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Total synthesis of eudesmane terpenes: cyclase phase

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Dedicated to Professor Brian Stoltz on the occasion of his receipt of the Tetrahedron Young Investigator Award

ABSTRACT

A full account of synthetic efforts toward dihydrojunenol, one of the lowest oxidized members of the eudesmane family of natural products, is presented. The final synthetic sequence illustrates a nine-step, gram-scale, enantioselective route to this bicyclic terpene with excellent stereocontrol and in 21% overall yield.

1. Introduction

The eudesmanes represent a broad family of sesquiterpenoid natural products containing approximately 1000 members, many of which exhibit antifungal, antibacterial, and anticancer activity.[1] These bicyclic terpenes are characterized by a 2-isopropyl-4a,8-dimethyldecahydronaphthalene framework, and most of its members are adorned with a variety of oxidation patterns. In order to target a variety of members within a class of terpenoid natural products using a unified synthetic approach, the logic of a 'two-phase approach' in terpene synthesis was conceived and demonstrated in the total synthesis of eudesmanes.[2] This design was inspired by terpene biosynthesis[3] and was executed in two separate phases—a 'cyclase phase' and an 'oxidase phase'.[4] In the context of eudesmane total synthesis, four targets were selected and retrosynthetically traced back to a common precursor bearing a lower oxidation state through the use of a retrosynthetic pyramid diagram. Thus, dihydrojunenol (**1**) became the target of a cyclase phase endpoint, which would then serve as the oxidase phase starting point toward polyhydroxylated eudesmanes **2**–**5** (Fig. 1).[2] In this full account, the evolution of our synthetic strategy toward **1** is described, culminating in a short, scalable and enantioselective route to this bicyclic terpene.

Although dihydrojunenol (**1**) was only recently isolated during the study of aroma components of the woody material *Bursera graveolens* by Yukawa and co-workers,[5] its structure was reported over 50 years ago as a result of hydrogenation of another natural product, junenol.[6] Despite its low molecular weight, **1** contains five contiguous stereocenters that pose a challenge for its total synthesis. Consequently,

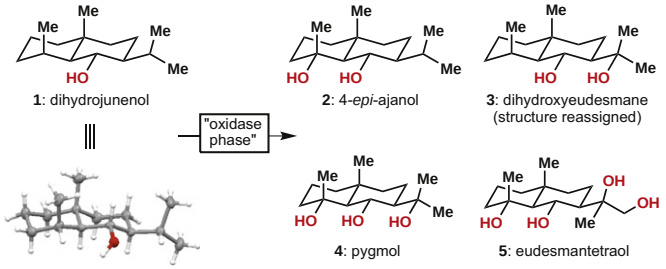

Figure 1. Dihydrojunenol (**1**), its X-ray structure and the eudesmane family of terpenes.

prior to the communication of this work,[2] it had only been synthesized once in a racemic, stereorandom fashion from farnesol.[7] Semisynthesis was the preferred route in the 1960s for the synthesis of **1**, as two such routes were devised from other eudesmane precursors.[6,8] Moreover, **1** could be accessed in one step from junenol,[9] and as such, the three semi-syntheses[6c,10,11] and one racemic total synthesis[12] of junenol could be considered as being formal syntheses of **1**.[13]

Early in this program, in order to obtain authentic samples of **1** for comparison, we repeated the procedure by Pedro and co-workers,[11] which we had judged to be the most efficient synthesis of either dihydrojunenol (**1**) or junenol. Although this nine-step synthesis toward **1** would rely on a natural product as the starting material, santonin (**6**) was a relatively cheap and commercially available option (Fig. 2). In our hands, the sequence[9,11] proceeded in 8% overall yield; along with the desired product **1**, two other isomers **7** and **8** were also obtained and their structures were verified by X-ray crystallography (crystals obtained as their *p*-nitrobenzoyl ester derivatives). Thus, this route not only provided us with a sample of **1**, but also furnished two valuable stereoisomers that would serve as markers for spectroscopic comparison in our total synthesis endeavors toward **1**.

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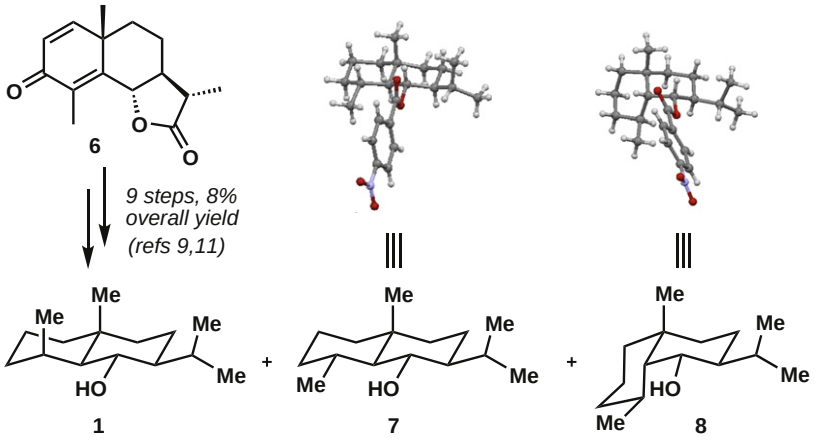


Figure 2. Previously reported semi-synthesis of dihydrojunenol (**1**) from santonin (**6**).[9,11]

2. Results and discussion

2.1. Initial synthetic strategy

Early forays toward the synthesis of dihydrojunenol (**1**) were conducted according to a retrosynthetic blueprint that simplified the target back to commercially available piperitone (dehydromenthone, **9**; Fig. 3a). This monocyclic enone can be procured in both enantiomeric forms and could, in principle, lead to the desired eudesmane skeleton in as few as three steps: (1) Substrate-controlled diastereoselective conjugate addition onto C10; (2) C4–C5 bond formation; and (3) net reduction to forge the stereotriad C4–C5–C6 (eudesmane numbering,[1] Fig. 3a). Although such a synthesis would rely entirely on a chiral pool source, this attractive three-step route would render the production of **1** highly efficient and scalable. To this end, alkene- and alkyne-bearing conjugate addition products were prepared, as well as some of their derivatives (Fig. 3b). To our dismay, the desired C4–C5 bond-forming reactions did not proceed in our hands to generate the desired decalin framework, most likely due to the steric congestion imposed by the adjacent quaternary center (C10). At this juncture, we devised an alternative strategy that delayed the introduction of the C14 methyl group until after the C4–C5 bond formation.

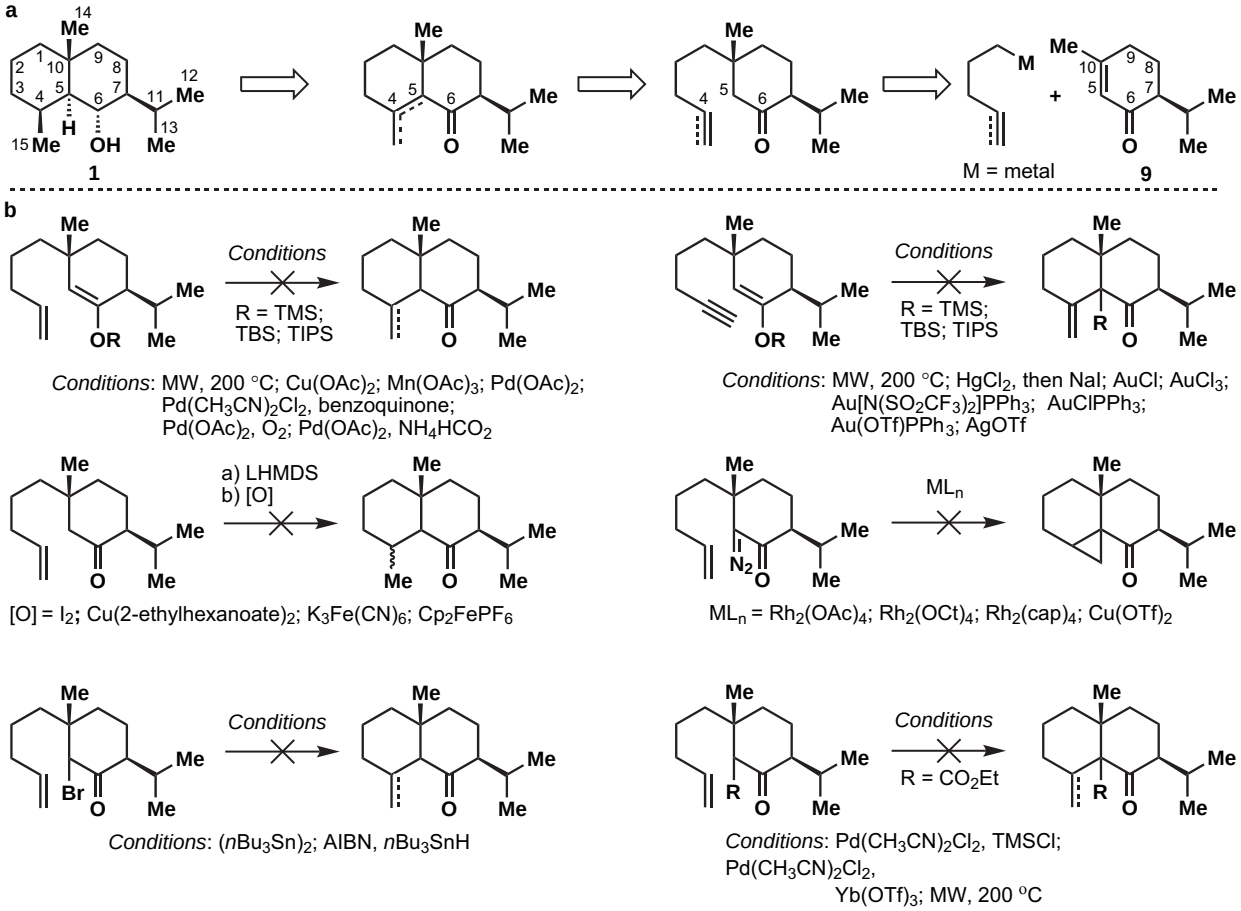


Figure 3. (a) Initial strategy to generate the decalin skeleton; (b) selected approaches.

2.2. Revised strategy and racemic synthesis

Equipped with the knowledge garnered from failed approaches, a revised synthetic strategy was conceived (Fig. 4). Retrosynthetically, net oxidation and C14 methyl group excision from **1** would lead to dienone **10**. With the all-carbon quaternary center at C10 no longer present, **10** could be disconnected at the C4–C5 linkage via *retro*-Heck coupling to evoke the monocyclic enone **11**. This enone could then be thought to arise from 2-iodocryptone (**13**) by a Grignard addition followed by a Dauben carbonyl transposition.[14] Finally, **13** could be generated from isovaleraldehyde and methyl vinyl ketone through the well-known Robinson annulation, followed by an electrophilic iodination.

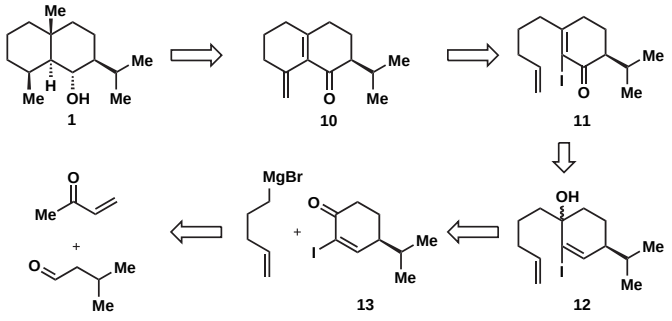
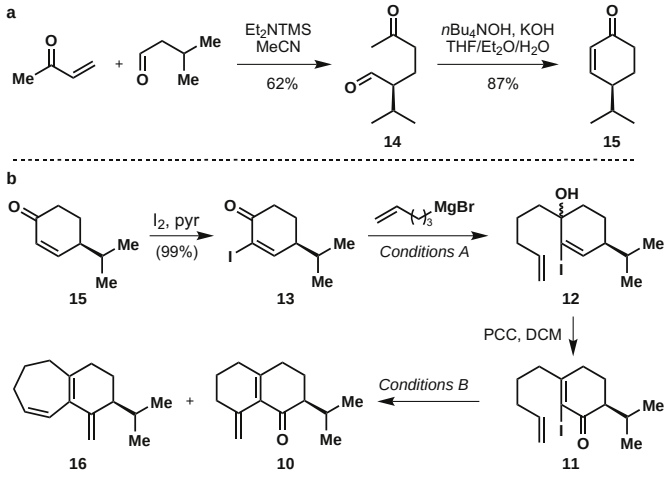


Figure 4. Revised strategy to construct the decalin skeleton.

In the forward direction, methyl vinyl ketone and isovaleraldehyde were mixed together in the presence of 20 mol% (diethylamino)trimethylsilane[15] to generate racemic 2-isopropyl-5-oxohexanal (**14**) in 62% yield (Fig. 5a). This known Michael addition product[16,17] was then treated with base under phase-transfer conditions[18] to afford racemic cryptone (**15**) in 87% yield. An efficient synthesis of **15** has been a long-standing problem, since it is a useful building block for the construction of various natural products; although more than a dozen other methods for cryptone synthesis are known, most of them require more than two steps and are less efficient, or generate olefin-transposed side products that are difficult to remove.[19,20] This enone procured in multigram quantities was then iodinated at the α-position in near-quantitative yield to install a functional group handle that would later become useful for C–C bond formation (Fig. 5b). Iodocryptone **13** thus generated was further subjected to a two-step alkylative carbonyl transposition,[14] consisting of pentenylmagnesium bromide addition followed by PCC oxidation. It is of note here that an unexpected solvent effect was observed during the Grignard addition, in which the use of THF or ether led to low (<20%) yields whereas toluene allowed efficient formation (>75%) of **12** as an inconsequential mixture of diastereomers. PCC oxidation of this mixture subsequently allowed smooth transformation into the desired monocyclic enone **11** (74% over two steps).



Entry	Conditions A [a]	Yield (%)	Entry	Conditions B [d]	Yield (%)
1	THF (0.1 M), -78 °C, 4 h	trace	1	$Pd(OAc)_2$, PPh_3, Et_3N, DMF	74[e]
2	Et_2O (0.1 M), -78 °C, 2 h	≤ 20	2	$Pd_2(dba)_3$, Et_3N, PhMe	80
3	PhMe (0.1 M), -78 °C, 4 h	≤ 5[b]	3	$Pd(OAc)_2$, Ag_2CO_3 (1.0 equiv.), PPh_3, Et_3N, MeCN	95
4	PhMe (0.1 M), -78 °C for 30 min; 0 °C for 30 min	74[c]			

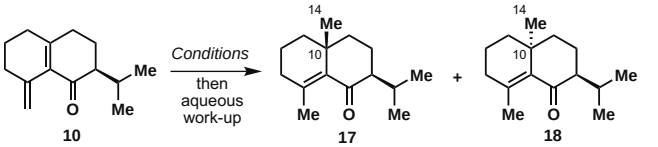
a. The Grignard reagent was prepared as a 0.7 M ether solution; b. Conversion was low; c. The yield was based on two steps (after PCC oxidation).

*d. 0.1 equiv. of $Pd(OAc)_2$ and 0.3 equiv. of PPh_3 (or 0.1 equiv. $Pd_2(dba)_3$) were used, along with 1.2 equiv. of Et_3N; e. ca. 20% of **16** was obtained.*

Figure 5. (a) Synthesis of racemic cryptone (**15**); (b) preparation of dienone **10**.

The installation of the necessary functional group handles provided the opportune moment to forge the previously problematic C4–C5 linkage. Without an adjacent quaternary center hindering the site of reaction, **11** smoothly underwent intramolecular ring closure under standard Heck conditions (using catalytic $Pd(OAc)_2$ and PPh_3) to generate bicyclic dienone **10** in 74% yield (Fig. 5b). It is of note that these preliminary reaction conditions gave way to ca. 20% of a 7-*endo* side product (**16**). Substituting $Pd(OAc)_2$ by $Pd_2(dba)_3$ eliminated this side product but did not significantly increase the reaction yield; however, the use of a stoichiometric Ag_2CO_3 additive[21] improved the formation of **10** to 95% yield. Access to bicyclic dienone **10** was thus achieved in short order (six steps) from cheap (<1 $/g) starting materials in multigram quantities.

At this point in time, all that separated dienone **10** from the desired natural product **1** were one methyl group addition and two strategic reductions, which would set four stereocenters overall. The remaining C14 methyl group was introduced via copper-mediated conjugate addition; however, this initially failed to give product when MeMgBr and CuI were employed (Fig. 6, entry 1). Substituting the active metal species to Me_2CuLi in ether allowed a diastereoselective 1,4-addition to proceed, albeit in abysmal yield. Employing Me_3SiCl as an additive[22] improved the reaction yield to 62%, but resulted in a 1:3 mixture of C10 epimers **17** and **18**, favoring the undesired stereoisomer **18** (entry 3). Modifying the reaction medium to toluene surprisingly shut down the reaction completely, whereas dichloromethane proved to be the solvent of choice, improving the combined yield to 78% (33% of **17** and 45% of **18**). When Me_3SiCl was eliminated in a control experiment (entry 6), the product ratio drastically changed, providing the 1,4-addition products as a 3:1 ratio of **17** to **18** in 73% combined yield (with 17% recovered starting material). These reaction conditions were eventually adopted as the optimal conditions. Performing this same reaction at a higher temperature for a shorter amount of time yet again altered reaction yields, but in unfavorable fashion (entry 7: 44% of **17** and 38% of **18**).



Entry	Conditions	Yield of 17 (%)
1	MeMgBr (2.5 equiv.), CuI (2.5 equiv.), THF (0.1 M), 0 °C, 1 h	trace[a]
2	Me_2CuLi (0.5 M in Et_2O, 1.5 equiv.), Et_2O (0.1 M), 0 °C, 2 h	≤ 10[a]
3	Me_2CuLi (as entry 2), TMSCl (5.0 equiv), Et_2O (0.1 M), 0 °C, 2 h	17 (+ 45[b])
4	Me_2CuLi (as entry 2), TMSCl (5.0 equiv), toluene (0.1 M), 0 °C, 2 h	trace[a]
5	Me_2CuLi (as entry 2), TMSCl (5.0 equiv), DCM (0.1 M), 0 °C, 2 h	33 (+ 45[b])
6	Me_2CuLi (as entry 2), DCM (0.1 M), 0 °C, 4 h	56 (+17[b])[c]
7	Me_2CuLi (as entry 2), DCM (0.1 M), RT, 1 h	44 (+ 38[b])

*a. Low conversion; b. Yield of the C10-epimer **18**; c. 17% recovered **10** was also obtained.*

Figure 6. Installation of the C14 methyl group.

With ample quantities of bicyclic enone **17** in hand, all that was required to generate dihydrojunenol (**1**) was to forge three contiguous stereocenters via two net reductions. Although one-step simultaneous reductions of C=C and C=O bonds in enones are known, many require harsh conditions such as high-pressure hydrogenation[23] or strong electroreduction,[24] and is otherwise nonselective.[25] Furthermore, the necessity for dihydrogen to add to **17** from the α-face of the C=C bond but from the β-face of the C=O bond precluded the use of hydrogenation as a means for one-step double reduction. Ultimately, we resorted to a known two-step reduction strategy[8] that hydrogenated the olefin first, followed by a dissolving metal reduction (Fig. 7). Hydrogenation over Pd on carbon set the stereocenters at C4 and C5, and without isolation, the resulting ketone was treated with sodium in ethanol, yielding **1** stereoselectively (only a single isomer was observed) in 87% yield over two steps. The eudesmane thus obtained in nine steps and in 19% overall yield was in excellent spectroscopic agreement with that reported in the literature.[5]

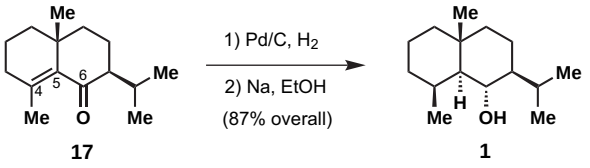
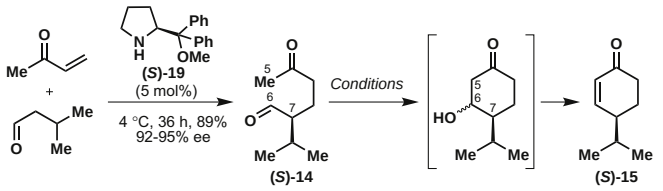


Figure 7. Stereoselective reductions and completion of dihydrojunenol.[8]

2.3. Enantioselective synthesis

With a short, robust synthesis of racemic **1** in hand, an enantioselective route was sought. Since the synthesis was designed in such a way that chiral information from the isopropyl-bearing C7 stereocenter is propagated onto the remaining four stereocenters of the bicyclic molecule, all that was required was the enantioselective formation of cryptone (**15**), and in turn, that of the keto-aldehyde **14** (vide supra). Examples of enantioselective Michael additions[26] onto methyl vinyl ketone[17] are known, which even encompassed our specific substrate.[17c,d] Thus, diphenylprolinol methyl ether **19**[27] was used in catalytic quantities (5 mol %) to generate the Michael adduct **14** in 89% yield and in 92–95% ee (Fig. 8). However, this straightforward enantioselective addition was followed by a challenging transformation, in which aldol condensation was required to occur without epimerizing the newly formed stereocenter. Conditions previously employed upon racemic **14** (see Fig. 5a) resulted in partial epimerization, thus reducing the enantiopurity to 56% ee. The use of pyridine at room temperature did not effect any conversion, whereas the use of LDA or silica gel resulted in decomposition of **14** (Fig. 8, entries 3 and 4). Assuming that the thermodynamic conditions required for dehydration were the cause of loss in enantiopurity, milder two-step procedures for aldol addition and dehydration were attempted. However, this triggered losses in both yield and in enantiopurity (entries 5 and 6). Intrigued by Chakraborti's report on the use of catalytic LiOH as an efficient base for Claisen–Schmidt condensations,[28] we became interested in similar reaction conditions. Thus, addition of 10 mol % LiOH in THF–H_2O at 0 °C, followed by in situ mesylation and elimination, resulted in a gratifying 78% yield and a retention of 74% ee (entry 7). Further investigation revealed that a solvent change to methanol increases the enantiopurity of **15**, and this solvent effect could perhaps be explained by the formation of a lithium alkoxide species that serves to deprotonate at the terminal methyl (C5) position rather than at the more hindered C7 position. Following this logic, a more bulky alcohol such as 2-propanol was employed, and this significantly mitigated the loss of enantiopurity due to epimerization (entry 9). In addition, these new conditions obviated the need for ensuing mesylation and elimination steps, due to the increased basicity of the active lithium alkoxide species. Consequently, an asymmetric synthesis of cryptone (**15**) was achieved in two steps, in 63% overall and in 89% ee, which proved to be superior to previous syntheses[19] of this simple terpene. Furthermore, this asymmetric synthesis of **15** fared better than our own racemic counterpart (54% over two steps; see Fig. 5a). With enantioenriched **15** in hand, the same synthetic sequence as the racemic synthesis was carried out (vide supra), resulting in a gram-scale enantioselective total synthesis of dihydrojunenol (**1**) in nine steps and in 21% overall yield.



Entry	Conditions	Yield (%); ee (%)
1	nBu$_4$NOH, KOH, THF/Et_2O/H_2O, 50 °C, 30 min	87; 56
2	pyridine, rt, 12 h	N/A [a]
3	LDA (1.0 equiv.), -78 °C, 30 min	N/A [b]
4	silica gel (5% v/v), 50 °C, 12 h	N/A [b]
5	DBU (1 equiv.), DCM, rt, 1 h; MsCl (5 equiv.), Et_3N (10 equiv.), rt, 1 h	75; 34
6	TBAF (0.5 equiv.), CH_3CN, rt, 2 h; then MsCl, Et_3N (as Entry 5)	34; 0
7	LiOH (0.1 equiv.), THF/H_2O (3:1), 0 °C, 30 min; then MsCl, Et_3N (as Entry 5)	78; 74
8	LiOH (0.1 equiv.), MeOH, 0 °C, 30 min; then MsCl, Et_3N (as Entry 5)	71; 80
9	LiOH (0.1 equiv.), iPrOH, rt, 24 h	71; 89

*a. No reaction; b. Decomposition of **14**.*

Figure 8. Enantioselective Michael addition and generation of enantioenriched cryptone (**15**).

3. Conclusion and strategic perspective

In summary, a full account of synthetic efforts toward dihydrojunenol (**1**) has been presented. Failed attempts at forging a C–C bond adjacent to an all-carbon quaternary center have led to a revised route that coupled together simple starting materials, methyl vinyl ketone and isovaleraldehyde, in enantioselective fashion. Key steps toward the synthesis of **1** involved an efficient, intramolecular Heck coupling followed by a copper-mediated conjugate addition that proceeded with excellent diastereoselectivity. This chemistry has thus enabled the first enantioselective total synthesis of **1** in 21% overall yield (Fig. 9). Moreover, this protecting group-free, nine-step route resulted in a gram-scale preparation of **1**, which allowed for the generation of ample quantities of this bicyclic terpene required for its subsequent use as a starting material in a systematic exploration of C–H oxidation chemistry.[2]

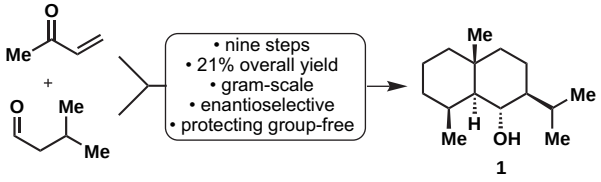


Figure 9. Summary of the approach.

The efficiency with which the total synthesis of a representative eudesmane, dihydrojunenol (**1**), was completed is partly due to the low oxidation state of the target, which was an intended feature of this study. Since there is only one heteroatom present in the target **1**, protecting group chemistry is destined to be relinquished or, at the very least, minimized.[29] A great variety of chemistry can be employed without fear for side reactions, including the use of harsh organometallic reagents. As demonstrated here, the mere choosing of a judicious retrosynthetic intermediate (such as **1** in the preparation of targets **2**–**5**) can free one from chemoselectivity issues[30] in

terpene synthesis. Finally, the synthesis outlined herein facilitates an adherence to the principles of redox economy,[31] since the installation of functional groups, which is commonly plagued by superfluous redox manipulations, is practically unnecessary in **1**.

4. Experimental section

4.1. General

All reactions were carried out under a nitrogen atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether (Et_2O), dichloromethane (DCM), toluene, methanol (MeOH), acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, ceric ammonium molybdate, or basic aqueous potassium permangante ($KMnO_4$), and heat as developing agents. E. Merck silica gel (60, particle size 0.043–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.5 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 or Varian Inova-400 instruments and calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$ at 7.26 ppm in ^1H NMR; 77.0 ppm in ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF time-of-flight mass spectrometer by electrospray ionization time-of-flight reflectron experiments. IR spectra were recorded on a Perkin-Elmer Spectrum BX FTIR spectrometer. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus. Optical rotations were obtained on a Perkin-Elmer 431 Polarimeter.

*4.1.1. (rac)-2-Isopropyl-5-oxohexanal (**14**).* In a flame-dried round-bottom flask, a mixture of freshly distilled isovaleraldehyde (20.0 mL, 0.18 mol, 1.0 equiv) and (diethylamino)trimethylsilane (6.9 mL, 0.037 mmol, 0.2 equiv) in MeCN (600 mL) was cooled to 0 °C. Freshly distilled methyl vinyl ketone (22.5 mL, 0.28 mol, 1.5 equiv) was added, and the resulting yellow, homogeneous solution was heated at reflux under nitrogen for 36 h. The crude mixture was cooled to room temperature and concentrated in vacuo, upon which the resulting thick oil was purified by column chromatography (silica gel, gradient from 10:1 to 1:1 hexanes/EtOAc) to provide (*rac*)-**14** (17.8 g, 62%), whose spectroscopic data was identical to previous reports.[15a,16]

*4.1.2. (S)-2-Isopropyl-5-oxohexanal (**14**).* In a flame-dried round-bottom flask, a mixture of freshly distilled isovaleraldehyde (8.1 mL, 74.8 mmol, 1.0 equiv), prolinol catalyst (***S***)-**19**[27] (1.01 g, 3.74 mmol, 0.05 equiv), and co-catalyst ethyl 3,4-dihydroxybenzoate (2.73 g, 15.0 mmol, 0.20 equiv) was cooled to 0 °C. Freshly distilled methyl vinyl ketone (9.1 mL, 112.2 mmol, 1.5 equiv) was then added, and the resulting brown, homogeneous solution was stirred under nitrogen at 4 °C for 36 h. The crude material was purified by column chromatography (silica gel, gradient from 10:1 to 1:1 hexanes/EtOAc) to provide (***S***)-**14** (10.3 g, 89%), whose spectroscopic data was identical to the previous report.[15a,16] [Note: This compound was prepared by following the reported procedure without further optimization. The enantiomeric excess (92–95%) was determined by ^1H NMR analysis of the corresponding L-valine methyl ester imine[32]].

*4.1.3. (rac)-4-Isopropylcyclohex-2-enone (**15**).* A solution of (*rac*)-**14** (0.50 g, 3.3 mmol, 1.0 equiv) in Et_2O (30 mL) and THF (10 mL) was stirred at room temperature. To this solution was added aqueous KOH solution (30 mL, 0.1 N) and nBu$_4$NOH (0.52 mL, 40% aq) in one portion. The mixture was heated to reflux for 3 h before cooling to room temperature. Et_2O (50 mL) was then added and the layers were separated. The aqueous layer was extracted with Et_2O (2×50 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from 10:1 to 5:1 hexanes/Et_2O) yielded cryptone, (*rac*)-**15**, as a colorless oil (0.39 g, 87%), and its spectroscopic data was identical to previous reports.[19]

*4.1.4. (S)-4-Isopropylcyclohex-2-enone (**15**).* A solution of (***S***)-**14** (2.21 g, 14.1 mmol, 1.0 equiv) in 2-propanol (47 mL, 0.3 M) was stirred at room temperature, upon which LiOH (33.7 mg, 1.4 mmol, 0.10 equiv) was added in one portion. After stirring for 24 h, the reaction was quenched with saturated aqueous NH_4Cl (100 mL). EtOAc (100 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (2×100 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (silica gel, gradient from 10:1 to 5:1 hexanes/Et_2O) yielded cryptone, (***S***)-**15**, as a colorless oil (1.38 g, 71%), whose spectroscopic data was identical to previous reports.[19] The enantiomeric excess (89%) was determined by chiral HPLC [AD-H, 2% isopropanol in hexanes, 0.5 mL/min, t_r 12.373 min (major), 13.687 min (minor)].

*4.1.5. (S)-2-Iodo-4-isopropylcyclohex-2-enone (**13**).* To a solution of compound (***S***)-**15** (9.05 g, 65.4 mmol, 1.0 equiv) in DCM (80 mL) and pyridine (80 mL) at 0 °C, iodine (19.9 g, 78.5 mmol, 1.2 equiv) was added in five portions over 10 min. After stirring at room temperature for 12 h, the brown solution was poured into saturated aqueous $Na_2S_2O_3$ (150 mL) and Et_2O (500 mL). The layers were separated and the organic phase was washed with aqueous HCl solution (1 N, 2×300 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was filtered through a short silica plug eluting with DCM to provide **13** as a yellow oil (17.3 g, 99%). R_f=0.5 (silica gel, 9:1 hexanes/EtOAc); $[\alpha]_D^{23}$ −26.4 (*c* 2.19, DCM); IR (film) ν_{max} 2954, 2358, 1687, 1582, 1322, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 2.78 (dt, *J*=16.5, 3.9 Hz, 1H), 2.41–2.51 (m, 2H), 2.03–2.06 (m, 1H), 1.78–1.85 (m, 2H), 0.97 (d, *J*=7.0 Hz, 3H), 0.95 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.3, 163.2, 103.9, 47.0, 36.2, 31.4, 25.2, 19.6, 19.4; HRMS (ESI) calcd for $C_9H_{13}IO$ $[M+Na]^+$ 286.9909, found 286.9906.

*4.1.6. (S)-2-Iodo-6-isopropyl-3-(pent-4-enyl)cyclohex-2-enone (**11**).* In a flame-dried round-bottom flask charged with argon, iodocryptone **13** (6.04 g, 22.9 mmol, 1.0 equiv) was dissolved in toluene (229 mL, 0.1 M) at −78 °C. A solution of freshly prepared Grignard reagent in Et_2O (0.7 M, 49 mL, 1.5 equiv) was added over 5 min. The resulting solution was stirred at −78 °C for 30 min and then the dry-ice bath was replaced with an ice bath. Stirring was continued for an additional 30 min at 0 °C before saturated aqueous NH_4Cl (300 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (2×100 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude alcohol thus obtained (ca. 22 mmol) was then dissolved in DCM (110 mL, 0.2 M). Molecular sieves (3 Å, 20 g) and PCC (5.90 g, 27.5 mmol, 1.2 equiv) were added and the resulting brown mixture was stirred at room

temperature for 6 h. The dark reaction mixture was then filtered through a short silica plug eluting with DCM to provide **11** as a colorless oil (5.64 g, 74% over two steps). R_f=0.4 (silica gel, 1:1 hexanes/DCM); $[\alpha]_D^{23}$+26.3 (*c* 1.14, DCM); IR (film) ν_{max} 2958, 2356, 1829, 1675, 1587, 1559, 1458, 1158, 911 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.80–5.86 (m, 1H), 5.05 (dd, *J*=17.1, 1.5 Hz, 1H), 5.02 (d, *J*=10.2 Hz, 1H), 2.58–2.63 (m, 1H), 2.45–2.52 (m, 3H), 2.35–2.41 (m, 1H), 2.25–2.28 (m, 1H), 2.14–2.17 (m, 2H), 1.94–1.99 (m, 1H), 1.76–1.82 (m, 1H), 1.58–1.64 (m, 2H), 0.94 (d, *J*=7.0 Hz, 3H), 0.85 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.2, 168.2, 137.9, 115.6, 107.8, 52.1, 44.1, 33.7, 32.0, 27.0, 26.4, 22.9, 20.8, 18.6; HRMS (ESI) calcd for $C_{14}H_{21}IO$ $[M+Na]^+$ 355.0535, found 355.0532.

*4.1.7. (S)-2-Isopropyl-8-methylene-3,4,5,6,7,8-hexahydronaphthalen-1(2H)-one (**10**).* Monocyclic enone **11** (3.43 g, 10.3 mmol, 1.0 equiv), triphenyl phosphine (0.81 g, 3.1 mmol, 0.3 equiv), silver carbonate (2.84 g, 10.3 mmol, 1.0 equiv), and Et_3N (1.71 mL, 12.3 mmol, 1.2 equiv) were added to MeCN (100 mL, 0.1 M) and the resulting mixture was thoroughly degassed with argon. Palladium (II) acetate (0.23 g, 1.03 mmol, 0.1 equiv) was then added. The reaction mixture was heated to 70 °C, and the homogenous, brown solution was stirred for 3 h under argon before being cooled back to room temperature. Aqueous HCl solution (1 N, 300 mL) was then added and the mixture was extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by column chromatography (silica gel, gradient from 4:1 to 1:2 hexanes/DCM) to provide compound **10** as a colorless oil (2.02 g, 95%). R_f=0.5 (silica gel, DCM); $[\alpha]_D^{23}$ +9.4 (*c* 0.32, DCM); IR (film) ν_{max} 2932, 1675, 1384, 1192 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.77 (br s, 1H), 5.04 (br s, 1H), 2.28–2.36 (m, 7H), 2.08–2.12 (m, 1H), 1.96–1.98 (m, 1H), 1.73–1.83 (m, 3H), 0.93 (d, *J*=6.9 Hz, 3H), 0.88 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.2, 156.7, 138.3, 130.9, 113.5, 54.2, 34.5, 32.9, 30.8, 26.6, 23.0, 22.9, 21.1, 19.0; HRMS (ESI) calcd for $C_{14}H_{20}O$ $[M+Na]^+$ 227.1412, found 227.1408.

*4.1.8. (2S,4aR)-2-Isopropyl-4a,8-dimethyl-3,4,4a,5,6,7-hexahydronaphthalen-1(2H)-one (**17**).* In a flame-dried round-bottom flask charged with argon, a solution of **10** (1.97 g, 9.6 mmol, 1.0 equiv) in DCM (96 mL, 0.1 M) was cooled to 0 °C. A freshly prepared Et_2O solution of lithium dimethylcuprate[33] (0.50 M, 29 ml, 1.5 equiv) was added in one portion. The reaction mixture was stirred for 4 h before being quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with Et_2O (3×200 mL), and then the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (silica gel, gradient from 4:1 to 1:1 hexanes/DCM). The first fraction provided the desired compound **17** (1.21 g, 56%). R_f=0.5 (silica gel, DCM); $[\alpha]_D^{23}$ +106 (*c* 0.22, DCM); IR (film) ν_{max} 2931, 2358, 2341, 1684, 1653, 1540, 1457, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.28–2.36 (m, 1H), 2.08–2.12 (m, 1H), 1.99–2.02 (m, 2H), 1.86–1.91 (m, 1H), 1.68 (s, 3H), 1.54–1.75 (m, 6H), 1.36–1.42 (m, 1H), 0.94 (s, 3H), 0.94 (d, *J*=6.4 Hz, 3H), 0.89 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.7, 140.3, 136.6, 57.8, 40.5, 38.6, 38.3, 33.1, 25.9, 25.3, 21.9, 21.2, 21.1, 18.6, 18.3; HRMS (ESI) calcd for $C_{15}H_{24}O$ $[M+Na]^+$ 243.1725, found 243.1715. A more polar fraction afforded recovered starting material **10** as a colorless oil (334.2 mg, 17%), and a third fraction consisted of the other diastereomer (2*S*,4a*S*)-2-*isopropyl*-4a,8-*dimethyl*-3,4,4a,5,6,7-*hexahydronaphthalen*-1(2*H*)-*one* (**18**) as a colorless oil (356.3 mg, 17%). R_f=0.34 (silica gel, DCM); IR (film) ν_{max} 2946, 2368, 2341, 1684, 1657, 1540, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.85–2.06 (m, 6H), 1.74 (s, 3H), 1.60–1.72 (m, 3H), 1.54–1.58 (m, 1H), 1.38–1.46 (m, 2H), 1.00 (s, 3H), 0.91 (d, *J*=6.2 Hz, 3H), 0.87 (d, *J*=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7, 139.1, 138.1, 58.6, 38.5, 38.2, 36.0, 33.0, 27.5, 26.3, 23.1, 21.7, 21.1, 20.1, 18.5; HRMS (ESI) calcd for $C_{15}H_{24}O$ $[M+Na]^+$ 243.1725, found 243.1719.

*4.1.9. Dihydrojunenol (**1**).* Under a blanket of hydrogen gas (1 atm), a solution of **17** (1.21 g, 5.5 mmol, 1.0 equiv) in EtOAc (55 mL, 0.1 M) was stirred with palladium on carbon (0.51 g, 0.55 mmol, 0.1 equiv) at room temperature for 30 min. The reaction mixture was filtered through a plug of silica gel topped with Celite (EtOAc elution) to provide a saturated ketone (ca. 1.4 g). Without further purification, this ketone was dissolved in anhydrous ethanol (55 mL, 0.1 M) under argon. Sodium (0.64 g, 27.5 mmol, 5.0 equiv) was added in five portions and the reaction mixture was stirred at room temperature for 30 min before being quenched with saturated aqueous NH_4Cl solution (50 mL). The quenched mixture was then extracted with Et_2O (3×100 mL), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by filtering through a plug of silica gel (Et_2O elution) to provide dihydrojunenol (**1**) as a colorless oil that slowly solidified at room temperature (1.07 g, 87% over two steps). This natural product had spectroscopic data identical to the previous report.[5] R_f=0.50 (silica gel, DCM); $[\alpha]_D^{23}$ 0 (*c* 0.70, DCM); lit.[5] 0 (*c* 1.01, $CHCl_3$); IR (film) ν_{max} 3261, 2930, 1472, 1345, 1160 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.52 (dt, *J*=5.4, 10.1 Hz, 1H), 2.18–2.25 (m, 2H), 1.60–1.66 (m, 2H), 1.41–1.49 (m, 2H), 1.34–1.39 (m, 2H), 1.20–1.32 (m, 3H), 1.03–1.16 (m, 4H), 0.97 (d, *J*=7.5 Hz, 3H), 0.93 (d, *J*=7.0 Hz, 3H), 0.89 (s, 3H), 0.86 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 69.4, 53.7, 51.9, 44.2, 42.2, 35.0, 33.5, 27.0, 26.5, 21.3, 20.8, 19.0, 17.3, 16.4, 14.7; HRMS (ESI) calcd for $C_{15}H_{28}O$ $[M+Na]^+$ 247.2038, found 247.2038.

4.2. X-ray crystallographic data

Crystallographic data for **1**, and for the *p*-nitrobenzoyl ester derivatives of **7** and **8** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/ (CCDC # 743414 for **1**, 766068 for the *p*-nitrobenzoyl ester derivative of **7**, and 766069 for the *p*-nitrobenzoyl ester derivative of **8**).

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