UC Berkeley

UC Berkeley Previously Published Works

Title

Enantiospecific Entry to a Common Decalin Intermediate for the Syntheses of Highly Oxygenated Terpenoids

Permalink

https://escholarship.org/uc/item/5p51q5rn

Journal

The Journal of Organic Chemistry, 84(18)

ISSN

0022-3263

Authors

Nagasawa, Shota
Jones, Kerry E
Sarpong, Richmond

Publication Date

2019-09-20

DOI

10.1021/acs.joc.9b01937

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Org Chem. Author manuscript; available in PMC 2020 December 29.

Published in final edited form as:

J Org Chem. 2019 September 20; 84(18): 12209–12215. doi:10.1021/acs.joc.9b01937.

Enantiospecific Entry to a Common Decalin Intermediate for the Syntheses of Highly Oxygenated Terpenoids

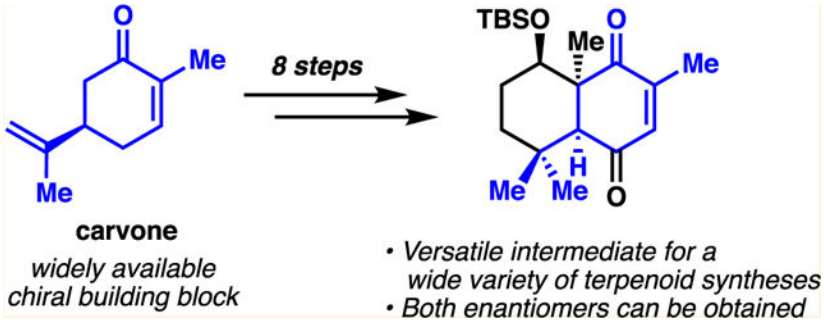
Shota Nagasawa[†], **Kerry E. Jones**, **Richmond Sarpong**[*]

Department of Chemistry, University of California, Berkeley, California 94720, United States

Abstract

Herein, we describe an enantiospecific route to one enantiomer of a common decalin core that is present in numerous highly oxygenated terpenoids. This intermediate is accessed in eight steps from (*R*)-carvone, an inexpensive, enantioenriched building block, which can be elaborated to the desired bicycle through sequential Fe(III)-catalyzed reductive olefin coupling and Dieckmann condensation. The same synthetic route may be applied to (*S*)-carvone to afford the enantiomer of this common intermediate for other applications.

Graphical Abstract



Terpenoids possessing decalin scaffolds are found in many families of natural products,[1] some of which express significant biological activity.[2] The structural features and biological function of decalin-containing secondary metabolites have made them attractive synthetic targets. Noteworthy examples of decalin-containing molecules that possess interesting structure and function include jungermatrobrunin A (**1**), an *ent*-kaurene diterpenoid, which showcases a rare endoperoxide bridge,[3a] and isodrimanial (**2**), a drimane sesquiterpenoid that displays significant cytotoxicity against the KB tumor cell line with an IC_{50} of 0.30 μM.[3b] These intriguing attributes have resulted in many synthetic studies aimed at the preparation of these decalin containing molecules.

[*]**Corresponding Author:** rsarpong@berkeley.edu.

[†]**Present Address:** Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3, Aoba, Aramaki, Aoba-ku, Sendai, 980-8578, Japan.

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b01937.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Several naturally occurring terpenoids including the labdane, *ent*-kaurene, drimane, cleistanthane, and isoprimarane terpenoid natural products, which possess highly oxygenated decalin cores, are highlighted in Figure 1.[3] The highly functionalized core in each of these compounds spurred us to identify a common intermediate such as decalin **3** and *ent*-**3**, which could provide access to each of these compounds. Indeed, racemic **3** has been elaborated to (±)-erigerol (**4**) by Kienzle and co-workers[4] and has also been taken forward to (±)-forskolin (**5**) in a synthesis by Švenda and co-workers.[5] In light of this previously demonstrated synthetic utility of **3**, we sought to prepare this decalin derivative in enantioenriched form as part of a broad campaign to access a diverse array of enantioenriched terpenoids.

As noted above, racemic 3 has been prepared previously by Kienzle and co-workers and was utilized in several natural product syntheses.[4] Specifically, from diene **10** and quinone **11**, a Diels–Alder cycloaddition constructed the decalin scaffold (Scheme 1a). Similar decalin derivatives have been prepared in enantioenriched form by exploiting a kinetic resolution, as demonstrated by Sih and co-workers[6] (see (±)-**12** → (+)-**13**; Scheme 1b). In principle, intermediate **3** could be obtained in enantioenriched form using porcine pancreatic lipase to effect a lipase ester hydrolysis of a decalin ester. However, enzymatic resolution provides a maximum yield of 50% and would necessitate several manipulations (e.g., an acylation or dehydrogenation) in order to obtain intermediate **3**. During the time when our studies were initiated, there had been no reported route to decalin 3 in enantioenriched form.[7] Given the synthetic utility of decalin **3** in complex molecule synthesis, we sought to develop an efficient and enantiospecific route for its preparation. Herein, we report an enantiospecific synthesis of one enantiomer of 3 from (*R*)-carvone (**14**), a cheap and commercially available "chiral pool" terpene that can be purchased in both enantiomeric forms (Scheme 1c). We envisioned a synthetic route that would employ three C–C bond forming transformations (radical coupling, Dieckmann condensation, and methylation) and one C–H oxidation step (γ-oxidation of enone).

Our initial attempts toward the synthesis of enantioenriched **3** began with an Fe(III)-catalyzed reductive olefin coupling, adapted from the work of Baran and co-workers,[7] between (*R*)-carvone (**14**) and methyl acrylate, which would install all the carbons necessary for the decalin scaffold (Scheme 2). However, under the reported reaction conditions, desired coupling product **15** was not obtained; rather, bicyclo[3.3.1]-nonane **16** was formed in low yield,[8] likely arising through sequential 1,4-additions (see brackets in Scheme 2).

We recognized that masking of the double bond of the enone functional group in (*R*)-carvone (**14**) could circumvent this undesired Giese-type addition. While protection of the enone through the conjugate addition of thiophenol was successful, subsequent reactions failed. Therefore, in our revised synthetic scheme, we began our synthesis with the Weitz–Scheffer[9] nucleophilic epoxidation of (*R*)-carvone (**14**) to yield epoxide **17** (Scheme 3). Subsequent Fe(III)-catalyzed intermolecular reductive olefin coupling with methyl acrylate afforded the desired ketoester (**18**) in good yield. Dieckmann condensation of ketoester **18** delivered the expected 1,3-diketone in the keto–enol form (**19**), and subsequent methylation of the α position of **19** with methyl iodide gave *cis*-fused bicycle **20**. The *cis*-configuration at the ring junction of **20** was confirmed by NOE correlations. Of note, the addition of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

tetrabutylammonium bromide was important in order to consistently achieve high conversion.

With diketone **20** in hand, we focused on the functionalizations required to advance the decalin core to **3** (Scheme 4). Reductive deoxygenation of the epoxide with bis(cyclopentadienyl)titanium(III) chloride (Cp_2TiCl), generated in situ from Cp_2TiCl_2 and zinc dust, afforded enone **21**.[10] Subsequent oxidation of the γ methylene of enone **21** was investigated with an array of transition metal catalysts and *tert*-butyl hydro-peroxide,[11] which yielded a mixture of C-4 and C-2 oxidation products in a 1.5–1.6:1 ratio. To our delight, oxidation of **21** using chromium trioxide and 3,5-dimethylpyrazole gave dienone **22** in moderate yield as the sole product.[12] Selective reduction of the C-8 carbonyl of enedione **22** was achieved with sodium borohydride in a dichloromethane–methanol solvent mixture[13] to provide alcohol **23**, which was subsequently protected to yield the desired silyl ether (i.e., **3**). Spectroscopic data for enantioenriched **3** were fully consistent with the previously reported data.[4,5] The synthetic sequence reported here is amenable to the multigram scale preparation of this compound.

We note that both enantiomers of **3** are accessible using this sequence, starting from either (*R*)- or (*S*)-carvone (**14**). Additionally, *cis*-decalin **3** can be epimerized to the corresponding *trans*-decalin (**24**) through treatment with basic aluminum oxide, according to Kienzle's protocol (Scheme 5).[4] Thus, all four diastereomers with respect to the decalin ring junctions are accessible through this synthetic route.

In summary, we have developed an eight-step sequence from (*R*)- or (*S*)-carvone (**14**) that provides access to an enantioenriched, highly oxygenated decalin structural motif using an Fe(III)-catalyzed reductive olefin coupling followed by a Dieckmann condensation. The resultant bicycle is a highly versatile intermediate that has been employed previously in the syntheses of labdane diterpenoids and may form the basis for the synthesis of other highly oxygenated terpenoids. Efforts in our laboratory that employ decalin **3** and *ent*-**3** in the synthesis of terpenoid natural products are currently ongoing.

EXPERIMENTAL SECTION

General.

Unless otherwise stated, all reactions were performed in flame-dried or oven-dried glassware under an atmosphere of nitrogen using Teflon coated stir bars. Reactions ran above room temperature were heated in an oil bath; room temperature is defined as 23 °C. All commercially available reagents were used without purification. Tetrahydrofuran (THF), methanol (MeOH), acetonitrile (MeCN), and triethylamine (Et_3N) were dried by passage through an activated alumina column under argon. Dichloromethane (DCM) was distilled over calcium hydride under nitrogen. Flash column chromatography was performed on Silicycle SiliaFlash P60 silica gel (230–400 mesh, 40–63 μm particle size). Automated flash chromatography was performed on Yamazen Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography systems with premium grade universal columns. Thin layer chromatography (TLC) and preparative TLC were performed on glass-backed Silicycle SiliaPlate 250 μm thickness, 60 Å porosity F-254 precoated plates. Compounds were

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

visualized with UV light (254 nm) and stained with *p*-anisaldehyde and heat, or potassium permanganate ($KMnO_4$) and heat. Nuclear magnetic resonance (NMR) spectra were obtained on Bruker AV-300 (NSF Grant CHE-0130862 and NSF Grant CHE-911557), AVQ-400 (NSF Grant CHE-0130862), AVB-400 (NSF Grant CHE-0130862, NIH Grant S10 RR 03353–01, and NSF Grant CHE-8703048), AV-500 (NIH Grant 1S10RR016634–01), and AV-600 (NIH Grant SRR023679A) instruments at UC Berkeley's College of Chemistry NMR Facility. Residual chloroform ($CHCl_3$) was used as an internal reference for ^1H (δ = 7.26 ppm) and ^{13}C (δ = 77.1 ppm). The following abbreviations were used to describe the NMR multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, q = quintet, m = multiplet. Coupling constants *J* are given in hertz. Infrared (IR) spectroscopy data were obtained on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Substances were dissolved in chloroform prior to direct application on the ATR unit. Frequency of absorption is given in cm^{-1}. High-resolution mass spectra (HRMS) were obtained on a PerkinElmer AxION 2 UHPLC-TOF Instrument (ESI) or an AutoSpec Premier mass spectrometer (Waters, Manchester, UK), equipped with an electron impact (EI). Optical rotations were measured on a PerkinElmer 241 Polarimeter. Melting points were measured on a Laboratory Devices Mel-Temp II.

Experimental Procedures.

Methyl (1R,5S,8R)-4,4,8-Trimethyl-7-oxobicyclo[3.3.1]nonane-2-carboxylate (16).—Prepared according to a modification of the procedure by Baran and co-workers:[7] (*R*)-carvone (**14**, 50.0 mg, 0.33 mmol, 1.0 equiv) was dissolved in a mixture of 1,2-dichloroethane (1.5 mL) and ethylene glycol (0.3 mL) in a flask open to the atmosphere. Iron(III) acetylacetonate (10.6 mg, 30.0 μmol, 0.1 equiv), methyl acrylate (0.11 mL, 0.99 mmol, 3.0 equiv), and anhydrous sodium phosphate dibasic (47 mg, 0.33 mmol, 1.0 equiv) were added to the rapidly stirring mixture. Phenylsilane (0.06 mL, 0.66 mmol, 2.0 equiv) was added dropwise. (CAUTION: rapid evolution of gas is observed.) The flask was fitted with a water jacketed reflux condenser, the mixture was heated to 60 °C for 1 h, and then additional phenylsilane (0.06 mL, 0.66 mmol, 2.0 equiv) was added and stirred 1 h. Upon observed completion by TLC the reaction mixture was cooled to room temperature and diluted with saturated aqueous sodium chloride (5 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 8 mL). The combined organic layers were washed with saturated aqueous sodium chloride (5 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The crude oil was then purified via gradient flash chromatography (Yamazen, eluting with 8–29% ethyl acetate in hexanes) to give the title compound **16** (21.5 mg, 0.090 mmol, 27%). The ^1H NMR and ^{13}C NMR spectra are consistent with those reported in the literature.[8] ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 2.94−2.88 (m, 1H), 2.73−2.62 (m, 2H), 2.47 (qdd, *J* = 6.9, 6.4, 0.9 Hz, 1H), 2.32 (ddd, *J* = 15.7, 5.7, 0.9 Hz, 1H), 2.20 (dq, *J* = 13.6, 3.3 Hz, 1H), 1.96 (dt, *J* = 13.6, 3.1 Hz, 1H), 1.88−1.83 (m, 1H), 1.48 (dd, *J* = 14.8, 3.8 Hz, 1H), 1.32 (d, *J* = 14.8 Hz, 1H), 1.00 (s, 3H), 0.97 (s, 3H), 0.94 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 175.4, 51.6, 48.8, 44.6, 41.9, 41.8, 40.1, 34.0, 33.4, 33.1, 29.2, 27.5, 12.0.

(1R,4R,6R)-1-Methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-one (Carvone Oxide, 17).—Prepared according to a modification of the procedure outlined by

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Mulzer and co-workers:[14] (*R*)-(−)-Carvone (**14**, 5.0 g, 33 mmol, 1.0 equiv) was added to HPLC grade methanol (83 mL) in a flask open to the environment, and the mixture was cooled to −20 °C. A 4.0 M solution of sodium hydroxide (2.5 mL, 9.9 mmol, 0.3 equiv) and a 35% aqueous hydrogen peroxide solution (3.7 mL, 43 mmol, 1.3 equiv) were added sequentially in a dropwise fashion. The solution was warmed to 0 °C within 1.5 h, and then additional 35% aqueous hydrogen peroxide solution (1.8 mL, 21 mmol, 0.6 equiv) was added. Afterward, the reaction mixture was stirred for 1 h. The excess hydrogen peroxide was quenched with 2 N hydrochloric acid (4 mL) and sodium thiosulfate (3.0 g, 0.5 equiv) and allowed to stir at room temperature for 30 min before the addition of water (100 mL) was added, and the aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified via column chromatography (20:1 hexanes/ethyl acetate) to yield carvone oxide **17** as a colorless oil (5.0 g, 30.0 mmol, 90% yield). Full characterization has been reported by Cao and co-workers. The ^{1}H NMR spectrum is consistent with that reported in the literature.[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.72 (s, 1H), 3.45 (dd, J = 3.2, 1.2 Hz, 1H), 2.71 (tt, J = 11.2, 4.8 Hz, 1H), 2.59 (ddd, J = 17.7, 4.7, 1.4 Hz, 1H), 2.37 (dt, J = 14.8, 3.3 Hz, 1H), 2.03 (dd, J = 17.6, 11.6 Hz, 1H), 1.90 (ddd, J = 14.8, 11.1, 1.2 Hz, 1H), 1.71 (s, 3H), 1.41 (s, 3H).

Methyl 4-Methyl-4-((1R,3R,6R)-6-methyl-5-oxo-7-oxabicyclo[4.1.0]heptan-3-yl)pentanoate (18).—Prepared according to a modification of the procedure by Baran and co-workers:[7] Epoxide **17** (1.0 g, 6.0 mmol, 1.0 equiv) was dissolved in a mixture of 1,2-dichloroethane (25 mL) and ethylene glycol (5 mL) in a flask open to the atmosphere. Iron(III) acetylacetonate (0.21 g, 0.59 mmol, 0.1 equiv), methyl acrylate (2.0 mL, 22 mmol, 3.0 equiv), and anhydrous sodium phosphate dibasic (0.85 g, 5.9 mmol, 1.0 equiv) were added to the rapidly stirring mixture. Phenylsilane (1.2 mL, 12 mmol, 2.0 equiv) was added dropwise. (CAUTION: rapid evolution of gas is observed.) The mixture was heated to 60 °C for 1 h, and then additional phenylsilane (0.6 mL, 6.0 mmol, 1.0 equiv) was added. Afterward, the reaction mixture was stirred 30 min. Upon observed completion by TLC the reaction mixture was cooled to room temperature and diluted with saturated aqueous sodium chloride (100 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 75 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the crude residue via column chromatography (10:1 hexanes/ethyl acetate) yielded methyl ester **18** as a colorless oil (0.94 g, 3.7 mmol, 62% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.43 (d, J = 3.6 Hz, 1H), 2.52−2.41 (m, 1H), 2.36−2.22 (m, 3H), 2.02−1.95 (m, 1H), 1.89 (dd, J = 17.4, 11.8 Hz, 1H), 1.69 (dd, J = 14.4, 11.6 Hz, 1H), 1.62−1.53 (m, 2H), 1.40 (s, 3H), 0.84 (s, 3H), 0.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2, 174.2, 61.1, 58.7, 51.6, 38.5, 34.7, 34.4, 33.8, 28.8, 24.3, 23.8, 23.7, 15.2. IR: $\tilde{\upsilon}$ = 2954, 2874, 1736, 1706, 1437, 1371, 1304, 1197, 1171, 1116 cm^{-1}. $[\alpha]^{20}_D$ = +69.2° (c 0.93, $CHCl_3$). HRMS (ESI): calcd for ([M + H], $C_{14}H_{23}O_4)^+$: m/z = 255.1591; found 255.1594. R_f = 0.26 (4:1 hexanes/ethyl acetate), red spot (*p*-anisaldehyde).

(1aR,6aS,7aR)-3-Hydroxy-1a,6,6-trimethyl-4,5,6,6a,7,7ahexahydronaphtho[2,3-b]oxiren-2(1aH)-one (19).—Methyl ester **18** (0.94 g, 3.7 mmol, 1.0 equiv) was dissolved

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

in THF (37 mL) and cooled to 0 °C. Potassium tert-butoxide (0.50 g, 4.4 mmol, 1.2 equiv) was added, and the mixture was stirred for 30 min. Upon completion by TLC, saturated aqueous ammonium chloride (50 mL) was added and the reaction mixture was warmed to room temperature. The aqueous layer was extracted with ethyl acetate (3 × 50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride (25 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash chromatography (10:1 hexanes/ethyl acetate) to give enol **19** as a white solid (0.69 g, 3.1 mmol, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.81 (s, 1H), 3.49 (d, J = 3.5 Hz, 1H), 2.48−2.24 (m, 4H), 1.64−1.42 (m, 6H), 1.01 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.1, 182.3, 106.0, 62.4, 57.6, 37.6, 36.3, 31.0, 29.0, 28.1, 23.7, 19.8, 15.8. mp: 41−44 °C. IR: $\tilde{\upsilon}$ = 2927, 2868, 1601, 1416, 1379, 1367, 1355, 1290, 1260, 1183, 934, 406 cm^{-1}. $[\alpha]^{20}_D$ = −45.4° (c 0.97, $CHCl_3$). HRMS (ESI): calcd for ([M + H], $C_{13}H_{19}O_3)^+$ m/z = 223.1329; found 223.1322. R_f = 0.55 (4:1 hexanes/ethyl acetate), UV-active, orange spot (p-anisaldehyde).

(1aR,2aS,6aS,7aR)-1a,2a,6,6-Tetramethylhexahydronaphtho[2,3-b]oxirene-2,3(1aH,2aH)-dione (20).—Enol **19** (4.4 g, 20 mmol, 1.0 equiv) was dissolved in anhydrous dimethylformamide (90 mL), followed by subsequent addition of potassium carbonate (12.3 g, 88.9 mmol, 4.5 equiv), tetrabutylammonium bromide (64 mg, 0.2 mmol, 0.01 equiv), and iodomethane (6.15 mL, 98.7 mmol, 5.0 equiv). This mixture was stirred in a closed vessel for 4.5 h at room temperature. Excess solid potassium carbonate was removed by filtration through fritted glass, and the filtrate was diluted with water (300 mL) and extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification via flash chromatography (9:1 hexanes/ethyl acetate) afforded 1,3-dione **20** (3.2 g, 13 mmol, 68% yield) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (d, J = 5.2 Hz, 1H), 2.57 (td, J = 14.4, 6.0 Hz, 1H), 2.46 (dd, J = 16.4, 7.2 Hz, 1H), 2.30 (ddd, J = 14.3, 4.6, 3.1 Hz, 1H), 2.15 (ddd, J = 16.4, 5.2, 2.2 Hz, 1H), 1.92 (dt, J = 7.0, 1.6 Hz, 1H), 1.75 (ddd, J = 13.8, 6.2, 3.1 Hz, 1H), 1.59 (td, J = 14.0, 4.5 Hz, 1H), 1.48 (s, 3H), 1.40 (s, 3H), 1.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 208.5, 64.3, 59.9, 58.8, 56.4, 40.5, 36.6, 34.2, 30.7, 22.9, 22.7, 20.6, 15.9. Mp: 128−131 °C. IR: $\tilde{\upsilon}$ = 2980, 2962, 2943, 2880, 1716, 1686, 1471, 1380, 1044, 1009, 851 cm^{-1}. $[\alpha]^{20}_D$ = +122.5° (c 1.13, $CHCl_3$). HRMS (ESI): calcd for ([M + Na], $C_{14}H_{20}NaO_3)^+$ m/z = 259.1305; found 259.1308. R_f = 0.37 (4:1 hexanes/ethyl acetate), yellow-orange spot (p-anisaldehyde).

(4aS,8aS)-4,4,7,8a-Tetramethyl-3,4,4a,8a-tetrahydronaphthalene-1,8(2H,5H)-dione (21).—Procedure adapted from Nugent.[9] THF (25 mL) was added to a flask charged with zinc (4.2 g, 64 mmol, 6.6 equiv) and bis(cyclopentadienyl)-titanium(IV) dichloride (5.33 g, 21.4 mmol, 2.2 equiv). After 15 min, 1,3-dione **20** (2.3 g, 9.7 mmol, 1.0 equiv) was added dropwise in THF (25 mL). After stirring the solution at room temperature for 1.5 h, saturated aqueous monosodium phosphate (50 mL), saturated aqueous sodium chloride (50 mL), and ethyl acetate (50 mL) were added. After 1 h, the mixture was filtered through Celite and the filtrate was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with saturated aqueous sodium chloride (25 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The resulting residue was purified via flash

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

chromatography (8:1 hexanes/ethyl acetate). This yielded **21** (1.87 g, 8.48 mmol, 87% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58−6.55 (m, 1H), 2.71−2.56 (m, 2H), 2.39 (dd, J = 21.0, 4.8 Hz, 1H), 2.28 (dt, J = 13.9, 3.3 Hz, 1H), 1.99 (d, J = 6.7 Hz, 1H), 1.77−1.69 (m, 4H), 1.61 (td, J = 13.9, 3.8 Hz, 1H), 1.33 (s, 3H), 0.97 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5, 200.6, 142.4, 133.8, 59.2, 54.1, 41.8, 37.1, 34.4, 30.4, 24.8, 23.0, 20.7, 16.0. Mp: 99−104 °C. IR: $\tilde{\nu}$ = 2958, 2928, 2874, 1713, 1653, 1455, 1424, 1372, 1361, 1030, 847, 754 cm^{-1}. [α] 20_D = +144.7° (c 1.14, $CHCl_3$). HRMS (ESI): calcd for ([M + H], $C_{14}H_{21}O_2$)$^+$ m/z = 221.1536; found 221.1543. R_f = 0.34 (4:1 hexanes/ethyl acetate), UV-active, yellow spot (*p*-anisaldehyde).

(4aS,8aS)-3,4a,8,8-Tetramethyl-6,7,8,8a-tetrahydronaphthalene-1,4,5(4aH)-trione (22).—Diketone **21** (1.87 g, 8.49 mmol, 1.0 equiv) was dissolved in 1,2-dichloroethane (50 mL) in a flask open to the environment. Chromium trioxide (17.0 g, 169 mmol, 20 equiv) and 3,5-dimethylpyrazole (16.2 g, 169 mmol, 20 equiv) were added sequentially at 0 °C, and after stirring at 0 °C for 10 min the mixture was heated to 50 °C. After 20 h, slight starting material remined as evident by TLC, the mixture was cooled to room temperature and filtered through a silica plug. The silica was washed with 1:1 hexanes/ethyl acetate, and the filtrate was concentrated. The resultant residue was subjected to flash chromatography (1:6 hexanes/ethyl acetate) resulting in triketone **22** (1.54 g) as a yellow solid, which contained minimal inseparable starting material. The mixture was carried forward without further purification. *NOTE: reaction goes to completion on small scales; portion of product further purified for full characterization*. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58−6.52 (m, 1H), 2.68 (s, 1H), 2.67 (td, J = 14.4, 6.0 Hz, 1H), 2.40 (dt, J = 14.8, 3.4 Hz, 1H), 2.01 (d, J = 1.6 Hz, 3H), 1.83−1.68 (m, 2H), 1.37 (s, 3H), 1.06 (s, 3H), 0.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.9, 200.1, 197.9, 148.2, 137.2, 68.5, 60.6, 41.1, 36.5, 35.2, 29.7, 24.3, 23.7, 16.4. mp: 63−66 °C. IR: $\tilde{\nu}$ = 2962, 2933, 2871, 1721, 1666, 1625, 1428, 1375, 1249, 1191, 1178, 1030, 978, 892 cm^{-1}. [α]$^{20}_D$ = +178.9° (c 1.21, $CHCl_3$). HRMS (ESI): calcd for ([M + Na], $C_{14}H_{18}NaO_3$)$^+$ m/z = 257.1148; found 257.1144. R_f = 0.28 (4:1 hexanes/ethyl acetate), UV-active, yellow spot (*p*-anisaldehyde).

(4aS,8R,8aS)-8-Hydroxy-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalene-1,4-dione (23).—Trike-tone **22** (1.54 g, 6.57 mmol, 1.0 equiv), with slight impurities, was dissolved in a mixture of methanol (33 mL) and dichloromethane (33 mL), and the solution was cooled to −78 °C. Sodium borohydride (0.25 g, 6.6 mmol, 1.0 equiv) was added and stirred for 1.5 h, before the addition of a second portion of sodium borohydride (0.25 g, 6.6 mmol, 1.0 equiv). After 1 h, acetone (50 mL) and water (50 mL) were added to quench excess borohydride and the mixture was warmed to room temperature. The mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with saturated aqueous sodium chloride (25 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was subjected to flash chromatography (1:8 hexanes/ethyl acetate) to yield alcohol **23** as a mixture with remaining starting material (1.31 g) as a yellow solid. This was carried forward without further purification. Full characterization has been reported by Švenda and co-workers. The ^{1}H NMR spectrum is consistent with that reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50−6.48 (m, 1H), 3.98 (br s, 1H), 3.15 (dd, J = 12.0, 4.3 Hz, 1H),

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2.35 (d, J = 1.3 Hz, 1H), 1.99 (d, J = 1.5 Hz, 3H), 1.89 (dq, J = 13.4, 3.9 Hz, 1H), 1.77 (qd, J = 13.4, 3.5 Hz, 1H), 1.53 (dt, J = 13.7, 3.6 Hz, 1H), 1.46 (s, 3H), 1.48−1.39 (m, 1H), 0.96 (s, 3H), 0.72 (s, 3H).

(4aS,8R,8aS)-8-((tert-Butyldimethylsilyl)oxy)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydro-naphthalene-1,4-dione (3).—Prepared according to a modification of the procedure outlined by Švenda and co-workers.[5] Alcohol **23** (1.31 g, 5.54 mmol, 1.0 equiv), with slight impurities, was dissolved in dichloromethane (28 mL), and the solution was cooled to −78 °C. 2,6-Lutidine (0.97 mL, 8.3 mmol, 1.5 equiv) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.27 mL, 5.54 mmol, 1.0 equiv) were added sequentially. After 1 h of stirring at −78 °C, additional *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.1 mmol, 0.2 equiv) was added. After stirring for an additional 20 min, saturated aqueous sodium bicarbonate (30 mL) was added and the reaction mixture was warmed to room temperature. The mixture was extracted with dichloromethane (3 × 30 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The crude residue was purified via flash chromatography in (20:1 → 8:1 hexanes/ethyl acetate) to yield 3 (1.70 g, 4.85 mmol, 57% over three steps) as a yellow solid. Full characterization has been reported by Švenda and co-workers. The ^{1}H NMR spectrum is consistent with that reported in the literature.[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.39−6.38 (m, 1H), 3.23 (dd, J = 11.8, 3.8 Hz, 1H), 2.29 (d, J = 1.4 Hz, 1H), 2.08−1.96 (m, 1H), 1.96 (d, J = 1.5 Hz, 3H), 1.63 (dq, J = 13.4, 3.7 Hz, 1H), 1.49 (dt, J = 13.7, 3.6 Hz, 1H), 1.41 (td, J = 13.6, 3.7 Hz, 1H), 1.32 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.71 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.5, 200.0, 151.7, 135.5, 78.5, 67.7, 51.8, 40.9, 35.3, 30.8, 28.1, 27.0, 26.0, 24.6, 18.2, 16.8, −3.7, −4.8. $[\alpha]^{20}_D$ = +29.5° (c 1.02, $CHCl_3$).

(4aR,8R,8aS)-8-((tert-Butyldimethylsilyl)oxy)-2,5,5,8a-tetramethyl-4a,5,6,7,8,8a-hexahydronaphthalene-1,4-dione (24).—Prepared according to a modification of the procedure outlined by Švenda and co-workers, originally by Kienzle and co-workers.[6,7] *cis*-Decalin **3** (10 mg, 28 μmol, 1.0 equiv) was dissolved in toluene (0.3 mL). Aluminum oxide (40.0 mg, 400 wt %) was added, and the heterogeneous mixture was heated to reflux at 100 °C and maintained at that temperature for 24 h. The reaction mixture was cooled and filtered through a silica plug to remove solid aluminum oxide. The silica plug was flushed with ethyl acetate. The filtrate was concentrated *in vacuo*. The resultant crude product was purified via flash chromatography in (20:1 hexanes/ethyl acetate) to yield *trans*decalin **24** (7.8 mg, 22 μmol, 80%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48 (m, 1H), 4.30 (m, 1H), 3.30 (s, 1H), 1.88 (d, J = 1.5 Hz, 3H), 1.86−1.66 (m, 2H), 1.59−1.49 (m, 1H), 1.24 (s, 3H), 1.14 (s, 6H), 1.10 (dt, J = 13.0, 3.1 Hz, 1H), 0.82 (s, 9H), 0.10 (s, 3H), 0.80 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.5, 201.2, 144.8, 138.7, 70.6, 55.9, 55.6, 35.1, 32.8, 32.4, 25.9, 24.9, 22.3, 21.3, 18.2, 15.9, −4.2, −5.1. Mp: 43−44 °C. IR: $\tilde{\nu}$ = 2936, 2928, 2854, 1683, 1469, 1377, 1251, 1084, 836 cm^{-1}. $[\alpha]^{20}_D$ = −108.4° (c 1.02, $CHCl_3$). HRMS (EI): calcd for ([M–CH_3], $C_{19}H_{31}O_3Si)^+$ m/z = 335.2037; found 335.2038. R_f = 0.61 (8:1 hexanes/ethyl acetate), UV-active, blue spot (*p*-anisaldehyde).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

ACKNOWLEDGMENTS

We thank College of Chemistry's NMR facility for resources provided and the staff for their assistance. Instruments in CoC-NMR are supported in part by NIH S10OD024998 and the Catalysis Facility of Lawrence Berkeley National Laboratory, which is supported by the Director, Office of Science, of the U.S. Department of Energy under Contract No. DE-AC02-05CH11231.

REFERENCES

(1). Li G; Kusari S; Spiteller M Natural products containing 'decalin' motif in microorganisms. Nat. Prod. Rep 2014, 31, 1175–1201. [PubMed: 24984916]

(2). Reviews:(a)Hanson JR Diterpenoids of terrestrial origin. Nat. Prod. Rep 2017, 34, 1233–1243. [PubMed: 28875214] (b)Fraga BM Natural sesquiterpenoids. Nat. Prod. Rep 2013, 30, 1226–1264. [PubMed: 23884176]

(3). For publications detailing the isolation of the terpenoids in Figure 1, see:(a)Qu JB; Zhu RL; Zhang YL; Guo HF; Wang XN; Xie CF; Yu WT; Ji M; Lou HX *ent*-Kaurane Diterpenoids from the Liverwort *Jungermannia atrobrunnea*. J. Nat. Prod 2008, 71, 1418–1422. [PubMed: 18665642] (b)Fotsop DF; Roussi F; Le Callonec C; Bousserouel H; Litaudon M; Gueritte F Isolation and characterization of two new drimanes from Zygogynum baillonii and synthesis of analogues. Tetrahedron 2008, 64, 2192–2197.(c)Waddell TG; Osborne CB; Collison R; Levine MJ; Cross MC; Silverton JV; Fales HM; Sokoloski EA Erigerol, a New Labdane Diterpene from *Erigeron Philadelphicus*. J. Org. Chem 1983, 48, 4450–4453.(d)Bhat SV; Bajqwa BS; Dornauer H; do Scusa NJ d.; Fehlhaber, H.-W. Structures and stereochemistry of new labdane diterpenoids from coleus forskohlii briq. Tetrahedron Lett. 1977, 18, 1669–1672.(e)Guo ZK; Yan T; Guo Y; Song YC; Jiao RH; Tan RX; Ge HM *p*-Terphenyl and Diterpenoid Metabolites from Endophytic *Aspergillus* sp. YXf3. J. Nat. Prod 2012, 75, 15–21. [PubMed: 22196792]

(4). (a)Kienzle F; Stadlwieser J; Rank W; Schonholzer P The Synthesis of the Labdane Diterpenoid Erigerol and of Analogous Compounds. Helv. Chim. Acta 1990, 73, 1108–1139.(b)Kienzle F; Stadlwieser J; Mergelsberg I Diels-Alder Reactions with 3-Cyclopropylideneprop-1-enyl Ethyl Ether as 1,3-Diene. Helv. Chim. Acta 1989, 72, 348–352.

(5). Hylse O; Maier L; Kucera R; Perecko T; Svobodova A; Kubala L; Paruch K; Svenda J A Concise Synthesis of Forskolin. Angew. Chem., Int. Ed 2017, 56, 12586–12589.

(6). Bold G; Chao S; Bhide R; Wu SH; Patel DV; Sih CJ; Chidester C A Chiral Bicyclic Intermediate for the Synthesis of Forskolin. Tetrahedron Lett. 1987, 28, 1973–1976.

(7). During the review of this manuscript, Pronin and co-workers reported a method to access enantioenriched decalin 3 by employing an oxazaborolidine-catalyzed enantioselective Diels–Alder reaction and Fe-catalyzed radical-polar crossover annulation; see:Thomas WP; Schatz DJ; George DT; Pronin SV A Radical-Polar Crossover Annulation To Access Terpenoid Motifs. J. Am. Chem. Soc 2019, 141, 12246–12250. [PubMed: 31329434]

(8). (a)Lo JC; Kim D; Pan CM; Edwards JT; Yabe Y; Gui JH; Qin T; Gutierrez S; Giacoboni J; Smith MW; Holland PL; Baran PS Fe-Catalyzed C-C Bond Construction from Olefins via Radicals. J. Am. Chem. Soc 2017, 139, 2484–2503. [PubMed: 28094980] (b)Lo JC; Yabe Y; Baran PS A Practical and Catalytic Reductive Olefin Coupling. J. Am. Chem. Soc 2014, 136, 1304–1307. [PubMed: 24428607]

(9). Srikrishna A; Hemamalini P; Venkateswarlu S A Regiospecific Radical Annulation Strategy to Functionalized Chiral Bicyclo[3.3.1]-Nonanes. Tetrahedron 1994, 50, 8781–8792.

(10). Weitz E; Scheffer AÜber die Einwirkung von alkalischem Wasserstoffsuperoxyd auf ungersättigte Verbindungen (About the action of basic hydrogenperoxide on unsaturated compounds). Ber. Dtsch. Chem. Ges. B 1921, 54, 2327–2344.

(11). Rajanbabu TV; Nugent WA Selective Generation of Free-Radicals from Epoxides Using a Transition-Metal Radical.A Powerful New Tool for Organic Synthesis. J. Am. Chem. Soc 1994, 116, 986–997.

(12). (a)Catino AJ; Forslund RE; Doyle MP Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation. J. Am. Chem. Soc 2004, 126, 13622–13623. [PubMed: 15493912] (b)Yu J-

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Q; Corey EJ A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β-Enones to 1,4-Enediones. J. Am. Chem. Soc 2003, 125, 3232–3233. [PubMed: 12630876]

(13). Salmond WG; Barta MA; Havens JL Allylic Oxidation with 3,5-Dimethylpyrazole. Chromium Trioxide Complex. Steroidal ^{5}-7-Ketones. J. Org. Chem 1978, 43, 2057–2059.

(14). Ward DE; Rhee CK Chemoselective Reductions with Sodium Borohydride. Can. J. Chem 1989, 67, 1206–1211.

(15). Weinstabl H; Gaich T; Mulzer J Application of the Rodriguez-Pattenden Photo-Ring Contraction: Total Synthesis and Configurational Reassignment of 11-Gorgiacerol and 11-Epigorgiacerol. Org. Lett 2012, 14, 2834–2837. [PubMed: 22590980]

(16). Feng JP; Shi ZF; Li Y; Zhang JT; Qi XL; Chen J; Cao XP An Improved Asymmetric Synthesis of Malyngamide U and Its 2′-Epimer. J. Org. Chem 2008, 73, 6873–6876. [PubMed: 18656980]

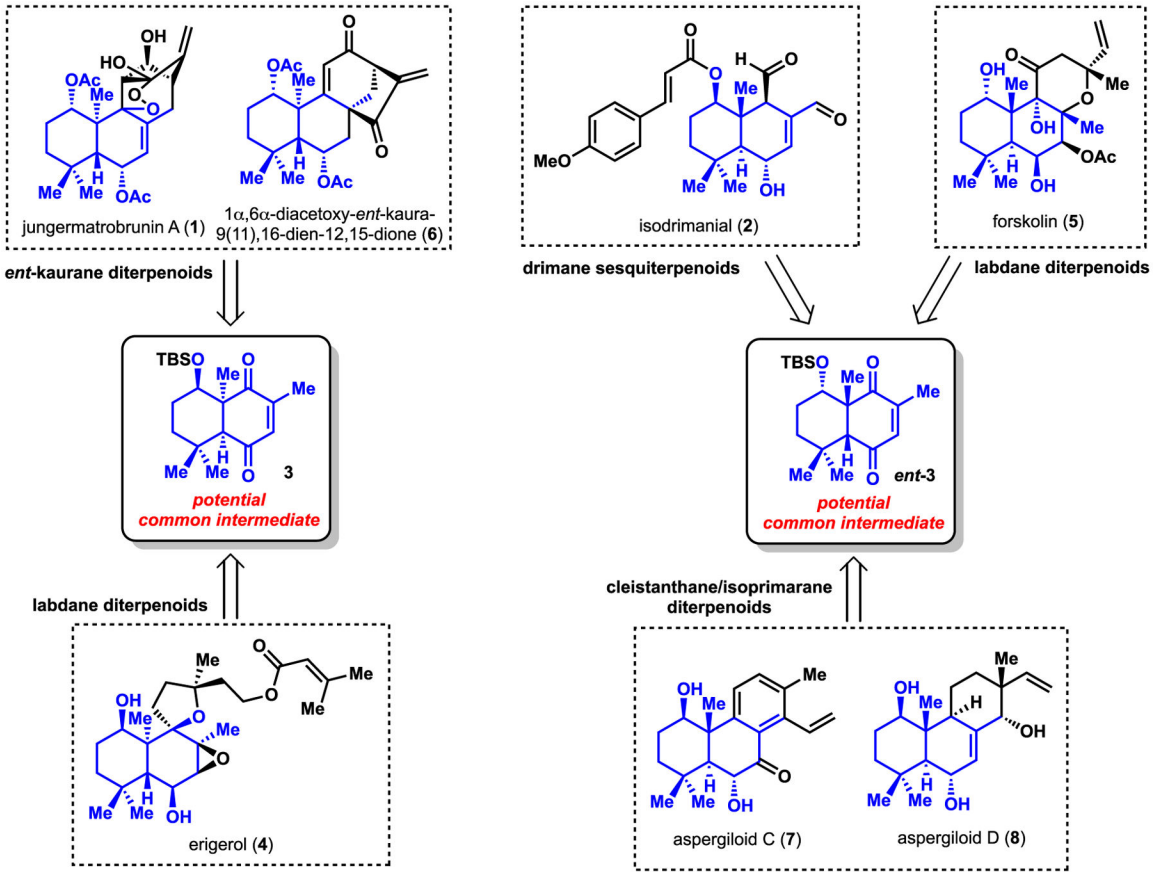


Figure 1.

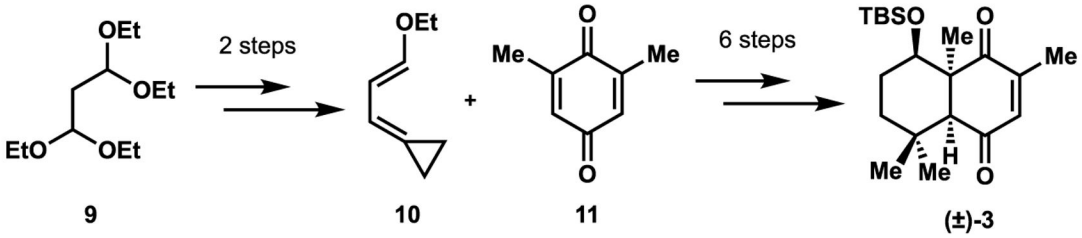
Selected terpenoids containing a highly oxygenated decalin core traced back to a plausible common intermediate.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

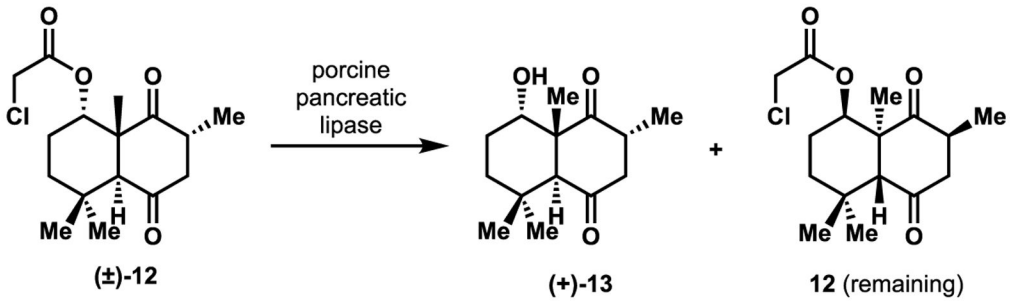
Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Previous work

a) racemic entry of intermediate **3** (Kienzle, 1989 and 1990)

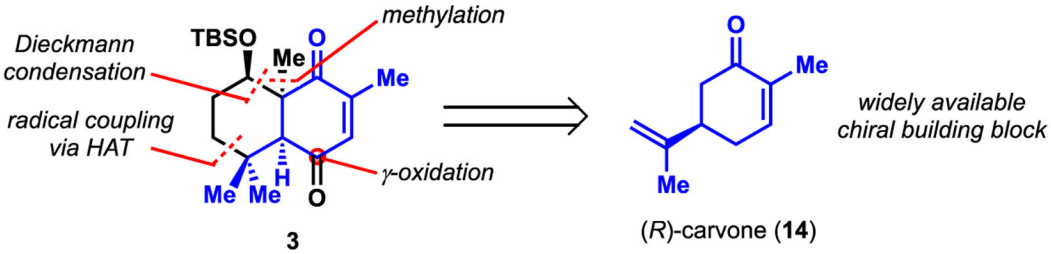


b) enzymatic kinetic resolution of similar substrates (Sih, 1987)



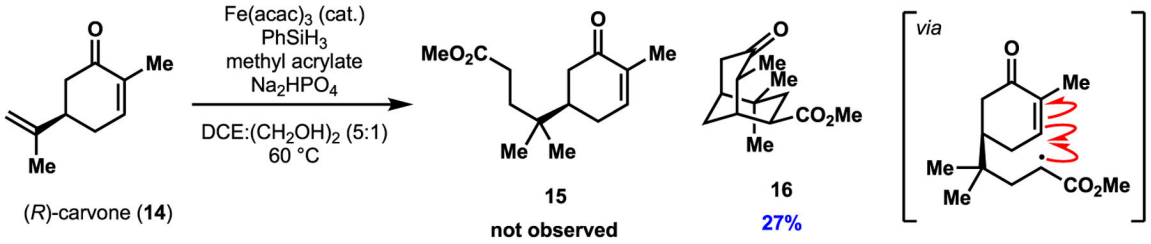
This work

c) enantiospecific entry of intermediate **3**



Scheme 1.

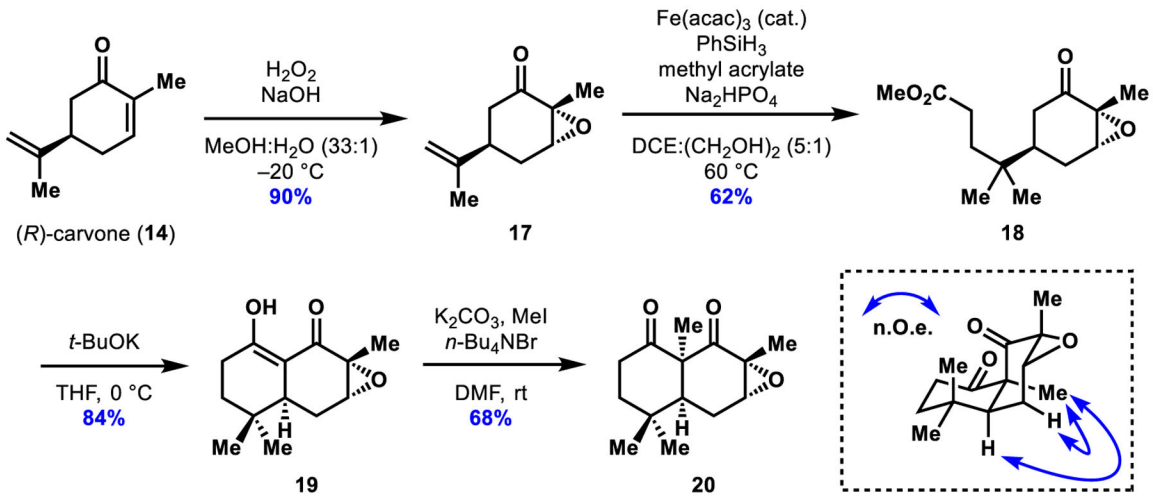
Access to the Intermediate 3



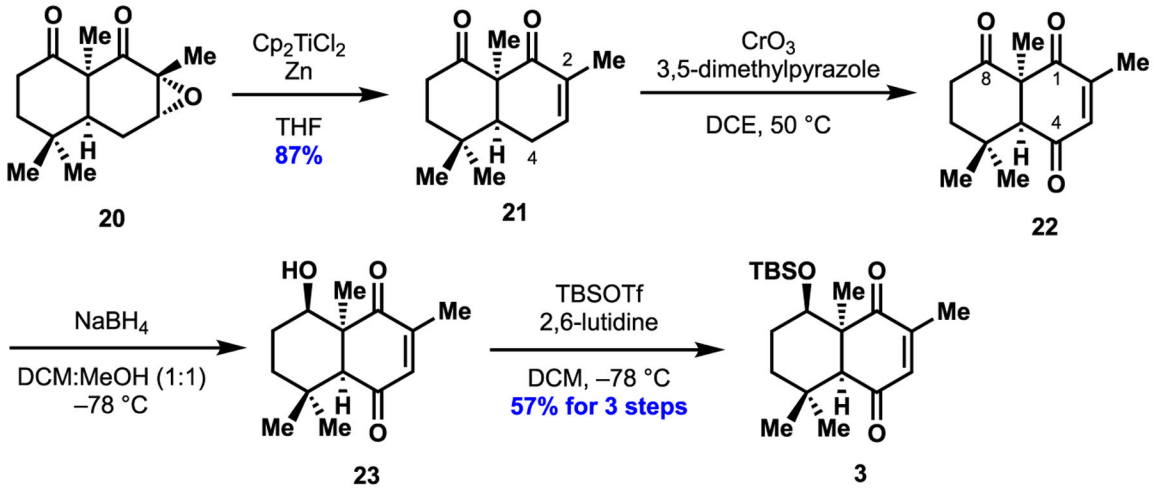
Scheme 2.
Formation of Bridged Bicycle 16

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



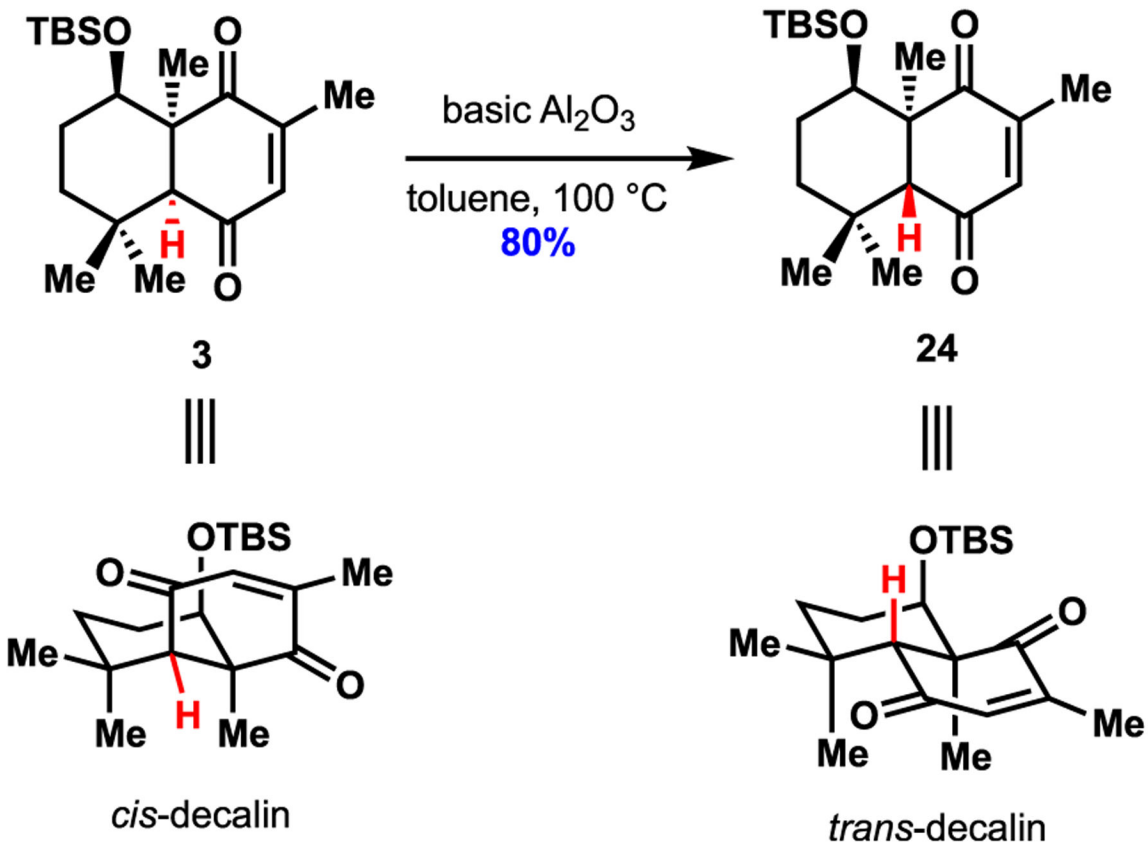
Scheme 3.
Synthesis of *cis*-Fused Decalin Compound 20



Scheme 4.
Completion of the Synthesis of Intermediate 3

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript



Scheme 5.
Epimerization of *cis*-Decalin 3 to *trans*-Decalin 24