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Ready Access to Functionally Embellished *cis*-Hydrindanes and *cis*-Decalins: Protecting Group-Free Total Syntheses of (±)-Nootkatone and (±)-Noreremophilane†

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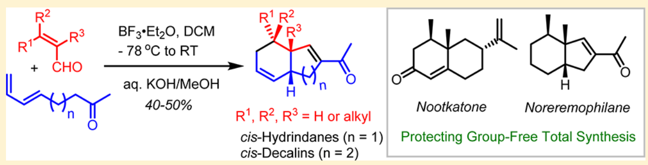
Supporting Information

ABSTRACT: A simple and efficient synthesis of functionalized *cis*-hydrindanes and *cis*-decalins was achieved using a sequential Diels–Alder/aldol approach in a highly diastereoselective manner. The scope of this method was tested with a variety of substrates and was successfully applied to the synthesis of two natural products in racemic form. The highlights of the present work provide ready access to 13 new *cis*-hydrindanes/*cis*-decalins, a protecting group-free total synthesis of an insect repellent Nootkatone, and the first synthesis of a Noreremophilane using the shortest sequence.



Natural products based entirely on the *cis*-hydrindane/*cis*-decalin skeleton or embodying this system as the core unit in their gross structures are frequently encountered in the literature. Many of these compounds exhibit interesting biological activities and are endowed with various functionalities and stereochemical patterns. All of these features aroused considerable interest in the synthetic community (Figure 1).[1] Along these lines, one of us (D.S.R.) recorded a simple method to access the *cis*-hydrindane skeleton using a Diels–Alder/aldol sequence in a highly diastereoselective manner and applied it to the synthesis of bakkenolide A in the year 2004.[2] Later, it was used for the synthesis of other natural products.[3] Here, we would like to report a fresh extension of this work to access several new *cis*-hydrindanes/*cis*-decalins and a short synthesis of two natural products starting from readily accessible materials.

Retrosynthetically, natural products based on the *cis*-hydrindane/*cis*-decalin skeleton could be constructed from the key intermediates, such as *cis*-hydrindane (**A**) or *cis*-decalin (**B**), which possess chemically differentiated double bonds. The intermediates **A** and **B** could be prepared by reacting appropriate dienophiles **C** with dienes **1** and **2**, respectively, using a previously developed Diels–Alder/aldol sequence, (Scheme 1). The starting components **1**, **2**, and **C** are commercially available or can be prepared using known literature procedures.

Our fresh exploration began with a $BF_3{\cdot}Et_2O$ mediated intermolecular Diels–Alder reaction[4] between diene **1**[2] and 2.5 equiv of dienophile methacrolein. Although the reaction works well with $MeAlCl_2$, we preferred using $BF_3{\cdot}Et_2O$ because of availability and safety. The crude Diels–Alder adduct was subjected to an intramolecular aldol condensation reaction with 15% aq KOH in MeOH to furnish *cis*-hydrindane **3** in a highly diastereoselective fashion (dr ∼ 98:2) with a moderate yield of 53%. Similarly, *cis*-decalin **4** was prepared by the reaction between **2**[5] and methacrolein in 50% yield with a dr ∼ 98:2 ratio.[6] The *cis*-hydrindane **5** and *cis*-decalin **6** were prepared from tiglic aldehyde by reacting with diene **1** and **2**, respectively. The diastereomeric ratio was found to be ∼95:5 in both cases. This methodology was successfully applied for the construction of various *cis*-hydrindanes/*cis*-decalins, and the details are compiled in Scheme 2. The observed diastereo- and regioselectivity can be explained on the basis of secondary orbital interactions and atomic coefficient preferences, respectively.[7] Accordingly, the stereochemistry was assigned to major isomers of all the hydrindanes (**3**, **5**, **7**, **9**, **11**, **13**, **15**) and decalins (**4**, **6**, **8**, **10**, **12**, **14**, **16**), as shown in drawings (Scheme 2).[8] The assigned *cis*-stereochemistry of the ring junction in compounds **7**, **8**, **9**, and **10** was further confirmed by 2D-NMR analysis to exclude any possibility of epimerization before the aldol condensation.[8] In the majority of hydrindane cases, the observed diastereoselectivity was high compared with that of decalin cases. In the case of hydrindanes **13** and **15**, low diastereoselectivity was observed, which may be explained by the presence of bulky substitution at α- and β-positions of the dienophile. It is worth mentioning that all of these compounds can be subjected to selective functional group transformations and stereoselective manipulations as they possess chemically differentiated double bonds present in two different rings and a rigid framework.

To enhance the utility of this simple method, we have taken up the protecting group-free total synthesis of Nootkatone, a popular natural product for several years. (+)-Nootkatone is a sesquiterpene first isolated from the heartwood of Alaskan yellow cedar (*Chamaecyparis nootkatensis*) and was later found in trace amounts in grapefruit (*Citrus paradise*), pummelo (*Citrus grandis*), and vetiver oil (*Vetiveria zizanioides*).[9] In addition to its applications in the flavor and fragrance fields, (+)-Nootkatone possesses very impressive insect repellent and/or insecticidal activity against various ticks, mosquitos, termites,

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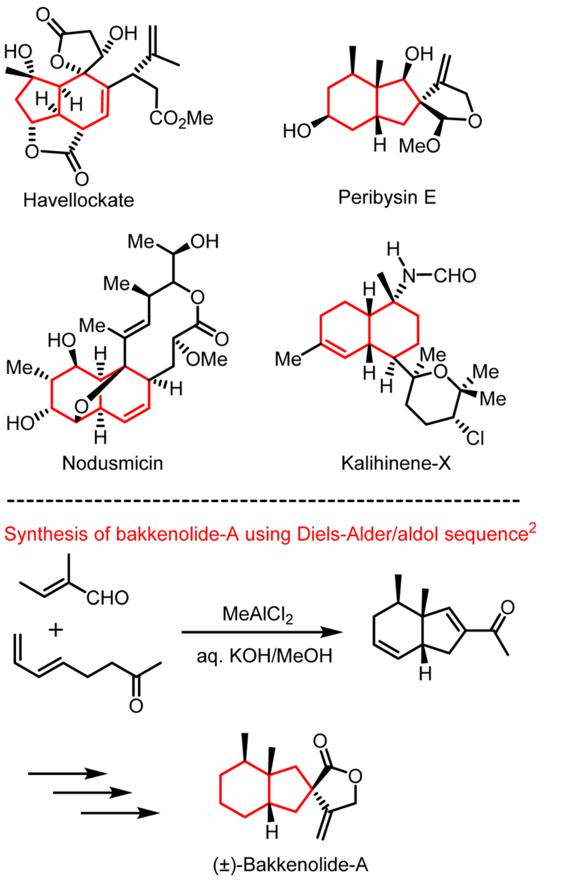
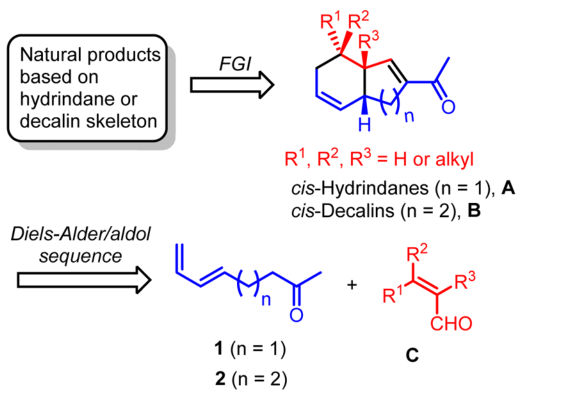
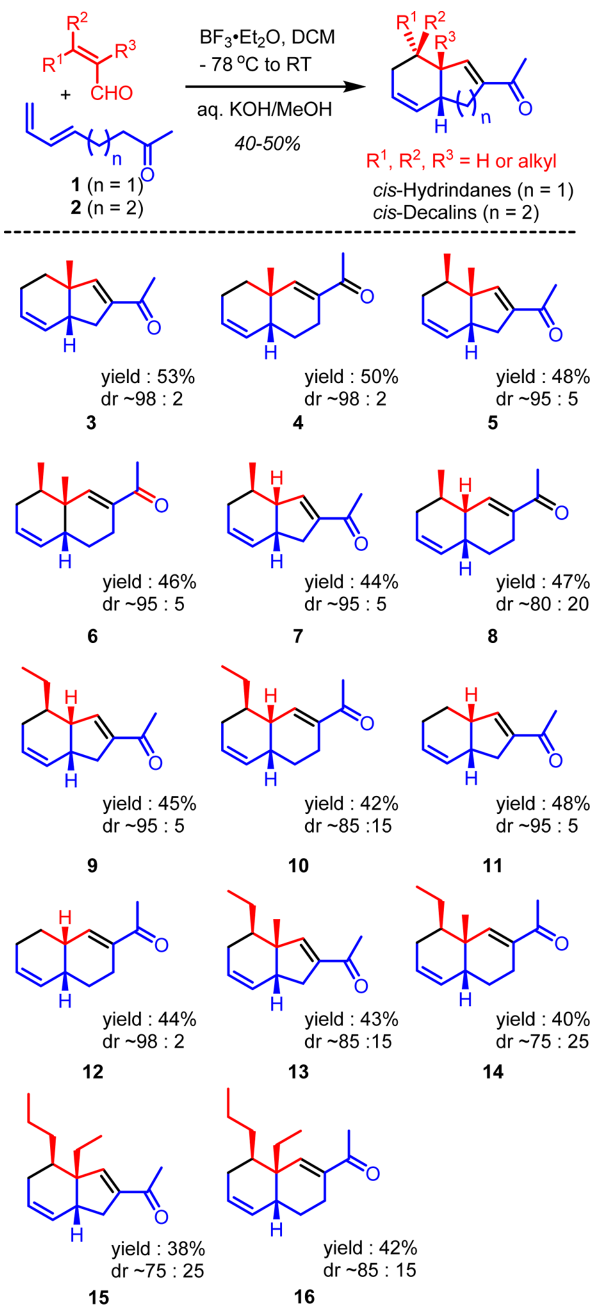


Figure 1. Structures of selected natural products based on the *cis*-hydrindane/*cis*-decalin motif and a previous approach to the synthesis of bakkenolide A from our group.

Scheme 1



Scheme 2

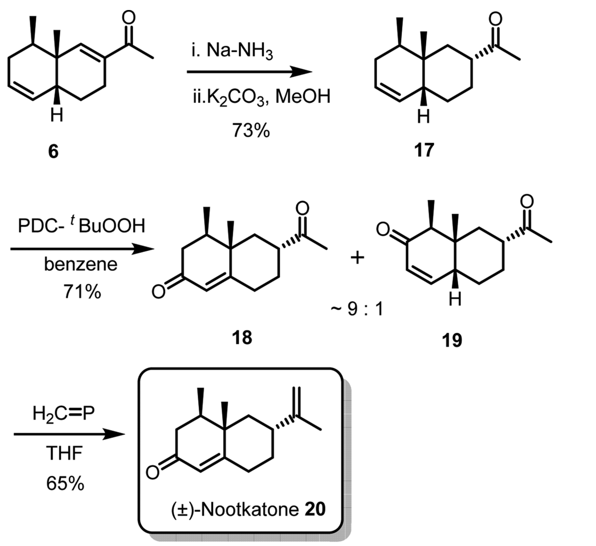


bed bugs, etc.[10] The mechanism of action of Nootkatone is believed to be by blocking the octopamine receptor, a neurotransmitter found in insects.[11] As humans do not have these receptors, compounds like Nootkatone are safe for human beings. Recently, it was found that Nootkatone acts as an AMP activated protein kinase (AMPK) activator, a serine/threonine kinase that is implicated in the control of energy metabolism and is considered to be a molecular target for the treatment of metabolic syndrome. Nootkatone induced the phosphorylation of AMPK and the downstream target acetyl-CoA carboxylase (ACC), and enhanced AMPK activities in vitro and in vivo.[12] Although several syntheses of Nootkatone were documented in the literature,[13,14] the recent findings made us take up the synthesis of this interesting molecule. In this context, it is worth highlighting that the recent synthesis of (+)-Nootkatone from Laine's group starting from pinene is capable of meeting industrial needs.[14] A short synthesis of (±)-Nootkatone is reported here using a novel route. Ultimately, our goal in this project is to generate a focused library of compounds around the Nootkatone scaffold toward identifying improved and safe candidates of AMPK modulators and insect repellents/insecticides.

The *cis*-decalin **6** prepared using the present methodology was utilized for the construction of (±)-Nootkatone. The enone double bond present in **6** was chemoselectively reduced using Na/liq. NH_3 conditions to give an ∼1:1 mixture of diastereomers, which, on exposure to K_2CO_3 in MeOH, furnished the single diastereomer **17** in 73% isolated yield. Allylic oxidation of **17** using the Chandrasekharan protocol[15]

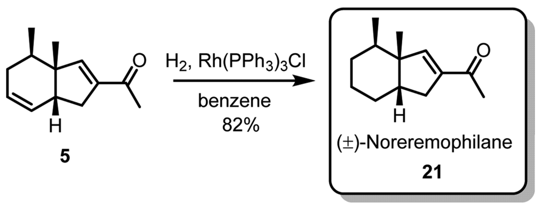
(^{t}BuOOH, PDC) produced the compound **18** as a major product with an enone moiety in the right place as that of the target molecule. In addition to the desired compound **18**, an undesired enone **19** was also isolated as a minor product (10% with respect to **18**).[16] Although, compound **19** is not the required intermediate in Nootkatone synthesis, the motif is present in related natural products. In addition, it can be used for the preparation of potential Nootkatone analogues. Both the compounds **18** and **19** were cleanly separated using silica gel column chromatography as they are well-separated on a tlc plate. Compound **18** on single carbon Wittig olefination furnished the target compound (±)-Nootkatone **20** in 65% yield (Scheme 3). All the spectral data (IR, ^{1}H and ^{13}C NMR) are found to be identical to those reported in the literature.[14] Thus, we have achieved the protecting group-free total synthesis of (±)-Nootkatone **20** in just five steps.

Scheme 3



To increase the utility of the developed method further, the first synthesis of a (±)-Noreremophilane **21**[17] sesquiterpene isolated from the roots of *Ligularia macrophylla* and *Ligularia virgaurea* was accomplished starting from hydrindane intermediate **5** through exclusive chemoselective reduction of the isolated double bond using Wilkinson's catalyst in 82% yield (Scheme 4).[18] All the spectral data (IR, ^{1}H and ^{13}C NMR) were found to be identical to those reported in the literature, which further confirmed the previously assigned structure.[17] Noreremophilane-related compounds are reported to have antibacterial and cytotoxicity activities.

Scheme 4



In summary, we have developed a facile and simple method for the practical preparation of *cis*-decalins and *cis*-hydrindanes in a highly diastereoselective manner using the Diels–Alder/aldol sequence. The synthesized hydrindanes and decalins loaded with orthogonal functional groups can serve as key intermediates in the synthesis of complex molecules. Considering the renewed interest in Nootkatone, we have synthesized the same in the shortest route using the modern concept of "protecting group-free total synthesis". In addition, we have accomplished the first total synthesis of a Noreremophilane, which confirmed the previously assigned structure based on NMR. All the compounds disclosed in this letter can serve as potential Nootkatone analogues. Our next focus on this project will be a systematic understanding of structure activity relationships (SARs) with respect to mosquito repellent activity and AMPK activity of these compounds. The results will be the subject of a full article from this group.

■ EXPERIMENTAL SECTION

General. All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen, unless otherwise mentioned, with magnetic stirring. Air-sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin-layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished either with UV light or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP, $KMnO_4$, Ninhydrin solution, or iodine adsorbed on silica gel, followed by heating with a heat gun for ~15 s. Column chromatography was performed on silica gel (100–200 or 230–400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. The aldehydes (*E*)-2-methylpent-2-enal and (*E*)-2-ethylhex-2-enal used in the present work were prepared from the known literature procedure (see: Abate, A.; Brenna, E.; Fregosi, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1997). All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 400 or 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in parts per million, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. HRMS (ESI) were recorded on on ORBITRAP mass analyzer (QExactive). Mass spectra were measured with ESI ionization in an MSQ LCMS mass spectrometer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0.

(*E*/*Z*)-Nona-6,8-dien-2-one (2). A stream of ozone was bubbled through a solution of 1-methylcyclopentene (5.0 g, 60.8 mmol) in CH_2Cl_2 (300 mL) at −78 °C until the solution turned into a pale blue color. Triphenylphosphine (16.6 g, 63.3 mmol) was added portionwise, allowed to warm room temperature, and stirred for 10 h. The solution was concentrated in vacuo. Purification by flash chromatography over silica gel (3:7; EtOAc−hexane) afforded the ketoaldehyde as a colorless oil (5.4 g, 78% yield).

To a solution of allyltriphenylphosphonium bromide (19.9 g. 52.1 mmol) in THF (80 mL) was added *n*-BuLi (26 mL, 52.1 mmol) dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then was added to the above ketoaldehyde (5.4 g, 47.36 mmol) in THF (50 mL) dropwise at the same temperature. After completion of the starting material by TLC, the reaction was quenched by adding saturated NH_4Cl (30 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Purification by flash chromatography over silica gel (0.5:9.5; EtOAc−hexane) afforded compound **2** (4.8 g, 73%, ~1:1 E,Z mixture) as a colorless oil. IRυ_{max}(film) 1715, 1648, 1365, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61–6.55 (m, 1 H), 6.31–6.24 (m, 1 H), 6.06–5.99 (m, 2 H), 5.66–5.60 (m, 1 H), 5.41–5.36 (m, 1 H), 5.19–4.94 (m, 4 H), 2.43–2.39 (m, 4 H), 2.20–2.16 (m, 2 H), 2.11 (s, 6 H), 2.08–2.05

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(m, 2 H), 1.77−1.64 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.9 (2C), 137.1, 134.2, 132.1, 131.9, 131.6, 130.2, 117.4, 115.3, 42.9, 42.8, 31.8, 30.0 (2C), 26.9, 23.5, 23.2.

1-((3a*S,7a*R**)-3a-Methyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (3).** To a solution of diene **1** (200 mg, 1.61 mmol) and methacrolein (0.34 mL, 4.03 mmol) in dry CH_2Cl_2 (10 mL) was added BF_3·OEt_2 (0.39 mL, 3.22 mmol) dropwise at −78 °C. The mixture was allowed to warm to room temperature and was stirred for 8 h at the same temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (3 × 5.0 mL), followed by H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude material obtained after the removal of solvent was dissolved in methanol (5.0 mL), cooled to 0 °C, and treated with 15% aqueous KOH (5.0 mL). After stirring for 1 h at room temperature, the reaction mass was diluted with petroleum ether (30 mL), washed with water (10 mL), 1 N HCl (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography over silica gel (0.5:9.5; EtOAc−petroleum ether) afforded dienone **3** (150 mg, 53%) as a light yellow oil. IRυ_{max}(film) 1663, 1637, 1216, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (s, 1 H), 5.73−5.61 (m, 2 H), 2.87−2.81 (m, 1 H), 2.35−2.32 (m, 1 H), 2.29 (s, 3 H), 2.27−2.21 (m, 1 H), 2.01−1.97 (m, 2 H), 1.54−1.51 (m, 2 H), 1.11 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 153.1, 143.2, 129.8, 126.0, 47.2, 44.4, 36.6, 30.7, 26.5, 24.6, 22.0; HRMS (ESI) calcd for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274, found 177.1274.

Compounds **5**, **7**, **9**, **11**, **13**, and **15** were prepared using the similar experimental procedure as described above.

1-((4a*R,8a*S**)-8a-Methyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethan-1-one (4).** To a solution of diene **2** (200 mg, 1.44 mmol) and methacrolein (0.30 mL, 3.62 mmol) in dry CH_2Cl_2 (10 mL) was added BF_3·OEt_2 (0.35 mL, 2.89 mmol) dropwise at −78 °C. The mixture was allowed to warm to room temperature and was stirred for 8 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ (3 × 5.0 mL), followed by H_2O (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Crude material obtained after the removal of solvent was dissolved in methanol (5.0 mL), cooled to 0 °C, and treated with 15% aqueous KOH (5.0 mL). After stirring for 4 h at room temperature, the reaction mass was diluted with petroleum ether (30 mL), washed with water (10 mL), 1 N HCl (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography over silica gel (0.5:9.5; EtOAc−petroleum ether) afforded dienone **4** (137 mg, 50%) as a light yellow oil. IRυ_{max} (film) 1669, 1640, 1452, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (s, 1 H), 5.69−5.64 (m, 1 H), 5.49−5.45 (m, 1 H), 2.29 (s, 3 H), 2.26−2.20 (m, 1 H), 2.16−2.10 (m, 1 H), 2.02−1.96 (m, 3 H), 1.84−1.79 (m, 1 H), 1.61−1.41 (m, 3 H), 1.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 149.0, 138.3, 130.3, 126.7, 39.9, 34.9, 32.6, 26.6, 25.6, 25.4, 22.6, 21.3; HRMS (ESI) calcd for $C_{13}H_{19}O$ [M + H]$^+$ 191.1430, found 191.1430.

Compounds **6**, **8**, **10**, **12**, **14** and **16** were prepared using the similar experimental procedure as described above.

1-((3a*S,4*R**,7a*R**)-3a,4-Dimethyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (5).** IRυ_{max}(film) 1669, 1637, 1452, 1237 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (s, 1 H), 5.67−5.66 (m, 2 H), 2.78 (dd, *J* = 15.5, 8.2 Hz, 1 H), 2.33−2.30 (m, 1 H), 2.28 (s, 3 H), 2.24−2.17 (m, 1 H), 1.96−1.89 (m, 1 H), 1.79−1.61 (m, 2 H), 0.98 (s, 3 H), 0.91 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 153.4, 143.3, 128.4, 125.9, 49.8, 46.9, 36.6, 33.2, 30.6, 26.5, 18.1, 15.9.

1-((4a*R,8*R**,8a*S**)-8,8a-Dimethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethanone (6).** IRυ_{max}(film) 1665, 1637, 1452, 1237 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (s, 1 H), 5.60−5.56 (m, 1 H), 5.53−5.48 (m, 1 H), 2.28 (s, 3 H), 2.12−2.00 (m, 2 H), 1.93−1.88 (m, 2 H), 1.90−1.63 (m, 3 H), 1.43 (ddd, *J* = 18.9, 9.15, 5.49 Hz, 1 H), 1.00 (s, 3 H), 0.96 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 149.3, 137.8, 130.1, 125.5, 40.4, 37.3, 34.2, 31.6, 25.6, 25.5, 22.6, 21.1, 15.1; HRMS (ESI) calcd for $C_{14}H_{21}O$ [M + H]$^+$ 205.1587, found 205.1586.

1-((3a*S,4*R**,7a*R**)-4-Methyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (7).** IRυ_{max}(film) 2962, 1669,1461 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, *J* = 3.2 Hz, 1 H), 5.71−5.67 (m, 2 H), 2.81−2.72 (m, 2 H), 2.51−2.49 (m, 1 H), 2.30 (s, 3 H), 2.25−2.20 (m, 1 H), 2.06−2.01 (m, 1 H), 1.71−1.66 (m, 1 H), 1.59−1.53 (m, 1 H), 1.02 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 147.5, 145.2, 129.3, 126.1, 51.6, 38.1, 36.5, 32.5, 31.0, 26.6, 19.7; HRMS (ESI) calcd for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274, found 177.1274.

1-((4a*R,8*R**,8a*S**)-8-Methyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethan-1-one (8).** IRυ_{max}(film) 2962, 1667, 1461, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 3.6 Hz, 1 H), 5.64−5.52 (m, 2 H), 2.35−2.27 (m, 1 H), 2.29 (s, 3 H), 2.26−2.20 (m, 2 H), 2.14−2.06 (m, 2 H), 1.77−1.68 (m, 3 H), 1.47−1.41 (m, 1 H), 1.09 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 143.7, 139.8, 130.3, 126.3, 41.2, 33.0, 32.8, 31.1, 26.3, 25.5, 22.6, 19.3; HRMS (ESI) calcd for $C_{13}H_{19}O$ [M + H]$^+$ 191.1430, found 191.1431

1-((3a*S,4*R**,7a*R**)-4-Ethyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (9).** IRυ_{max}(film) 2962, 1669, 1461, 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, *J* = 3.3 Hz, 1 H), 5.69−5.65 (m, 2 H), 2.78−2.72 (m, 2 H), 2.63−2.63 (m, 1 H), 2.30 (s, 3 H), 2.27−2.23 (m, 1 H), 2.15−2.09 (m, 1 H), 1.76−1.64 (m, 1 H), 1.59−1.54 (m, 1 H), 1.47−1.42 (m, 1 H), 1.29−1.26 (m, 1 H), 0.91 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 147.9, 145.1, 129.4, 125.9, 49.7, 37.8, 37.2, 36.5, 28.5, 26.6, 26.4, 11.5; HRMS (ESI) calcd for $C_{13}H_{19}O$ [M + H]$^+$ 191.1430, found 191.1430.

1-((4a*R,8*R**,8a*S**)-8-Ethyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethan-1-one (10).** IRυ_{max}(film) 2962, 1667, 1461, 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, *J* = 3.7 Hz, 1 H), 5.64−5.44 (m, 2 H), 2.38−2.35 (m, 1 H), 2.29−2.28 (m, 1 H), 2.27 (s, 3 H), 2.26−2.15 (m, 2 H), 2.13−2.05 (m, 1 H), 1.78−1.72 (m, 1 H), 1.67−1.52 (m, 4 H), 1.41−1.33 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 144.3, 139.8, 129.9, 126.4, 39.1, 38.0, 31.9, 28.7, 26.3, 25.6, 25.5, 21.8, 11.7; HRMS (ESI) calcd for $C_{14}H_{21}O$ [M + H]$^+$ 205.1587, found 205.1586.

1-((3a*S,7a*R**)-3a,4,5,7a-Tetrahydro-1*H*-inden-2-yl)ethan-1-one (11).** IRυ_{max}(film) 2962, 1669, 1461, 1380 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75−6.70 (m, 1 H), 5.70−5.53 (m, 2 H), 2.55−2.46 (m, 1 H), 2.30 (s, 3 H), 2.24−2.16 (m, 1 H), 2.06−2.00 (m, 2 H), 1.95−1.86 (m, 1 H), 1.79−1.68 (m, 1 H), 1.56−1.28 (m, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 145.0, 143.3, 131.2, 127.0, 39.9, 33.3, 28.6, 25.8, 25.4, 22.1; HRMS (ESI) calcd for $C_{11}H_{15}O$ [M + H]$^+$ 163.1117, found 163.1117.

1-((4a*R,8a*S**)-3,4,4a,7,8,8a-Hexahydronaphthalen-2-yl)-ethan-1-one (12).** IRυ_{max}(film) 2962, 1668, 1461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75−6.71 (m, 1 H), 5.73−5.56 (m, 2 H), 2.52−2.46 (m, 1 H), 2.38−2.31 (m, 1 H), 2.30 (s, 3 H), 2.24−2.18 (m, 1 H), 2.14−2.08 (m, 1 H), 2.06−2.01 (m, 1 H), 1.93−1.89 (m, 1 H), 1.81−1.70 (m, 1 H), 1.53−1.27 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 145.2, 139.6, 131.5, 127.3, 40.1, 33.5, 28.6, 26.0, 25.6, 24.5, 22.3; HRMS (ESI) calcd for $C_{12}H_{17}O$ [M + H]$^+$ 177.1274, found 177.1273.

1-((3a*S,4*R**,7a*R**)-4-Ethyl-3a-methyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (13).** IRυ_{max}(film) 2962, 1669, 1461,cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (s, 1 H), 5.72−5.65 (m, 2 H), 2.82−2.78 (m, 1 H), 2.30 (s, 3 H), 2.25−2.13 (m, 2 H), 1.67−1.60 (m, 2 H), 1.49−1.35 (m, 2 H), 1.26−1.23 (m, 1 H), 1.00 (s, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 153.6, 143.3, 128.2, 125.8, 49.9, 47.6, 40.6, 36.7, 27.2, 26.6, 23.3, 18.7, 12.8; HRMS (ESI) calcd for $C_{14}H_{21}O$ [M + H]$^+$ 205.1587, found 205.1587.

1-((4a*R,8*R**,8a*S**)-8-Ethyl-8a-methyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethan-1-one (14).** IRυ_{max}(film) 2962, 1669, 1233 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1 H), 5.63−5.50 (m, 2 H), 2.36−2.32 (m, 1 H), 2.29 (s, 3 H), 2.19−2.04 (m, 2 H), 1.87−1.84 (m, 1 H), 1.81−1.68 (m, 2 H), 1.63−1.58 (m, 1 H), 1.51−1.39 (m, 2 H), 1.22−1.16 (m, 1 H), 1.0 (s, 3 H), 0.90 (t, *J* = 7.32 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 149.6, 137.6, 130.2, 125.4, 41.4, 40.9, 37.6, 27.6, 25.6, 25.5, 22.6, 21.5, 21.4, 12.8; HRMS (ESI) calcd for $C_{15}H_{23}O$ [M + H]$^+$ 219.1743, found 219.1743.

1-((3a*S,4*R**,7a*R**)-3a-Ethyl-4-propyl-3a,4,5,7a-tetrahydro-1*H*-inden-2-yl)ethan-1-one (15).** IRυ_{max}(film) 2962, 1667, 1461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1 H), 5.68−5.67 (m, 2

H), 2.88−2.75 (m, 1 H), 2.60−2.52 (m, 1 H), 2.31 (s, 3 H), 2.26−2.17 (m, 1 H), 2.12−2.04 (m, 1 H), 1.80−1.62 (m, 2 H), 1.42−1.38 (m, 1 H), 1.38−1.23 (m, 3 H), 0.93−0.85 (m, 5 H), 0.77 (t, J = 7.32 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 152.8, 149.1, 131.5, 125.5, 55.5, 41.2, 36.5, 32.3, 28.2, 27.3, 26.6, 21.1, 14.5, 9.2, 8.9; HRMS (ESI) calcd for $C_{16}H_{25}O$ $[M + H]^+$ 233.1900, found 233.1899.

1-((4a*R,8*R**,8a*S**)-8a-Ethyl-8-propyl-3,4,4a,7,8,8a-hexahydronaphthalen-2-yl)ethan-1-one (16).** IRυ_{max}(film) 2962, 1669, 1461 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (s, 1 H), 5.61−5.47 (m, 2 H), 2.34−2.33 (m, 1 H), 2.30 (s, 3 H), 2.16−2.13 (m, 1 H), 2.09 −2.04 (m, 3 H), 1.83−1.78 (m, 1 H), 1.74−1.71 (m, 1 H), 1.60−1.49 (m, 2 H), 1.47−1.41 (m, 2 H), 1.21−1.16 (m, 1 H), 0.96−0.85 (m, 5 H), 0.76 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 148.9, 139.3, 130.2, 125.7, 43.9, 40.6, 38.2, 36.3, 30.6, 27.6, 25.6, 25.5, 21.4, 14.6, 8.3 (2C) ; HRMS (ESI) calcd for $C_{17}H_{27}O$ $[M + H]^+$ 247.2056, found 247.2054.

1-((2*R,4a*R**,8*R**,8a*S**)-8,8a-Dimethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-2-yl)ethan-1-one (17).** A solution of α,β-unsaturated ketone **6** (0.5 g, 2.45 mmol) in THF (20 mL) was added to liquid ammonia (20 mL) at −78 °C. Sodium (0.67 g, 29.4 mmol) was added in small pieces, and the reaction mixture was stirred at −78 °C for 1 h. After consumption of starting material (by TLC), solid NH_4Cl (1.0 g) was added and ammonia was allowed to evaporate at room temperature. Water (10 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over Na_2SO_4, and the solvent was concentrated to afford the ketone as a 1:1 mixture of diastereomers. The crude material was treated with K_2CO_3 (1.35 g, 9.80 mmol) in MeOH (20 mL) and refluxed for 2 h. The solvent was removed under vacuum, and the crude residue was diluted with water (10 mL) and extracted with ether (2 × 30 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Purification by flash chromatography over silica gel (0.5:9.5; EtOAc−hexanes) afforded **17** (368 mg, 73%) as a colorless oil. IRυ_{max}(film) 1709, 1453, 1352 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.59−5.48 (m, 2 H), 2.46−2.40 (m, 1 H), 2.13 (s, 3 H), 2.02−1.97 (m, 2 H), 1.88−1.84 (m, 1 H), 1.78−1.72 (m, 2 H), 1.63−1.53 (m, 1 H), 1.34−1.23 (m, 2 H), 1.06−1.00 (m, 2 H), 0.83−0.81 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 131.1, 125.2, 46.4, 44.1, 38.2, 34.6, 32.6, 29.9, 28.7, 28.1, 27.2, 21.6, 14.6; HRMS (ESI) calcd for $C_{14}H_{23}O$ $[M + H]^+$ 207.1743, found 207.1743.

(4*R,4a*S**,6*R**)-6-Acetyl-4,4a-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (18).** To a solution of the ketone **17** (250 mg, 1.21 mmol) in benzene (20 mL) at 15 °C were added PDC (3.6 g, 9.70 mmol) and ^{t}BuOOH (2.5 mL). After the reaction mixture stirred for 15 min, it was brought to ambient temperature and further stirred for 12 h. The reaction mixture was diluted with ether (30 mL), filtered through a Celite bed, and washed with ethyl acetate (2 × 10 mL).The filtrate was concentrated in vacuo. Purification by flash chromatography over silica gel (2:8; EtOAc−hexanes) afforded **18** (170 mg, 63%) and **19** (20 mg, 8%) as colorless oils. IRυ_{max}(film) 1708, 1665, 1354 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1 H), 2.77−2.71(m, 1 H), 2.52−2.38 (m, 2 H), 2.28−2.25 (m, 2 H), 2.19 (s, 3 H), 2.10−2.01 (m, 3 H), 1.49−1.38 (m, 1 H), 1.25−1.21 (m, 1 H), 1.10 (s, 3 H), 0.97 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 199.4, 168.7, 125.3, 48.8, 42.1, 40.3, 40.0, 38.9, 32.1, 28.6, 28.3, 16.8, 15.0.; HRMS (ESI) calcd for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536, found 221.1534.

(1*S,4a*R**,7*R**,8a*R**)-7-Acetyl-1,8a-dimethyl-4a,5,6,7,8,8a-hexahydronaphthalen-2(1H)-one (19).** IRυ_{max}(film) 1708, 1675, 1451, 1354 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, J = 5.7 Hz, 10.0 Hz, 1 H), 5.91 (d, J = 10.3 Hz, 1 H), 2.71 (m, 1 H), 2.46 (tt, J = 12.3 Hz, 2.7 Hz, 1 H), 2.16 (s, 3 H), 2.05−1.97 (m, 2 H), 1.94−1.86 (m, 2 H), 1.50−1.35 (m, 2 H), 1.17−1.08 (m, 1 H), 1.04 (d, J = 6.7 Hz, 3 H), 0.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 201.6, 150.6, 127.8, 46.5, 45.0, 43.3, 38.8, 38.2, 28.3, 28.0, 27.2, 23.2, 6.7; HRMS (ESI) calcd for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1536, found 221.1534.

(4*R,4a*S**,6*R**)-4,4a-Dimethyl-6-(prop-1-en-2-yl)-4,4a,5,6,7,8-hexahydronaph thaen-2(3*H*)-one ((±)-Nootkatone 20).** To a suspension of methyl triphenylphosphonium bromide (148 mg, 0.40 mmol) in dry THF (5.0 mL) was added potassium *tert*-butoxide (40 mg, 0.34 mmol) at 0 °C. After 5 min, the solution became canary yellow color, and to that, diketone compound **18** (30 mg, 0.136 mmol) in THF (5.0 mL) was added and allowed to stirred at 0 °C for 1 h. The reaction was quenched with H_2O (5.0 mL) and extracted with ether (2 × 25 mL). The combined organic layer was washed with water (5.0 mL) and brine (5.0 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography over silica gel (1:9; EtOAc−hexanes) afforded (±)-Nootkatone **20** (19 mg, 65%). IRυ_{max}(film) 2923, 1668, 1606, 1459 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (s, 1 H), 4.74 (s, 1 H), 4.72(s, 1 H), 2.50 (ddt, J = 15.3, 5.0, 1.8 Hz, 1 H), 2.40−2.24 (m, 4 H), 2.04−1.89 (m, 3 H),1.74 (s, 3 H), 1.40−1.29 (m, 2 H), 1.11 (s, 3 H), 0.96 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 170.7, 149.3, 124.8, 109.4, 44.0, 42.2, 40.6, 40.5, 39.5, 33.2, 31.7, 21.0, 17.0, 15.0.

1-((3a*S,4*R**,7a*S**)-3a,4-Dimethyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-2-yl)ethan-1-one ((±)-Noreremophilane 21).** The compound **5** (30 mg, 0.16 mmol) and Wilkinson's catalyst $[(PPh_3)_3RhCl]$ (29 mg, 0.03 mmol) were placed in an oven-dried round-bottom flask. Dry benzene (5.0 mL) was added via syringe, the flask was then flushed with hydrogen gas to expel the argon. The reaction was allowed to proceed at room temperature under hydrogen balloon pressure for 12 h. Upon completion of reaction (monitored by TLC), the mixture was passed through an alumina column and concentrated. Purification by flash chromatography over silica gel (0.5:9.5; EtOAc−petroleum ether) afforded (±)-Noreremophilane **21** (25 mg, 82% yield) as a colorless liquid. IRυ_{max}(film) 1668, 1606, 1367 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 6.30 (d, J = 2.0 Hz, 1 H), 2.57 (dd, J = 16.1, 8.3 Hz 1 H), 2.43 (ddd, J = 16.1, 11.3, 2.26 Hz, 1 H), 1.97 (s, 3 H), 1.78−1.73 (m, 1 H), 1.44−1.41 (m, 1 H), 1.38−1.35 (m, 1 H), 1.34−1.31 (m, 1 H), 1.22−1.17 (m, 1 H), 1.13−1.11 (m, 1 H), 1.10−1.08 (m, 1 H), 0.86−0.85 (m, 1 H), 0.84 (s, 3 H), 0.67 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 195.6, 153.1, 143.9, 49.6, 46.5, 36.9, 33.6, 29.3, 25.9, 24.4, 22.2, 17.3 (2C). HRMS (ESI) calcd for $C_{13}H_{21}O$ $[M + H]^+$ 193.1587, found 193.1589.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra of all new compounds and 2D NMR spectra of compounds **7**, **8**, **9**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

†In memory of Prof. A. Srikrishna, IISc, Banglore (1955−2013), who made significant contributions to the field of organic chemistry.

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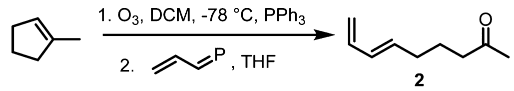

(6) The ratio of diastereomers was determined using ^{1}H NMR of the product after the flash chromatography purification of the crude material. We have also cross-checked the ratios with the crude material (in seven cases, **5**, **6**, **7**, **8**, **9**, **10**, **13**) and found that they are similar with the purified product ratios.

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