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A total synthesis of (-)-Hortonone C

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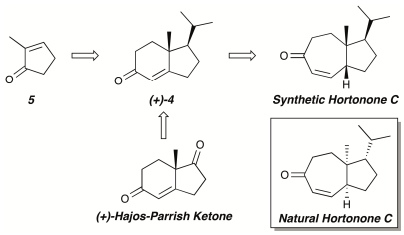

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A total synthesis of (-)-Hortonone C

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ABSTRACT

A total synthesis of the cytotoxic terpenoid hortonone C was accomplished and its absolute stereochemistry confirmed. Intermediate (+)-**4** was synthesized using either an asymmetric conjugate addition strategy, or by elaboration of the Hajos-Parrish ketone. Reduction of (+)-**4** under dissolving-metal conditions and trapping the enolate intermediate served to control the cis-stereochemistry at the ring fusion and provide a silyl enol ether necessary for ring expansion. Comparison of optical rotation data confirmed that the absolute configuration of natural hortonone C is (6*S*,7*S*,10*S*).

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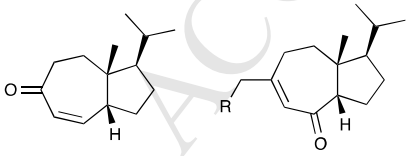
1. Introduction

Terpenoids are regarded as one of the largest and most important classes of natural products, many of which possess anticancer, antifungal, antiviral and antibacterial activity.[1] Terpenoids are also structurally diverse, possessing a wide variety of carbocyclic systems often with multiple stereocenters and oxygenation patterns, making them attractive targets for total synthesis.[2,3] The hortonones A-C (**1**-**3**, fig. 1) are a group of hexahydroazulenone natural products possessing an unprecedented rearranged skeleton that was isolated from a collection of plants belonging to the genus *Hortonia* in Sri Lanka.[4]



Hortonone C (**1**) R = H: Hortonone A (**2**) R = OH: Hortonone B (**3**)

Figure 1. Structure of the hortonones A-C

Of these, hortonone C showed promising in vitro activity towards MCF-7 cancer cells, (IC_{50} = 5 μg/mL) while hortonone A and B were not active at concentrations as high as 100 μg/mL.[4] The structure and relative stereochemistry of the hortonones was elucidated based on NMR studies, but their absolute stereochemistry was not assigned. Recently, the first total synthesis of the hortonones was reported by Minehan,[5] using the Inhoffen-Lythgoe diol, a degradation product of ergocalciferol (vitamin D_2) as chiral starting material. The work also served to unveil the absolute stereochemistry of the hortonones. Herein, we would like to report our own efforts towards the synthesis of hortonone C and the confirmation of its absolute stereochemistry.

2. Results and discussion

At the beginning of our work, the absolute stereochemistry of the hortonones was unknown. Based on the isolation report,[4] we decided to target the (6*R*,7*R*,10*R*) enantiomer (Figure 1). Hortonone C contains a 5,7 cis-fused bicyclic system with 3 contiguous stereocenters and an α,β-unsaturated ketone. Several approaches for the stereoselective construction of 5,7 cis-fused bicyclic systems are known in the literature.[6] The most commonly employed methods include intramolecular aldol reactions,[7] ring-closing metatheses,[8] and metal-catalyzed cycloisomerizations.[9] In addition, ring expansion strategies are well precedented.[10] We

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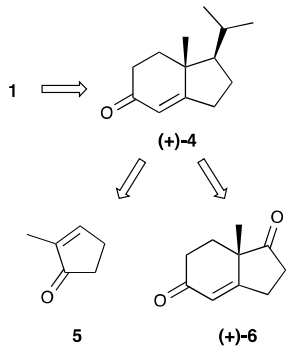
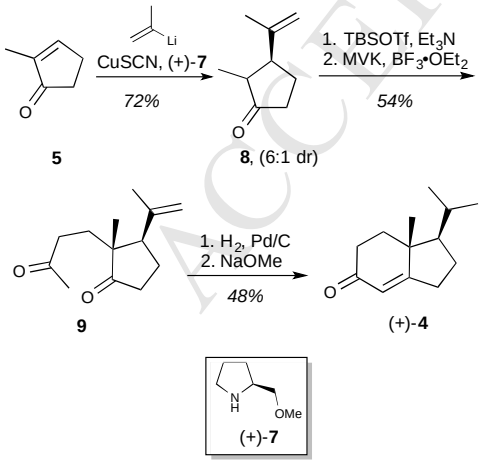
envisioned the construction of the cycloheptenone ring of hortonone C to derive from a ring expansion event on known hydrindanone (+)-**4**[11] having two out of three required stereocenters already in place. In turn, hydrindanone (+)-**4** could be prepared by conjugate addition of an isopropyl unit to 2-methyl-2-cyclopenten-1-one (**5**) followed by cyclization, or derived from readily available Hajos-Parrish Ketone (+)-**6**[12] (Scheme 1)



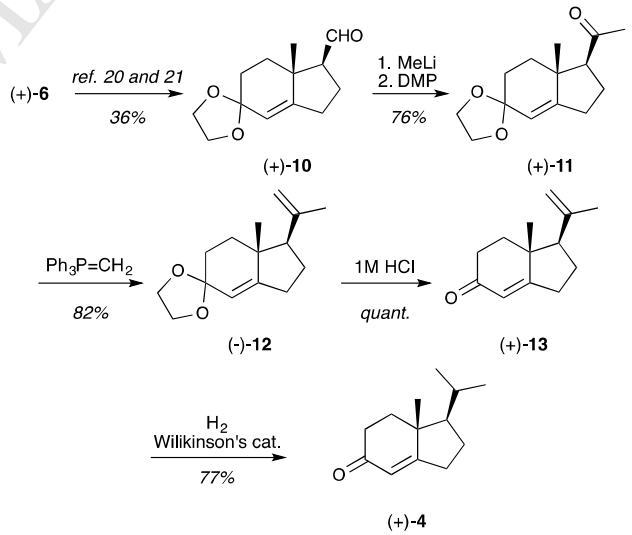
Scheme 1. Retrosynthesis of intermediate (+)-**4**.

While non-enantioselective conjugate addition reactions on cyclopentenone **5** are well documented, the asymmetric versions of these transformations are recognized as a synthetic challenge.[13,14,15] We sought to implement a short synthesis of (+)-**4** by using an asymmetric conjugate addition developed by Quinkert in his synthesis of confertin[16,17] and showcased by Danishefsky in the synthesis of guanacastepene A.[18] This sequence, while allowing access to enantioenriched (+)-**4**, requires the use of excess amounts of a chiral additive derived from L-proline. Despite the need for excess chiral additive, we decided to explore this option first. Following the Danishefsky report,[11] cyclopentenone **5** was treated with a cuprate derived from isopropenyllithium and cuprous thiocyanate in the presence of chiral additive (+)-**7**[16,19] (Scheme 2) to yield **8**. Ketone **8** was then transformed into the corresponding tetrasubstituted silyl enol ether and subjected to Lewis acid-promoted conjugate addition to methyl vinyl ketone (MVK) to deliver diketone (+)-**9** as a single diastereomer (^{1}H NMR). Hydrogenation and cyclization gave UV-active enone (+)-**4**. At this point, chiral stationary phase HPLC analysis showed that this route produced (+)-**4** with 94% ee. (See supporting information).



Scheme 2. Synthesis of (+)-**4**.

Comparison of characterization data for (+)-**4**, including optical rotation, matched well with the Danishefsky report,[11] however, the sense of asymmetric induction of the initial conjugate addition was in contrast with that described originally by Quinkert,[16] despite the fact that both reports describe the use of the same chiral additive derived from L-proline. With these results, we felt necessary to unambiguously assign the absolute configuration of our synthetic (+)-**4** by an independent synthesis route that could use chiral material of well-established absolute configuration. Based on the work of Yamashita,[20] and Deslongchamps,[21] readily available Hajos-Parrish ketone (+)-**6**[12] was converted into known aldehyde (+)-**10** in 5 steps and 36% overall yield (Scheme 3). Nucleophilic addition of CH_3Li in THF delivered the corresponding secondary alcohol as mixture of diastereomers, which converged into methyl ketone (+)-**11** upon oxidation with the Dess-Martin reagent.[22] Wittig olefination delivered diene (-)-**12**, which required selective reduction at the 1,1-disustituted alkene in the presence of the trisubstituted olefin. To this end, hydrogenation of (-)-**12** using Wilkinson's catalyst was attempted, but no reaction was observed after 48 h. Fortunately, the required selective reduction was observed when enone (+)-**13** was subjected to hydrogenation with Wilkinson's catalyst, affording hydrindanone (+)-**4** in 77% yield. The characterization data for (+)-**4**, prepared by this independent route, again matched well with the Danishefsky report.[11] Chiral stationary phase HPLC analysis showed that the obtained product had 88% ee, confirming that this method produced the same major enantiomer as the asymmetric cuprate addition route (See supporting information).



Scheme 3. Synthesis of (+)-**4** from (+)-**6**.

Having secured a reliable route to enone (+)-**4**, we focused our efforts on the ring expansion sequence and completion of the synthesis. Enone (+)-**4** was treated with TMS-diazomethane and a Lewis acid in the anticipation that these conditions would promote regioselective ring expansion,[23,24,25] and that the expected β,γ-unsaturated ketone would undergo isomerization, either during workup or on a separate step, to the conjugated enone corresponding to hortonone C. Unfortunately, all attempts to induce direct ring expansion on enone (+)-**4** using TMS-diazomethane and either $BF_3{\cdot}OEt_2$[25] or $AlMe_3$[24] were unsuccessful, affording either recovery of unreacted starting material or complex mixtures under

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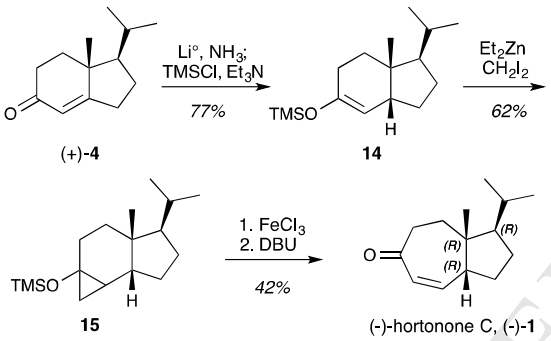
more forcing conditions. We then turned our attention to a different strategy, in which enone (+)-**4** could be subjected to conjugate reduction, and the ensuing enolate could be used as an entry to the required ring expansion. Based on the work by de Meijere[26] on a similar substrate, treatment of enone (+)-**4** under dissolving metal conditions, followed by trapping of the enolate with TMSCl afforded silyl enol ether **14** (Scheme 4). Silyl enol ether **14** could be purified and immediately subjected to cyclopropanation[27] to furnish **15** in good yield. Although the ^{1}H NMR of **15** showed the presence of a single diastereomer, the stereochemistry of the cyclopropane ring was not assigned. With the required substrate on hand, the final ring expansion was attempted. Transformation of trimethylsilyloxy-cyclopropanes into cycloheptenones is well precedented in the literature;[10] however, in the case of **15** this transformation proved to be challenging. Treatment of **15** under standard conditions[28] (2 equiv. $FeCl_3$, DMF, 0 °C to rt, 24 h, then NaOAc, MeOH, reflux) resulted in complete consumption of the starting material, but low yields of the desired final product. Attempts at increasing the efficiency of this transformation either by direct elimination, by addition of pyridine as a base, or purification of the beta-chloro intermediate did not improve the results. Eventually, our best results were obtained by heating a toluene solution of the crude chloride intermediate in the presence of DBU as a base to obtain (-)-**1** in 42% yield from **15**.



Scheme 4. Synthesis of hortonone C (-)-**1**.

Although the yield of this final sequence was modest, comparison of NMR data of the synthetic material with that of the natural product showed a complete match. The sign of the optical rotation of our synthetic hortonone C {$[\alpha]^{22}_D$ –57.2 (*c* 1.0, $CHCl_3$)} showed that we had synthesized the enantiomer of the natural product {lit.[4] $[\alpha]^{20}_D$ +74 (*c* 4.4, $CHCl_3$)}, therefore, the absolute stereochemistry of natural hortonone C must be described as (6*S*,7*S*,10*S*), in agreement with the Minehan report.[5] Evaluation of cytotoxicity using the MTT assay as described previously[29] demonstrated that synthetic hortonone C (-)-**1** was not active (IC_{50} >100 μM) against MCF-7 breast cancer cells, indicating that the absolute stereochemistry of the natural product is essential for activity

3. Conclusions

In summary, we have accomplished an enantioselective total synthesis of the enantiomer of the cytotoxic terpenoid hortonone C. The synthesis features the conjugate reduction of a key enone intermediate under metal dissolving conditions as a strategy to control the stereochemistry of the cis-ring fusion as well as delivering a silyl enol ether useful for ring expansion. The sequence is practical and was useful to confirm the absolute stereochemistry of the natural product. As demonstrated by Minehan,[5] transformation of hortonone C into the structurally related hortonones A and B is possible, therefore our efforts also represent a formal total synthesis of the hortonones A and B. In addition, our synthetic approach could be easily adapted to prepare the natural enantiomers of the hortonones by simply using D-Proline to prepare either the enantiomeric (-)-Hajos-Parrish ketone, or the (-)-**7** pyrrolidine ligand needed for the initial asymmetric conjugate addition. Such flexibility could be critical for further biological evaluations of hortonone C and its analogs.

4. Experimental section

4.1. General

All moisture sensitive reactions were conducted in oven-dried glassware under an atmosphere of dry nitrogen. Reaction solvents were dried and degassed by passing through a column of activated alumina in a solvent purification system or freshly distilled from the appropriate drying agent. All other solvents and reagents were purchased from commercial suppliers and used as received, unless otherwise specified. ^{1}H and ^{13}C NMR spectra were recorded using a 400 MHz Bruker instrument. Data for ^{1}H NMR are reported as follows: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are given in Hertz. IR measurements were performed in a Nicolet FT IR as thin films. Optical rotations were measured on a Rudolph Autopol III or a Jasco DIP-1000 polarimeter. HPLC analyses used a chiralpak IC column, eluting with a mixture of hexane-isopropanol (65:35) at a flow rate of 0.5 mL/min. and UV detection at 254 nm. High-resolution mass spectrometry analyses were conducted at the University of New Mexico Mass Spectrometry facility.

*4.2. (3S)-2-methyl-3-(prop-1-en-2-yl)cyclopentan-1-one (+)-(**8**)*

Under a nitrogen atmosphere, 2-bromopropene (0.25 mL, 2.81 mmol) was taken in 14 mL of dry ether and cooled to -78 ºC. To this, *tert*-Butyllithium (3.67 mL of a 1.53 M solution in pentane) was added dropwise via syringe and the mixture stirred for 30 min. The resulting isopropenyllithium solution was cannulated into a septum-sealed flask containing cuprous thiocyanate (0.171 g, 1.4 mmol) and powdered 4Å molecular sieves (0.54 g) in 7.0 mL of dry Et_2O. The mixture was stirred for 1 h and allowed to warm up to -25 °C. Then the mixture was cooled to -60 °C and treated with a solution of ligand (+)-**7**[16,19] (0.35 mL, 2.71 mmol) in 5.0 mL of dry Et_2O. Stirring continued for 30 min. as the mixture was allowed to warm up to -50 °C. Finally, ketone **5** (69 μL, 0.7 mmol) was added by syringe at -100 °C and the resulting mixture was stirred for 2 h at the same temperature before it was quenched with 10 mL of ice-cold ammonium chloride saturated solution, and diluted with 20 mL of Et_2O. After stirring for 15 min., the mixture was filtered through Celite®. The aqueous layer was separated and extracted with Et_2O. Combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel flash column chromatography using 9:1 hexanes-Et_2O afforded 0.069 g of ketone **8** as a 6:1 mixture of diastereomers in 72% yield. Physical and spectral data were in agreement with the literature values.[16]

*4.3. (2R,3R)-2-methyl-2-(3-oxobutyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (**9**)*

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A solution of ketone **8** (0.039 g, 0.282 mmol) in 2 mL of dry acetonitrile was treated with Et_3N (43 µL, 0.31 mmol), followed by freshly distilled TMSCl (39 µL, 0.31 mmol). To the mixture was added dropwise a solution of NaI (0.046 g, 0.310 mmol) in 2 mL of dry acetonitrile. The reaction mixture was stirred at room temperature for 3 h before filtering and the solids were washed with pentane. The combined pentane layer was concentrated to obtain the corresponding silyl enol ether (0.059 g, *quant.)* as a colorless oil, which was directly used in the next reaction without purification: A solution of silyl enol ether derived from **8** (0.059 g, 0.282 mmol) in 1.0 mL of dry CH_2Cl_2 was cooled to -10 °C and treated with methyl vinyl ketone (17 µL, 0.216 mmol) followed by dropwise addition of $BF_3{\cdot}OEt_2$ (3 µL, 0.021 mmol) and a solution of L- menthol (38 µL, 0.216 mmol) in 1.0 mL of dry CH_2Cl_2. The mixture was stirred at the same temperature for 1 h, then allowed to warm up to 0 °C and quenched with $NaHCO_3$ saturated solution. The mixture was then extracted with CH_2Cl_2, and the combined organic layer dried over $MgSO_4$, filtered and concentrated. Purification by flash column chromatography using 3:1 hexanes-EtOAc afforded diketone **9** (0.024 g, 54% from **8**) as a colorless oil. Spectroscopic data were in agreement with the literature values.[11]

*4.4. (1R,7aR)-1-isopropyl-7a-methyl-1,2,3,6,7,7a-hexahydro-5H-inden-5-one (+)-(**4**).*

A solution of diketone **9** (0.024 g, 0.115 mmol) in 1.5 mL dry benzene was treated with 3.5 mg of 5% wt Pd/C (50 % paste in water). The headspace of the flask was flushed with hydrogen, and the mixture was stirred at room temperature under an atmosphere of hydrogen. After 48 h, the mixture was filtered through a short plug of silica and the solids rinsed with EtOAc. The combined filtrate was concentrated and the residue was purified by silica gel flash chromatography using 6:1 hexanes-EtOAc to give the corresponding diketone intermediate as colorless oil. (0.018 g, 75%). ^{1}H, ^{13}C NMR and optical rotation data was in agreement with the literature values.[11] 0.018 g (0.085 mmol) of the above-obtained diketone intermediate was treated with 0.12 mL of a 0.5 M solution of sodium methoxide in methanol. The mixture was stirred and heated to reflux for 12 h before saturated NaCl solution was added. The mixture was extracted with Et_2O, and the combined organic layer washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by silica gel flash column chromatography using 5:1 hexanes-EtOAc gave (+)-**4** (0.007 g, 48%) as colorless oil. Chiral stationary phase HPLC analysis indicated this product had 94% ee. Spectroscopic data were in agreement with the literature values.[11]

*4.5. (1S,7aR)-7a-methyl-1,2,3,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolane]-1-carbaldehyde (+)-(**10**)*

Aldehyde (+)-**10** Was prepared in five steps and 36% overall yield from known Hajos-Parrish ketone (+)-**6**[12] using the sequence described by Deslongchamps[21] with the following modification: $NaBH_4$ reduction of the Hajos-Parrish ketone (+)-**6** was carried out using the method of Yamashita and Hirama.[20] Characterization data for (+)-**10** matched those described by Deslongchamps.[21]

*4.6. 1-((1S,7aR)-7a-methyl-1,2,3,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolan]-1-yl)ethan-1-one (+)-(**11**)*

A solution of aldehyde (+)-**10** (0.604 g, 2.719 mmol) in 25 mL of dry THF was cooled to -78 °C and treated with a solution of $CH_3Li{\cdot}LiBr$ in Et_2O (2.2 M, 2.34 mL, 5.143 mmol) drop-wise via syringe. The reaction mixture was stirred at the same temperature for 2 h before an additional equivalent of CH_3Li was added. Stirring continued for 1 h at the same temperature before the mixture was warmed up to room temperature, and slowly quenched by drop-wise addition of water and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by SiO_2 column chromatography using 3:2 hexanes-EtOAc afforded the corresponding secondary alcohol intermediate (0.568 g, 2.383 mmol, 87%) as a 10:1 inseparable mixture of diastereomers. Data for major diastereomer: R_f : 0.5 (hexanes/EtOAc = 1:1); IR (thin film) ν 3562, 2929, 2872, 2353, 1638, 1070 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 3.96 (m, 5H), 2.49-2.21 (m, 4H), 1.87-1.79 (m, 3H), 1.67-1.52 (m, 3H), 1.26-1.25 (d, *J* = 6.36 Hz, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9 (C), 121.4 (CH), 109.1 (C), 69.1 (CH), 64.5 (CH_2), 64.4 (CH_2), 59.4 (CH), 45.2 (CH), 37.4 (CH_2), 36.1 (C), 33.9 (CH_2), 31.0 (CH_2), 23.7 (CH_3), 16.1 (CH_3); HRMS (ESI+) m/z: $[M+Na]^+$ Calc'd for $C_{14}H_{22}NaO_3$ 260.1467; Found 261.1465. To a solution of the above-obtained secondary alcohol intermediate (0.199 g, 0.836 mmol) in 8.0 mL of dry CH_2Cl_2 was added Dess-Martin periodinane (0.531 g, 1.253 mmol) in one portion. The reaction mixture was stirred at room temperature for 1 h before quenching with 1:1 mixture of aq. saturated $Na_2S_2O_3$ and aq. saturated $NaHCO_3$ solution, and extracting with CH_2Cl_2. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification by SiO_2 column chromatography using 3:2 hexanes-EtOAc afforded ketone (+)-**11** (0.171 g, 87%). R_f : 0.6 (hexanes/EtOAc = 1:1); $[\alpha]^{21}_D$ +29.9 (*c* 0.5, $CHCl_3$); IR (thin film) ν 3047, 1727, 1356, 119 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (s, 1H), 3.97 (m, 4H), 3.03-2.98 (m, 1H), 2.85-2.77 (m, 1H), 2.44-2.21 (m, 3H), 2.17 (s, 3H), 2.10-2.04 (m, 1H), 1.87-1.72 (m, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9 (C), 144.2 (C), 121.3 (CH), 109.0 (C), 64.4 (CH_2), 64.4 (CH), 47.0 (C), 37.9 (CH_2), 36.0 (CH_2), 31.7 (CH_2), 31.3 (CH_3), 29.9 (CH_2), 17.5 (CH_3); HRMS (ESI+) m/z: $[M+H]^+$ Calc'd for $C_{14}H_{21}O_3$ 237.1491; Found 237.1484.

*4.7. (1R,7aR)-7a-methyl-1-(prop-1-en-2-yl)-1,2,3,6,7,7a-hexahydrospiro[indene-5,2'-[1,3]dioxolane] (-)-(**12**)*

To a stirring solution of methyltriphenylphosphonium iodide (0.899 g, 2.517 mmol) in 35.0 mL of dry THF cooled to -10 ºC under nitrogen atmosphere was added *n*-BuLi (1.97 M solution in hexane, 1.27 mL, 2.517 mmol) drop-wise. The mixture was stirred for 1 h at the same temperature before a solution of ketone (+)-**11** (0.119 g, 0.503 mmol) in 15 mL of dry THF was added via syringe drop-wise at 0 °C. The reaction mixture was allowed to slowly warm up to room temperature and stirred for 48 h before quenching with saturated solution NH_4Cl and extracting with EtOAc. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by SiO_2 column chromatography using 9:1 hexanes-EtOAc afforded diene (-)-**12** (0.096 g, 82%). R_f : 0.5 (hexanes/EtOAc = 9:1); $[\alpha]^{24}_D$ -58.3 (*c* 0.9, $CHCl_3$); IR (thin film) ν 3043, 2923, 2872, 1442, 1352, 1082 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H), 4.87 (s, 1H), 4.78 (s, 1H), 3.97-3.91 (m, 4H), 2.55-2.31 (m, 4H), 2.25-2.18 (m, 1H), 1.91-1.79 (m, 2H), 1.77 (s, 3H), 1.72-1.58 (m, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.2 (C), 145.0 (C), 121.6 (CH), 111.2 (CH_2), 109.3 (C), 64.5 (CH_2), 64.3 (CH_2), 58.7 (CH), 46.2 (C), 37.7 (CH_2), 36.5 (CH_2), 33.8 (CH_2), 31.4 (CH_2), 24.4 (CH_3), 16.7 (CH_3); HRMS (ESI+) m/z: $[M+H]^+$ Calc'd for $C_{15}H_{23}O_2$ 235.1698; Found 235.1693

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*4.8. (1R,7aR)-7a-methyl-1-(prop-1-en-2-yl)-1,2,3,6,7,7a-hexahydro-5H-inden-5-one (+)-(**13**).*

To a solution of diene (-)-**12** (0.381 g, 1.625 mmol) in 3.2 mL of acetone at room temperature, was added 2.8 mL of a 1M HCl solution drop-wise. The resulting cloudy solution was stirred at the same temperature for 24 h before quenching with saturated $NaHCO_3$ solution and diluting with EtOAc. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to obtain enone (+)-**13** (0.309 g, *quant.*). R_f : 0.7 (hexanes/EtOAc = 5:1); $[\alpha]^{22}_D$ +83.3 (*c* 0.7, $CHCl_3$); IR (thin film) ν 2970, 2361, 1666, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (s, 1H), 4.92 (s, 1H); 4.75 (s, 1H), 2.69 (dd, *J* = 10.5, 10.3 Hz, 1H), 2.51-2.38 (m, 2H), 2.33-2.27 (m, 1H), 2.23-2.18 (m, 1H), 2.09-2.05 (m, 1H), 2.02-1.90 (m, 1H), 1.87-1.78 (m, 2H); 1.74 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9 (C), 178.9 (C), 142.9 (C), 121.9 (CH), 113.0 (CH_2), 56.5 (CH), 45.1 (C), 36.0 (CH_2), 33.4 (CH_2), 28.6 (CH_2), 25.2 (CH_2), 24.0 (CH_3), 16.8 (CH_3); HRMS (ESI+) m/z: $[M+H]^+$ Calc'd for $C_{13}H_{19}O$ 191.1436; Found 191.1435

*4.9. (1R,7aR)-1-isopropyl-7a-methyl-1,2,3,6,7,7a-hexahydro-5H-inden-5-one (+)-(**4**).*

To a stirring solution of enone (+)-**13** (0.271 g, 1.425 mmol) in 6 mL of dry benzene, was added Wilkinson's catalyst (0.179 g, 0.193 mmol). The headspace of the flask was flushed with hydrogen and the mixture was stirred under a hydrogen atmosphere at room temperature for 48 h. ^1H NMR analysis of an aliquot indicated complete consumption of the starting material. The mixture was concentrated and the residue was purified by SiO_2 column chromatography (5:1 hexanes-EtOAc to afford enone (+)-**4** (0.211 g, 77%). Spectroscopic data matched literature values[11] and our own previous results using the asymmetric cuprate addition route (see sect. 4.4). Chiral HPLC analysis showed (+)-**4** obtained by this method has 88% ee. $[\alpha]^{26}_D$ +66.6 (*c* 0.5, $CHCl_3$)

*4.10. (((1R,3aR,7aR)-1-isopropyl-7a-methyl-2,3,3a,6,7,7a-hexahydro-1H-inden-5-yl)oxy)trimethylsilane (**14**).*

Anhydrous ammonia (~20 mL) was condensed at -78 °C in a two-neck flask containing lithium metal (0.024 g, 3.490 mmol), pre-washed with hexanes and dried. A deep blue color solution was observed. Immediately, the ammonia line was replaced with a nitrogen line to purge the system thoroughly. After stirring vigorously for about 15 minutes to completely dissolve the Li metal, a solution of enone (+)-**4** (0.112 g, 0.582 mmol) and *t*-BuOH (0.11 mL, 1.164 mmol) in 3.0 mL of dry THF was added to the deep blue suspension via cannula at -78 ºC. The reaction mixture was stirred continuously under a steady flux of nitrogen for 2 h before excess of lithium metal was destroyed at -78 °C by careful drop-wise addition of isoprene (0.13 mL, 1.396 mmol) (this reaction is exothermic and the addition of isoprene should be done very slowly). After the solution became colorless, the excess ammonia was evaporated by slowly warming up to -20 °C and the contents of the flask were placed under high vacuum for 15 minutes to ensure complete removal of the ammonia. The gray residue thus obtained was taken in 3 mL of dry THF and treated with an equimolar mixture of TMSCl (0.40 mL, 3.224 mmol) and Et_3N (0.440 mL, 3.224 mmol) in 1 mL of dry THF at -10 °C. The mixture was stirred and slowly warmed up to room temperature overnight. After 18 hours, it was then poured into a saturated solution of $NaHCO_3$, and diluted with diethyl ether. The combined organic layer was separated and washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to obtain the crude silyl enol ether as pale yellow oil. Quick purification by neutral alumina column chromatography using 9:1 hexanes-EtOAc afforded the silyl enol ether intermediate **14** (0.119 g, 77%). Due to its unstable nature, intermediate was taken to the next step without extensive characterization. R_f : 0.9 (hexanes/EtOAc = 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.69 (m, 1H), 2.09-2.05 (m, 1H), 2.0-1.95 (m, 2H), 1.87-1.78 (m, 2H), 1.72-1.66 (m, 1H), 1.60-1.51 (m, 2H), 1.44-1.35 (m, 1H), 1.24-1.33 (m, 1H), 1.21-1.14 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.89 (s, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7 (C), 109.9 (CH), 50.4 (CH), 48.5 (CH), 41.1 (C), 34.1 (CH_2), 30.1 (CH), 29.7 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 22.9 (CH_3), 22.7 (CH_3), 21.7 (CH_3), 0.3 (CH_3).

*4.11. (((3aR,4R,6aR)-4-isopropyl-3a-methyloctahydrocyclopropa[e]inden-1a(1H)-yl)oxy)trimethylsilane (**15**).*

A well-stirred solution of silyl enol ether **14** (0.060 g, 0.225 mmol) in 1.0 mL of dry Et_2O was cooled to 0 °C and treated with Et_2Zn (1M solution in hexanes, 1.35 mL, 1.35 mmol) drop-wise followed by addition of CH_2I_2 (0.21 mL, 2.70 mmol) over 5 minutes. The cooling bath was removed and the mixture was stirred for 24 hours at room temperature before cooling back to 0 °C and quenching with 2 M NaOH. The mixture was diluted with Et_2O, and the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by SiO_2 column chromatography using 95:5 hexanes-EtOAc afforded cyclopropyl ether **15** (0.039 g, 0.139 mmol, 62%). R_f : 0.9 (hexanes/EtOAc = 9:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.98-2.15 (m, 2H), 1.84-1.86 (m, 2H), 2.62-1.69 (m, 2H), 1.50-1.59 (m, 2H), 1.31-1.45 (m, 2H), 1.03-1.12 (m, 1H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H) 0.81-0.87 (m, 2H), 0.75 (s, 3H), 0.40 (t, *J* = 5.7 Hz, 1H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.1 (C), 49.1 (CH), 48.9 (CH), 41.0 (C), 32.2 (CH_2), 31.8 (CH_2), 28.8 (CH), 28.5 (CH_2), 27.1 (CH_2), 25.9 (CH_3), 24.8 (CH), 23.1 (CH_3), 22.8 (CH_3), 16.5 (CH_2), 1.5 (CH_3). HRMS analysis of cyclopropyl ether **15** was not successful using APCI or ESI.

*4.12. Synthetic Hortonone C (-)-(**1**).*

A solution of cyclopropyl ether **15** (0.018 g, 0.06 mmol) in 1.1 mL of dry DMF was cooled to 0 °C and treated with a solution of $FeCl_3$ (0.0768 g, 0.474 mmol) in 0.6 mL of dry DMF (prepared at 0 °C). The mixture was stirred for 12 h, allowing it to gradually reach room temperature before quenching with water and extracting with EtOAc. The organic layer was washed with 1M HCl solution, saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated. The residue was taken in 1 mL of dry toluene and treated with DBU (90 µL, 0.60 mmol). The mixture was stirred and heated to 40 °C for 6 h before diluting with EtOAc and quenching with water. The aqueous layer was further extracted with EtOAc and the combined organic layer was washed with 1M HCl, $NaHCO_3$ saturated solution and brine, dried over $MgSO_4$, filtered and concentrated. Purification by SiO_2 column chromatography followed by preparative TLC using 9:1 hexanes-EtOAc afforded synthetic hortonone C (-)-**1** (0.0053 g, 42%). Spectroscopic data were in agreement with the isolation report[4] and the Minehan synthesis.[5] R_f : 0.4 (hexanes/EtOAc = 9:1); $[\alpha]^{22}_D$ -57.2 (*c* 1.0, $CHCl_3$) ^1H NMR (400 MHz, Acetone-d_6) δ 6.38 (dd, *J* = 12.0, 4.8 Hz, 1H), 5.79 (dt, *J* = 12.0, 1.8 Hz, 1H), 2.60-2.68 (m, 1H), 2.49 (ddd, *J* = 17.3, 11.6, 1.8 Hz, 1H), 2.44 (ddt, *J* = 17.3, 7.3, 1.7 Hz,

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1H), 1.99-2.05 (m, 2H), 1.87 (ddd J = 14.4, 7.2, 1.7 Hz, 1H), 1.67-1.73 (m, 1H), 1.53-1.64 (m, 2H), 1.44-1.49 (m, 1H), 1.30-1.35 (m, 1H), 1.02 (s, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.90 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 204.2 (C), 152.4 (CH), 131.5 (CH), 57.2 (CH), 51.7 (CH), 48.8 (C), 40.3 (CH_2), 35.9 (CH_2), 30.9 (CH), 30.6 (CH_2), 29.9 (obs), 23.4 (CH_3), 23.2 (CH_3), 21.5 (CH_3); HRMS (ESI+) 207.1749 calc'd for $C_{14}H_{23}O$ $[M+H]^+$, found 207.1749

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Supplementary Material

Copies of NMR spectra and HPLC traces.