_2Cl_2 solution, 1.20 mL, 1.20 mmol) at 0°C. The reaction mixture was stirred at room temperature for 4 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with Et_2O. The extract was washed with brine, dried and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (20:1) to give the crude dithiane. To a solution of the crude dithiane in EtOH (12 mL) was added Zn (1.58 g, 24.2 mmol) and the reaction mixture was refluxed for 5 h. The reaction mixture was cooled to room temperature, and Zn was filtered off. The filtrate was concentrated to dryness to leave the residue, which was chromatographed with hexane–AcOEt (20:1 to 10:1) to give **11a** (260 mg, 79%) and **11b** (61.5 mg, 19%). Compound **11a** was a colorless solid: mp 70–72°C (from hexane); IR 3612, 3555, 3449, 1632 cm^{-1}; ^{1}H NMR δ 6.23 (1H, dddd, *J*=6.3, 8.3, 10.3, 17.1 Hz), 5.17 (1H, dd, *J*=1.5, 17.1 Hz), 5.04 (1H, dd, *J*=1.5, 10.3 Hz), 4.33 (1H, s), 3.97 (1H, t, *J*=8.8 Hz), 2.94 (1H, dt, *J*=2.4, 14.2 Hz), 2.89–2.83 (2H, m), 2.79–2.75 (1H, m), 2.47 (1H, dd, *J*=8.3, 14.7 Hz), 2.37 (1H, dd, *J*=6.4, 12.7 Hz), 2.12–2.02 (2H, m), 1.95 (1H, dt, *J*=5.4, 13.2 Hz), 1.85–1.76 (1H, m), 1.73 (1H, s), 1.58 (1H, ddd, *J*=4.9, 9.8, 14.7 Hz), 1.52–1.44 (1H, m), 1.21 (3H, s), 1.13 (3H, s); ^{13}C NMR δ 138.5, 115.8, 81.4, 60.0, 49.6, 49.5, 36.4, 35.6, 31.8, 30.9, 29.5, 26.0, 20.4, 20.4; MS *m/z* 272 (M^+, 6.0); Anal. Calcd for $C_{14}H_{24}OS_2$: C, 61.71; H, 8.88. Found: C, 61.35; H, 8.92. Compound **11b** was a colorless solid: mp 106–109°C (from hexane); IR 3620, 3568, 3472, 1634 cm^{-1}; ^{1}H NMR δ 5.97 (1H, dddd, *J*=5.9, 8.8, 10.3, 17.1 Hz), 5.17 (1H, dd, *J*=1.0, 17.1 Hz), 5.08 (1H, dd, *J*=1.0, 10.3 Hz), 4.14 (1H, s), 3.86 (1H, dd, *J*=2.4, 7.8 Hz), 2.99 (1H, ddd, *J*=2.4, 12.7, 14.2 Hz), 2.93–2.85 (2H, m), 2.81 (1H, ddt, *J*=1.5, 13.7, 3.4 Hz), 2.71 (1H, dd, *J*=5.9, 14.2 Hz), 2.58 (1H, dd, *J*=8.8, 13.7 Hz), 2.16–2.03 (2H, m), 1.90–1.78 (3H, m), 1.69 (1H, bs), 1.63–1.56 (1H, m), 1.36 (3H, s), 1.05 (3H, s); ^{13}C NMR δ 137.2, 116.9, 82.5, 60.3, 51.5, 50.7, 38.3, 37.6, 31.9, 31.3, 30.3, 26.0, 19.9, 19.2; MS *m/z* 272 (M^+, 10); Anal. Calcd for $C_{14}H_{24}OS_2$: C, 61.71; H, 8.88. Found: C, 61.46; H, 8.95.

1.1.6. (1*R,2*S**,3*S**)-2-Allyl-1-(*tert*-butyldimetylsiloxy)-2,3-dimethyl-3-(1,3-dithian-2-yl)cyclopentane (12).** To a solution of **11a** (641 mg, 2.35 mmol) in DMF (2.4 mL) was added imidazole (384 mg, 5.64 mmol), DMAP (28.7 mg, 2.35×10^{-1} mmol) and TBDMSCl (425 mg, 2.82 mmol) at room temperature. After being stirred for 1 day, the reaction mixture was quenched by addition of H_2O, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (30:1) to give **12** (849 mg, 93%) as a colorless oil: IR 1634 cm^{-1}; ^{1}H NMR δ 6.21 (1H, ddt, *J*=9.7, 17.1, 7.3 Hz), 5.07 (1H, dd, *J*=1.5, 17.1 Hz), 4.95 (1H, dd, *J*=1.5, 9.7 Hz), 4.46 (1H, s), 3.94 (1H, t, *J*=8.3 Hz), 2.94 (1H, ddd, *J*=2.5, 12.7, 14.2 Hz), 2.88–2.81 (2H, m), 2.76 (1H, ddt, *J*=1.5, 13.7, 3.4 Hz), 2.48 (1H, ddt, *J*=7.3, 14.6, 1.5 Hz), 2.21 (1H, dd, *J*=7.3, 14.6 Hz), 2.06–2.01 (1H, m), 1.98–1.90 (2H, m), 1.85–1.76 (1H, m), 1.58–1.42 (2H, m), 1.11 (3H, s), 1.09 (3H, s), 0.88 (9H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR δ 139.0, 114.4, 80.9, 59.8, 50.5, 49.4, 36.6, 36.2, 31.8, 30.9, 29.9, 26.1, 25.8, 21.5, 20.5, 18.0, −4.4, −5.0; MS *m/z* 386 (M^+, 13); Anal. Calcd for $C_{20}H_{38}OS_2Si$: C, 62.11; H, 9.90. Found: C, 61.95; H, 10.05.

1.1.7. (1*R,2*S**,3*R**)-2-Allyl-1-(*tert*-butyldimetylsiloxy)-3-ethynyl-2,3-dimethylcyclopentane (13).** To a solution of NCS (243 mg, 1.82 mmol) and $NaHCO_3$ (278 mg, 3.31 mmol) in acetone (6.3 mL) was added a solution of **12** (320 mg, 0.83 mmol) in acetone (2.0 mL) at 0°C. The

solution was stirred for 20 min, quenched by addition of saturated aqueous $Na_2S_2O_3$. Acetone was evaporated off and the residue was diluted with water, and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (20:1) to give the crude aldehyde. To a solution of $TMSCHN_2$ (2.00 M hexane solution, 0.62 mL, 1.24 mmol) in THF (1.5 mL) was added ^{n}BuLi (1.32 M hexane solution, 0.88 mL, 1.16 mmol) at −78°C and the reaction mixture was stirred for 30 min. Then a solution of the crude aldehyde in THF (0.6 mL) was added to this THF solution of freshly prepared lithiotrimethylsilyldiazomethane at the same temperature. The reaction mixture was stirred at −78°C for 1 h and then at 0°C for 1 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane to give **13** (169 mg, 70%) as a colorless oil: IR 3304, 2104, 1638 cm^{-1}; ^1H NMR δ 6.01 (1H, dddd, J=6.6, 8.2, 10.2, 16.8 Hz), 5.07–4.95 (2H, m), 3.86 (1H, dd, J=4.6, 6.9 Hz), 2.57 (1H, dd, J=6.6, 13.5 Hz), 2.26 (1H, dd, J=8.2, 13.5 Hz), 2.20–1.93 (2H, m), 2.13 (1H, s), 1.75–1.60 (2H, m), 1.19 (3H, s), 0.90 (9H, s), 0.79 (3H, s), 0.04 (6H, s); ^{13}C NMR δ 137.4, 116.0, 91.4, 80.9, 69.5, 50.0, 42.8, 38.3, 38.1, 32.0, 25.8, 25.1, 19.9, 18.0, −4.2, −5.1; MS m/z 292 (M^+, 0.9); Anal. Calcd for $C_{18}H_{32}OSi$: C, 73.90; H, 11.03. Found: C, 74.19; H, 11.28.

1.1.8. (1*R,2*S**,3*R**)-2-Allyl-3-etynyl-2,3-dimethyl-1-pivaloyloxycyclopentane (14).** To a solution of **13** (342 mg, 1.17 mmol) in CH_3CN (5.9 mL) was added PivCl (0.72 mL, 5.85 mmol) and scandium trifluoromethanesulfonate (28.8 mg, 5.85×10^{-2} mmol) at 0°C. The reaction mixture was stirred at room temperature for 10 h, quenched by addition of saturated aqueous $NaHCO_3$, and extracted with Et_2O. The extract was washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (30:1) to give **14** (295 mg, 96%) as a colorless oil: IR 3306, 2104, 1717, 1638 cm^{-1}; ^1H NMR δ 5.77 (1H, dddd, J=5.9, 8.8, 10.3, 17.1 Hz), 5.05 (1H, dd, J=2.4, 17.1 Hz), 5.02 (1H, dd, J=2.4, 10.3 Hz), 4.80 (1H, dd, J=3.0, 6.8 Hz), 2.75 (1H, dd, J=5.9, 13.7 Hz), 2.28–2.21 (1H, m), 2.20 (1H, s), 2.17–2.11 (2H, m), 1.75 (1H, ddd, J=8.3, 10.3, 13.2 Hz), 1.69–1.62 (1H, m), 1.23 (3H, s), 1.20 (9H, s), 0.82 (3H, s); ^{13}C NMR δ 178.0, 135.6, 117.2, 90.8, 81.8, 70.1, 49.7, 43.8, 38.7, 38.5, 37.6, 30.1, 27.0, 23.4, 19.6; MS m/z 262 (M^+, 2.1); Anal. Calcd for $C_{17}H_{26}O$: C, 77.82; H, 9.99. Found: C, 77.58; H, 10.28.

1.1.9. (1*R,8*S**,9*R**)-1,8-Dimethyl-9-pivaloyloxytricyclo-[6.3.0.0^{2,6}]undec-2(3)-en-4-one (16).** To a solution of **14** (52.5 mg, 0.20 mmol) in Et_2O (1.0 mL) was added $Co_2(CO)_8$ (103 mg, 0.30 mmol) at room temperature and the reaction mixture was stirred for 30 min. Et_2O was evaporated off and the residue was passed through a short pad of silica gel with hexane–AcOEt (10:1) to give the crude alkyne–$Co_2(CO)_6$ complex. A solution of the crude alkyne–$Co_2(CO)_6$ complex in CH_3CN (4.0 mL) was heated at 70°C for 1 h. CH_3CN was evaporated off and the residue was chromatographed with hexane–AcOEt (10:1) to give **16** (55.8 mg, 96%, α/β=62:38) as a colorless oil: IR 1720, 1701, 1622 cm^{-1}; selected data for ^1H NMR δ 5.82 (0.38×1H, d, J=2.0 Hz), 5.80 (0.62×1H, d, J=2.0 Hz), 4.90 (0.38×1H, t, J=5.4 Hz), 4.69 (0.62×1H, dd, J=5.9, 10.7 Hz), 1.23 (0.38×9H, s), 1.20 (0.38×3H, s), 1.19 (0.62×9H, s), 1.19 (0.62×3H, s), 1.18 (0.62×3H, s), 1.15 (0.38×3H, s); MS m/z 290 (M^+, 4.3); Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.57; H, 9.22.

1.1.10. (1*R,2*S**,6*S**,8*S**,9*R*)- and (1*R**,2*R**,6*R**,8*S**,9*R**)-1,8-Dimethyl-4-methylenetricyclo[6.3.0.0^{2,6}]undecan-9-ol (17 and 18).** A solution of **16** (18.1 mg, 6.23×10^{-2} mmols) in AcOEt (1.3 mL) was hydrogenated in the presence of 5% Pd–C (0.9 mg) under a hydrogen atmosphere at room temperature for 14 h. The catalyst was filtered off and the filtrate was concentrated to leave the crude saturated ketones. According to the procedure described for conversion of **7** to **8**, the crude material was treated with methylenetriphenylphosphorane to give the crude *exo*-methylene derivatives. To a solution of the crude *exo*-methylene derivatives in CH_2Cl_2 (0.6 mL) was added DIBAL-H (1.04 M toluene solution, 0.18 mL, 1.87×10^{-1} mmol) at −78°C. The reaction mixture was stirred for 1 h, quenched by addition of saturated aqueous NH_4Cl and 10% HCl, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. The residue was chromatographed with hexane–AcOEt (15:1) to give **17** (8.8 mg, 58%) and **18** (5.5 mg, 36%). Compound **17** was a colorless solid: mp 85–87°C (from hexane); IR 3612, 3452, 1655 cm^{-1}; ^1H NMR δ 4.85 (1H, s), 4.81 (1H, s), 3.63 (1H, t, J=7.3 Hz), 2.49–2.11 (7H, m), 1.88–1.74 (1H, m), 1.64–1.38 (4H, m), 1.03 (3H, s), 0.99–0.94 (1H, m), 0.95 (3H, s); ^{13}C NMR δ 153.1, 105.9, 81.9, 60.0, 54.2, 51.3, 42.2, 40.3, 39.5, 38.7, 35.5, 32.4, 24.7, 22.4; MS m/z 206 (M^+, 7.8); Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.22; H, 10.85. Compound **18** was a colorless solid: mp 56–58°C (from hexane); IR 3609, 3454, 1653 cm^{-1}; ^1H NMR δ 4.79 (2H, s), 3.84 (1H, t, J=8.3 Hz), 2.72–2.58 (1H, m), 2.54–2.44 (1H, m), 2.37–2.27 (2H, m), 2.23–2.15 (1H, m), 2.12–1.84 (3H, m), 1.60–1.43 (3H, m), 1.39 (1H, s), 1.10–1.01 (1H, m), 0.98 (3H, s), 0.87 (3H, s); ^{13}C NMR δ 154.7, 105.2, 80.8, 57.2, 54.2, 53.2, 41.1, 40.6, 39.8, 34.3, 30.9, 30.5, 25.0, 20.0; MS m/z 206 (M^+, 5.4); HREIMS calcd for $C_{14}H_{22}O$ (M^+): 206.1671; found: 206.1669.

1.1.11. (±)-Ceratopicanol (1). To a solution of **17** (15.1 mg, 7.32×10^{-2} mmol) in benzene (0.7 mL) was added CH_2I_2 (0.02 mL, 0.25 mmol) and $ZnEt_2$ (1.01 M hexane solution, 0.22 mL, 0.22 mmol) and the reaction mixture was stirred for 5 h at room temperature. The reaction mixture was quenched by addition of 10% HCl, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane–AcOEt (10:1) to give the crude cyclopropane derivative. A solution of the crude cyclopropane derivative in MeOH and 10% HCl (10:1, 0.4 mL) was hydrogenated in the presence of PtO_2 (1.6 mg, 7.00×10^{-3} mmol) under 17 atm of H_2 at room temperature for 1 day. The catalyst was filtered off and the filtrate was diluted with water, and extracted with AcOEt. The extract was washed with brine, dried, and concentrated to dryness. Chromatography of the residue with hexane–AcOEt (10:1) gave (±)-ceratopicanol (**1**)

(13.2 mg, 81%) as a colorless solid: mp 66–67°C (from hexane)[lit.[4a] 67–68°C (from hexane)]; IR 3607, 3452 cm^{-1}; ^1H NMR δ 3.72 (1H, dd, J=7.3, 8.8 Hz), 2.55–2.46 (1H, m), 2.36 (1H, ddd, J=8.3, 8.3, 11.2 Hz), 2.17 (1H, dd, J=9.8, 14.2 Hz), 1.94–1.88 (1H, m), 1.70 (1H, ddd, J=1.5, 8.3, 12.7 Hz), 1.61–1.55 (1H, m), 1.52–1.32 (4H, m), 1.49 (1H, s), 1.24 (1H, dd, J=5.4, 12.7 Hz), 1.08 (1H, dd, J=6.8, 14.2 Hz), 1.06 (3H, s), 1.06 (3H, s), 0.90 (3H, s), 0.89 (3H, s); ^{13}C NMR δ 82.6, 58.8, 54.9, 51.2, 48.8, 44.2, 41.9, 41.7, 40.8, 39.5, 31.6, 30.6, 28.6, 23.9, 21.2; MS m/z 222 (M^+, 19); Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.84; H, 11.98.

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