Enantioselective Total Synthesis of

(−)-Laurenditerpenol

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SUPPORTING INFORMATION: PART A

General: All reactions were carried out under a dry argon atmosphere with anhydrous, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reactions were magnetically stirred with Teflon stir bars, and temperatures were measured externally. Reactions requiring anhydrous conditions were carried out in oven dried (120 °C, 24 h) or flame dried (vacuum < 0.5 Torr) glassware. Yields refer to chromatographically and spectroscopically (1H NMR) homogeneous materials unless otherwise noted. All reagents were obtained from Aldrich Chemical Co. Inc. and used without further purification. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm E.Merck silica gel plates (60F-254). E.Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-250 or a Bruker Advance DRX-500 instrument as noted individually. Chemical shifts are measured in parts per million (δ) relative to the deuterated solvent used in the experiment. Multiplicities are designated as singlet (s), doublet (d), triplet (t), or multiplet (m). Broad or obscured peaks are indicated as “br” or “obs” respectively. Where peak assignments are made, they are based on 2D homonuclear or heteronuclear NMR spectra, copies of which are provided along with 1H and 13C NMR spectra in Supporting Information: Part B. Mass spectra were recorded using an Agilent (ESI-TOF) instrument. Optical rotations were recorded using a Perkin-Elmer 241 polarimeter.
Preparation of the fully functionalized C(9)–C(15) segment (19).

(+)-(1R,2R,3R,4S)-1,4-Dimethyl-7-oxa-bicyclo[2.2.1]heptan-2,3-dicarboxylic acid diethyl ester (9) was prepared according to the literature procedure.¹

(+)-(1S,2R,3S,4R)-3-(Hydroxymethyl)-1,4-dimethyl-7-oxa-bicyclo[2.2.1]heptan-2-carboxylic acid ethyl ester (13a).

A stirred solution of 9 (0.44 g, 1.6 mmol) in ethanol (9 mL) was cooled to 0 °C and a solution of LiOH (90 mg, 2.0 mmol) in water (3 mL) was added in small portions. The mixture was stirred for 18 h at 0 °C and then it was poured in ice-cold 1.0 M aqueous HCl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed sequentially with water (3 × 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained was purified by flash column chromatography (7:3 hexane-ethyl acetate + 2% AcOH) to produce a mixture of the corresponding monoethyl esters 12a and 12b (0.37 g) as a light yellow oil.

To an ice-cold solution of the above monoesters (0.37 g, 1.5 mmol) in THF (10 mL) was added 1 M solution of BH₃·THF in THF (2.5 mL, 2.5 mmol) and the mixture was stirred at 0 °C for 24 h. Then EtOH (10 mL) was added dropwise and the mixture was allowed to warm up to ambient temperature. Subsequently it was concentrated under reduced pressure and the residue thus obtained was purified by flash column chromatography (8:2→7:3 hexane-ethyl acetate) to produce, in order of elution:

(a) Alcohol 13b as colourless oil (46.8 mg, 0.20 mmol; 13% yield from 9). ¹H NMR (500 MHz, CDCl₃) δ 4.22–4.08 (m, 2 H, OCH₂CH₃), 3.66–3.60 (m, 1 H, CHHOH), 3.56–3.50 (m, 1 H, CH₂OH), 2.66–2.62 (m, 1 H, CHCO₂Et, exo), 2.41 (dd, J = 10.9, 5.4 Hz 1 H, CHCH₂OH, endo), 2.12–2.05 (br s, 1 H), 1.80–1.71 (m, 2 H), 1.65–1.46 (m, 2 H), 1.56 (s, 3 H), 1.40 (s, 3 H), 1.25 (t, J = 7.1 Hz, 3 H, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 172.5, 85.3, 85.0, 63.6, 60.9, 57.5, 51.2, 38.5, 33.7, 20.9, 17.9, 14.2; HR-ESI-TOF: m/z: 251.1256, [M+Na⁺] for the compound C₁₂H₂₀O₄ requires 251.1259; Optical rotation: [α]²³D +2.12 (c 1.18, acetone), and

(b) Alcohol 13a as colourless oil (271.6 mg, 1.19 mmol; 74% yield from 9). ¹H NMR (500 MHz, CDCl₃) δ 4.21–4.12 (m, 1 H, OCHHCH₃), 4.11–4.05 (m, 1 H, OCHHCH₃), 3.70–3.54 (m, 2 H, CH₂OH), 2.53–2.45 (m, 1 H, CHCH₂OH, exo), 2.37–2.31 (m, 1 H, CHCO₂Et, endo), 2.26–1.94 (br

m, 1 H), 1.89–1.80 (m, 1 H), 1.68–1.58 (m, 2 H), 1.55–1.44 (m, 1 H), 1.48 (d, J = 3.5 Hz, 3 H), 1.37 (d, J = 4.0 Hz, 3 H), 1.24 (dt, J = 7.1, 3.7 Hz, 3 H, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 85.3, 84.9, 62.9, 60.6, 57.0, 54.6, 39.6, 32.1, 20.8, 18.8, 14.2; HR-ESI-TOF: m/z: 251.1256, [M+Na⁺] for the compound C₁₂H₂₀O₄ requires 251.1259; Optical rotation: [α]²³D +31 (c 0.98, acetone). Enantiomeric purity was determined by HPLC analysis (Column: Daicel Chemical Industries, ChiralPak AD; Eluent: n-Hexane/iso-Propanol 9:1; Flow rate: 0.5 mL/min; Detector: UV at 220 nm; τ_major = 17.2 min, τ_minor = 14.3 min,) to be 92%. See Supporting Information Part B for chromatograms.

The above alcohols were assigned the indicated structures based on comparison of the chemical shifts of the protons at C(2) and C(3) for the two isomers (vide supra and related COSY spectra in Supporting Information Part B) and taking into account that the ¹H-NMR signal for H_exo is expected² downfield compared to the corresponding signal for H_endo.

(−)-(((1R,2S,3S,4S)-1,4-Dimethyl-3-(hydroxymethyl)-7-oxa-bicyclo[2.2.1]heptan-2-yl)methoxy)(tert-butyl)dimethylsilane (15).

To a solution of 13a (271.6 mg, 1.19 mmol) in DMF (1.5 mL) were added in sequence imidazole (0.18 g, 2.6 mmol) and TBSCI (0.27 g, 1.8 mmol). The mixture was stirred at ambient temperature for 24 h and then water (15 mL) was added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained (14 contaminated by minor amount of TBSOH as judged by ¹H-NMR) was used without any further purification in the next step.

The above silyl ether was dissolved in THF (5 mL). The solution was cooled at −78 °C and then 1.0 M DIBAL solution in THF (6.0 mL, 6.0 mmol) was slowly introduced. The mixture was stirred at this temperature for 4 h. It was diluted by slow addition of EtOAc (20 mL) and the temperature was allowed to rise to 0 °C over 30 min. Saturated aqueous Rochelle salt (15 mL) was added and the mixture was stirred vigorously for 45 min until the two phases became clear. It was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash column chromatography (9:1 hexane-ethyl acetate) of the residue thus obtained provided alcohol 15 (321.8 mg, 1.07 mmol; 90% yield from 13a). ¹H NMR (500 MHz, CDCl₃) δ 3.62–3.56 (m, 2 H), 3.45 (dd, J = 9.4, 9.2 Hz, 1 H), 3.31 (dd, J = 9.5, 9.2 Hz, 1 H), 3.09–2.80 (br s, 2H), 3.02–2.95 (m, 2 H), 2.57–2.52 (m, 1 H), 2.27 (m, 2 H), 2.23–2.18 (m, 1 H), 2.04–1.99 (m, 1 H), 1.90–1.82 (m, 2 H), 1.78–1.71 (m, 1 H), 1.70–1.63 (m, 1 H), 1.60–1.53 (m, 2 H), 1.47 (d, J = 3.5 Hz, 3 H), 1.36 (d, J = 4.0 Hz, 3 H), 1.25 (dt, J = 7.1, 3.7 Hz, 3 H, CH₂CH₃; ¹³C NMR (125 MHz, CDCl₃) δ 173.5, 85.3, 84.9, 62.9, 60.6, 57.0, 54.6, 39.6, 32.1, 20.8, 18.8, 14.2; HR-ESI-TOF: m/z: 251.1256, [M+Na⁺] for the compound C₁₂H₂₀O₄ requires 251.1259; Optical rotation: [α]²³D +31 (c 0.98, acetone). Enantiomeric purity was determined by HPLC analysis (Column: Daicel Chemical Industries, ChiralPak AD; Eluent: n-Hexane/iso-Propanol 9:1; Flow rate: 0.5 mL/min; Detector: UV at 220 nm; τ_major = 17.2 min, τ_minor = 14.3 min,) to be 92%. See Supporting Information Part B for chromatograms.

The above alcohols were assigned the indicated structures based on comparison of the chemical shifts of the protons at C(2) and C(3) for the two isomers (vide supra and related COSY spectra in Supporting Information Part B) and taking into account that the ¹H-NMR signal for H_exo is expected² downfield compared to the corresponding signal for H_endo.

(−)-(((1R,2S,3S,4S)-1,4-Dimethyl-3-(hydroxymethyl)-7-oxa-bicyclo[2.2.1]heptan-2-yl)methoxy)(tert-butyl)dimethylsilane (15).

To a solution of 13a (271.6 mg, 1.19 mmol) in DMF (1.5 mL) were added in sequence imidazole (0.18 g, 2.6 mmol) and TBSCI (0.27 g, 1.8 mmol). The mixture was stirred at ambient temperature for 24 h and then water (15 mL) was added. The mixture was extracted with Et₂O (3 × 5 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained (14 contaminated by minor amount of TBSOH as judged by ¹H-NMR) was used without any further purification in the next step.

The above silyl ether was dissolved in THF (5 mL). The solution was cooled at −78 °C and then 1.0 M DIBAL solution in THF (6.0 mL, 6.0 mmol) was slowly introduced. The mixture was stirred at this temperature for 4 h. It was diluted by slow addition of EtOAc (20 mL) and the temperature was allowed to rise to 0 °C over 30 min. Saturated aqueous Rochelle salt (15 mL) was added and the mixture was stirred vigorously for 45 min until the two phases became clear. It was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash column chromatography (9:1 hexane-ethyl acetate) of the residue thus obtained provided alcohol 15 (321.8 mg, 1.07 mmol; 90% yield from 13a). ¹H NMR (500 MHz, CDCl₃) δ 3.62–3.56 (m, 2 H), 3.45 (dd, J = 9.4, 9.2 Hz, 1 H), 3.31 (dd, J = 9.5, 9.2 Hz, 1 H), 3.09–2.80 (br s,

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1H), 1.76–1.63 (m, 2 H), 1.60–1.48 (m, 3 H), 1.48–1.39 (m, 1 H), 1.37 (s, 3 H), 1.28 (s, 3 H), 0.83 (s, 9 H), 0.02 (s, 6 H); 13C NMR (125 MHz, CDCl3) δ 84.3, 84.2, 64.1, 63.9, 56.2, 54.0, 39.3, 32.4, 25.8, 20.9, 18.1, 17.9, −5.7; HR-ESI-TOF: m/z: 323.2014, [M+Na]+ for the compound C16H32O3Si requires 323.2018; Optical rotation: [α]23D −7.4 (c 0.07, acetone).

(−)-(((1R,2S,3R,4S)-1,4-Dimethyl-3-((phenylthio)methyl)-7-oxa-bicyclo[2.2.1]heptan-2-yl)methoxy)-(tert-butyl)dimethylsilane (16).

To a solution of alcohol 15 (257.0 mg, 0.855 mmol) and diphenyl disulfide (384 mg, 1.76 mmol) in toluene (5 mL) was added n-Bu₃P (0.40 mL, 1.6 mmol) and the mixture was stirred at ambient temperature for 18 h. It was then charged directly onto a column of silica gel. Elution initially with hexane and then with 5-10% hexane-ethyl acetate provided thioether 16 (320.5 mg, 0.816 mmol; 95%) as an oil. 1H NMR (500 MHz, CDCl3) δ 7.34–7.24 (m, 4 H), 7.19–7.14 (m, 1 H), 3.88 (dd, J = 10.5, 4.9 Hz, 1 H), 3.47 (t, J = 10.0 Hz, 1 H), 3.21 (dd, J = 12.1, 4.8 Hz, 1 H), 2.76 (dd, J = 11.6, 10.8 Hz, 1 H), 2.02–1.94 (m, 1 H), 1.86–1.79 (m, 1 H), 1.68–1.58 (m, 1 H), 1.58–1.44 (m, 3 H), 1.48 (s, 3 H), 1.42 (s, 3 H), 0.90 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H); 13C NMR (125 MHz, CDCl3) δ 137.0, 128.9, 128.6, 125.7, 86.0, 84.5, 64.0, 57.4, 48.9, 39.1, 37.4, 32.2, 25.9, 21.9, 18.6, 18.2, −5.4, −5.5; HR-ESI-TOF: m/z: 415.2111, [M+Na]+ for the compound C22H36O2SSi requires 415.2103; Optical rotation: [α]23D −43.5 (c 1.65, acetone).

(−)-(((1R,2S,3R,4S)-1,3,4-Trimethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl)methanol (18).

Raney® 2800 active catalyst slurry in water (4 mL) was washed sequentially with water (3 × 10 mL) and MeOH (3 × 10 mL). To a suspension of this catalyst in MeOH (2 mL) was added a solution of thioether 16 (316.7 mg, 0.807 mmol) in MeOH (15 mL). The mixture was stirred at ambient temperature for 1 h. It was then passed through a short bed of Celite®. The filtrates were concentrated under reduced pressure to provide an oil that was dissolved in AcOH/THF/H2O (3:1:1, 10 mL) and stirred at ambient temperature for 18 h. The mixture was then poured in water (15 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed sequentially with a saturated aqueous NaHCO3 solution (2 × 10 mL) and brine (10 mL), dried over Na2SO4 and concentrated under reduced pressure. Flash column chromatography (1:1 hexane-ethyl acetate) of the residue thus obtained provided alcohol 18 (122.2 mg, 0.718 mmol; 89% yield from 16) as an amorphous white solid. 1H NMR (500 MHz, CDCl3) δ 3.71 (dd, J = 10.7, 7.1 Hz, 1
H), 3.61 (dd, J = 10.7, 7.9 Hz, 1 H), 1.85–1.77 (m, 1 H), 1.76 (br s, 1 H), 1.65–1.57 (m, 1 H), 1.56–1.46 (m, 3 H), 1.43 (s, 3 H), 1.42–1.35 (m, 1 H), 1.28 (s, 3 H), 0.94 (d, J = 6.9 Hz, 3 H); 13C NMR (125 MHz, CDCl3) δ 84.8, 84.7, 64.2, 60.1, 46.0, 39.0, 32.2, 21.5, 18.7, 17.9; Spectral data are in agreement with the ones reported in the literature.3 MS (ESI+): m/z: 153.08, [M-H2O+H]+ for the compound C10H18O2 requires 153.13; Optical rotation: [α]23D –2.3 (c 2.78, acetone).

(−)(1R,2R,3R,4S)-2-(Iodomethyl)-1,3,4-trimethyl-7-oxa-bicyclo[2.2.1]heptane (19).

Triphenyl phosphine (477 mg, 1.82 mmol) and imidazole (302 mg, 4.44 mmol) were dissolved in dichloromethane (5 mL). To this vigorously stirred solution iodine (427 mg, 1.68 mmol) was added in one portion at 0 °C and the mixture was allowed to gradually warm up to ambient temperature over 40 min. It was then re-cooled to 0 °C and a solution of alcohol 18 (86.6 mg, 0.509 mmol) in dichloromethane (2 mL) was added dropwise. Upon completion of the addition, the mixture was allowed to gradually warm up to ambient temperature and then it was heated at 40 °C for 6 h. At ambient temperature, silica gel was added and solvents were cautiously removed under reduced pressure. The free flowing solid thus obtained was loaded as a slurry in hexane onto a pre-packed silica gel column in the same solvent. Elution with hexane (until excess triphenylphosphine was removed) and then with 5% EtOAc in hexane provided iodide 19 (131.1 mg, 0.468 mmol; 92% yield) as a white solid. 1H NMR (500 MHz, CDCl3) δ 3.15 (dd, J = 13.6, 9.7 Hz, 1 H), 3.13 (dd, J = 17.5, 9.7 Hz, 1 H), 1.85–1.76 (m, 2 H), 1.64 (ddd, J = 12.4, 12.4, 4.1 Hz, 1 H), 1.59–1.53 (m, 1 H), 1.51–1.39 (m, 2 H), 1.41 (s, 3 H), 1.27 (s, 3 H), 1.03 (d, J = 6.9 Hz, 3 H); 13C NMR (125 MHz, CDCl3) δ 85.7, 84.9, 60.1, 50.4, 38.5, 31.6, 20.7, 18.5, 18.1, 5.9; Spectral data are in agreement with the ones reported in the literature.2a Optical rotation: [α]23D –42.5 (c 3.12, acetone).

Alkyl–Alkyl Cross-Coupling Studies.

(1S,2R,3R,4R)-1,2,4-Trimethyl-3-((S)-4-methylcyclohex-3-enyl)butyl)-7-oxa-bicyclo[2.2.1]-heptane (21)

A stirred 0.5 M solution of 9-BBN in THF (3.0 mL, 1.5 mmol) was cooled to 0 °C and (S)-limonene (0.2 mL, 1.2 mmol) was added dropwise. The mixture was stirred at 0 °C and at ambient temperature for 3 h to provide borane 20, which was used directly in the coupling reactions.

In a separate flask were added racemic iodide\(^4\) 19 (20.8 mg, 74.2 µmol), palladium acetate (6.6 mg, 29 µmol), tricyclohexyl phosphine (18.8 mg, 67 µmol) and potassium phosphate monohydrate (77 mg, 334 µmol). Air in the flask was evacuated and argon was introduced. THF (1.5 mL) was added and the mixture was stirred for 15 min at 0 °C while argon was bubbled through it. Then 0.2 mL of the above borane 20 solution were added dropwise. After stirring for 1 h at 0 °C, the yellow mixture was allowed to warm up to ambient temperature and stirring was continued for additional 12 h. The orange-brown mixture thus obtained was poured in water (5 mL). Extraction with EtOAc (3 × 5 mL) and concentration of the combined organic phases under reduced pressure provided a deep brown residue which upon flash column chromatography (hexane–2% EtOAc in hexane) furnished coupling product 21 (4.7 mg, 25 µmol; 22% yield) as a mixture of diastereomers. Unreacted iodide 19 (5.9 mg, 21 µmol; 28% yield) was also recovered. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.39 (s, 1 H), 2.05–1.47 (m, 8 H), 1.64 (s, 3 H), 1.47–1.09 (m, 10 H), 1.36 (s, 3 H), 1.28 (s, 3 H), a series of signals at 0.92 (d, \(J = 6.9\) Hz), 0.89 (d, \(J = 6.9\) Hz), 0.86 (d, \(J = 7.1\) Hz) and 0.85 (d, \(J = 7.0\) Hz) integrating for 6 H; MS (ESI+): \(m/z\): 291.25 ([M+H\(^+\)]).

**Preparation of the fully functionalized C(1)–C(8) segment (30).**

**Methyl 2-((S)-4-methylcyclohex-3-enyl)propanoate (25)** was prepared according to the literature procedure.\(^5\)

**Methyl 2-((S)-4-oxa-bicyclo[3.2.0]heptan-3-yl)propanoate (26)**

\[\begin{align*}
\text{25} & \xrightarrow{\text{m-CPBA, Na\textsubscript{2}HPO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C, 30 min}} \text{26}
\end{align*}\]

To a stirred, ice cold solution of ester 25 (6.9 g, 38 mmol) in dichloromethane (300 mL) were added sequentially Na\textsubscript{2}HPO\textsubscript{4} (16 g, 114 mmol) and m-CPBA (9.8 g, 57 mmol). The mixture was stirred at 0 °C for 30 min. Then the reaction was stopped by addition of 0.3 M aqueous solution of Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} (200 mL) and extracted with dichloromethane (3 × 50 mL). The combined organic phases were washed sequentially with a saturated aqueous NaHCO\textsubscript{3} solution (3 × 100 mL) and brine (100 mL), dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Flash column chromatography (8:2 hexane-ethyl acetate) of the residue thus obtained provided a mixture of

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epoxides 26 (6.5 g, 33 mmol; 86% yield) as an oil. ¹H NMR (500 MHz, CDCl₃) δ 3.59 (br s, 3 H), a series of signals at 2.93 (br d, J = 6 Hz), 2.89 (d, J = 5.3 Hz) and 2.87 (d, J = 5.2 Hz) integrating for 1 H, 2.25–1.28 (m, 7 H), 1.23 (br s, 3 H), 1.21–0.88 (m, 4 H); ¹³C NMR (125 MHz, CDCl₃) δ 176.2, 176.1, 176.0, 60.1, 60.0, 58.8, 58.7, 57.4, 57.3, 57.1, 57.0, 51.2, 51.1, 44.5, 44.1, 43.9, 43.5, 35.8, 35.5, 32.3, 32.2, 30.3, 29.4, 28.9, 28.7, 28.6, 28.3, 27.3, 25.5, 24.2, 24.1, 24.0, 23.7, 22.8, 21.9, 14.0, 14.0, 13.8, 13.5; HR-ESI-TOF: m/z: 415.2149, [M+Na⁺] for the compound C₁₁H₁₈O₃ requires 221.1154.

(3R,3aR,7aS)-3,3a,4,5-Tetrahydro-3,6-dimethylbenzofuran-2(7aH)-one, (3R,3aR,7aS)-“Wine lactone” (28a) and (3S,3aR,7aS)-3,3a,4,5-tetrahydro-3,6-dimethylbenzofuran-2(7aH)-one, (3S,3aR,7aS)-“Wine lactone” (28b)

To diphenyldiselenide (5.9 g, 19 mmol) was added dry and degassed MeOH (120 mL). To this stirred mixture at ambient temperature was added NaBH₄ (1.5 g, 40 mmol) in small portions. Upon disappearance of the initial yellow color, a solution of epoxides 26 (6.3 g, 32 mmol) in dry and degassed MeOH (20 mL) was added dropwise. The mixture was stirred at ambient temperature for 30 min and then heated to reflux for additional 2.5 h. At ambient temperature, the reaction was carefully quenched with 1 M aqueous HCl (100 mL) and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed sequentially with a saturated aqueous NaHCO₃ solution (100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue thus obtained was dissolved in hexane-ethyl acetate (7:3) and passed through a short bed of silica gel eluting with the same solvent system. Concentration in vacuo provided as oil a mixture of selenoethers (10.7 g) that was used in the next step without any further purification.

To a stirred ice cold solution of the above oil in THF (250 mL) was added dropwise 30% H₂O₂ (35 mL, 309 mmol). Upon completion of the addition, the mixture was allowed to gradually warm up to ambient temperature over 2 h. Then it was heated to reflux for 10 h. At ambient temperature, water (500 mL) was added and the mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed sequentially with a saturated aqueous NaHCO₃ solution (3 × 100 mL) and brine (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. Flash column chromatography (9:1 hexane-ethyl acetate) of the residue thus obtained provided (+)-(3R,3aR,7aS)-“wine lactone” (28a) and (–)-(3S,3aR,7aS)-“wine lactone” (28b).

(+)-(3R,3aR,7aS)-“Wine lactone” (28a): 1.2 g, 7.2 mmol (23% yield from 26); colourless oil that solidifies on standing; ¹H NMR (500 MHz, CDCl₃) δ 5.48 (br s, 1 H), 4.89–4.84 (m, 1 H), 2.43–2.34
(m, 1 H), 2.28–2.19 (m, 1 H), 1.85–1.76 (m, 1 H), 1.75–1.65 (obs m, 1 H), 1.71 (s, 3 H), 1.23 (d, J = 7.2 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.6, 140.7, 118.7, 75.3, 40.3, 37.5, 25.9, 23.6, 22.2, 13.9; Spectral data are in agreement with the ones reported in the literature.$^{5,6}$ HR-ESI-TOF: $m/z$: 189.0885, [M+Na$^+$] for the compound C$_{10}$H$_{14}$O$_2$ requires 189.0891; Optical rotation: $[\alpha]_{23}^{20}$ +12.5 (c 1.07, acetone).

(–)Y(3$^S$,3a$^R$,7a$^S$)Y“Wine lactone” (28b): 1.1 g, 6.6 mmol (22% yield from 26); amorphous white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.65 (br s, 1 H), 4.64–4.58 (m, 1 H), 2.92–2.83 (m, 1 H), 2.38–2.28 (m, 1 H), 2.05–1.91 (m, 2 H), 1.77 (s, 3 H), 1.71–1.63 (m, 1 H), 1.24–1.10 (obs m, 1 H), 1.18 (d, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 179.2, 144.4, 117.4, 75.1, 40.6, 38.2, 29.3, 24.1, 20.1, 9.7; Spectral data are in agreement with the ones reported in the literature.$^5$ HR-ESI-TOF: $m/z$: 189.0883, [M+Na$^+$] for the compound C$_{10}$H$_{14}$O$_2$ requires 189.0891; Optical rotation: $[\alpha]_{23}^{20}$ –50.6 (c 0.68, acetone).

(–)-(1$^S$,6$^R$)-6-((R)-1-hydroxypropan-2-yl)-3-methylcyclohex-2-enol (SI-1)

This diol (SI-1; 737.1 mg, 4.3 mmol) was obtained as a white solid in 85% yield applying the literature procedure$^7$ on (+)-28a (846.7 mg, 5.1 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 5.68 (br s, 1 H), 4.28 (br s, 1 H), 3.65 (dd, $J$ = 10.6, 3.1 Hz, 1 H), 3.57 (dd, $J$ = 10.6, 6.4 Hz, 1 H), 3.35–2.80 (br s, 2 H), 1.92–1.72 (m, 3 H), 1.70–1.59 (obs m, 1 H), 1.66 (s, 3 H), 1.53–1.45 (m, 1 H), 1.23–1.15 (m, 1 H), 1.01 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (125 MHz, C$_6$D$_6$) $\delta$ 124.3, 66.0, 64.7, 44.5, 37.5, 31.7, 23.4, 22.0, 16.1; HR-ESI-TOF: $m/z$: 193.1200, [M+Na$^+$] for the compound C$_{10}$H$_{18}$O$_2$ requires 193.1204; Optical rotation: $[\alpha]_{23}^{20}$ –167 (c 1.82, acetone).

(–)-(R)-2-((1$^R$,2$^S$)-2-Hydroxy-4-methylcyclohex-3-enyl)propyl 2,2-dimethyl propanoate (SI-2)

1.0 g (3.9 mmol, 91% yield) of SI-2 was obtained as a clear oil that solidifies upon storage at $–20$ °C applying the literature procedure$^7$ on (–)-(1$^S$,6$^R$)-6-((R)-1-hydroxypropan-2-yl)-3-methylcyclohex-2-enol (737.1 mg, 4.3 mmol). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.59 (br d, $J$ = 3.4 Hz, 1 H), 4.22 (dd, $J$ = 10.9, 3.9 Hz, 1 H), 4.09 (br s, 1 H), 3.99 (dd, $J$ = 10.9, 6.4 Hz, 1 H), 2.04–1.85 (m, 3 H), 1.72–1.62 (obs m, 2 H), 1.68 (s, 3 H), 1.42 (dddd, $J$ = 12.9, 12.8, 12.8, 5.9 Hz, 1 H), 1.32–1.21 (m, 1 H), 1.18 (s, 9 H), 1.02 (d, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 178.7,

139.5, 123.3, 67.8, 64.8, 41.7, 38.8, 33.5, 31.2, 27.2, 23.3, 20.4, 15.6; Spectral data are in agreement with the ones reported in the literature for (±)-(R)-2-((1R,2S)-2-hydroxy-4-methylcyclohex-3-enyl)propyl 2,2-dimethyl propanoate.⁷ HR-ESI-TOF: m/z: 277.1776, [M+Na⁺] for the compound C₁₅H₂₆O₃ requires 277.1780; Optical rotation: [α]²³D −12.4 (c 1.04, acetone).

(−)-(R)-2-[(1R,2S)-2-[(1,1-Dimethylethyl)dimethylsilyloyl]-4-methylcyclohex-3-enyl]propyl 2,2-dimethyl propanoate (SI-3)

1.0174 g (2.76 mmol, 94% yield) of SI-3 was obtained as a clear oil applying the literature procedure⁷ on (−)-(R)-2-((1R,2S)-2-hydroxy-4-methylcyclohex-3-enyl)propyl 2,2-dimethyl propanoate (747.0 mg, 2.94 mmol). ¹H NMR (500 MHz, CDCl₃) δ 5.48 (m, 1 H), 4.11 (dd, J = 10.6, 3.7 Hz, 1 H), 4.10 (obs m, 1 H), 3.99 (dd, J = 10.6, 6.8 Hz, 1 H), 2.02–1.85 (m, 3 H), 1.66 (s, 3 H), 1.63–1.49 (m, 2 H), 1.28–1.23 (m, 1 H), 1.19 (s, 9 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.85 (s, 9 H), 0.06 (s, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 179.1, 138.4, 124.4, 68.1, 66.3, 42.2, 39.3, 33.7, 31.7, 27.6, 26.3, 23.7, 20.6, 18.6, 15.7, −2.7, −4.1; Spectral data are in agreement with the ones reported in the literature for (±)-(R)-2-[(1R,2S)-2-[(1,1-dimethylethyl)dimethylsilyloyl]-4-methylcyclohex-3-enyl]propyl 2,2-dimethyl propanoate.⁷ HR-ESI-TOF: m/z: 391.2641, [M+Na⁺] for the compound C₂₁H₄₀O₃Si requires 391.2644; Optical rotation: [α]²³D −108 (c 0.97, acetone).

(−)-(R)-2-[(1R,2S)-2-[(1,1-Dimethylethyl)dimethylsilyloyl]-4-methylcyclohex-3-enyl]propan-1-ol (29)

385.4 mg (1.35 mmol, 92% yield) of alcohol 29 was obtained as a clear oil applying the literature procedure⁷ on (−)-(R)-2-((1R,2S)-2-hydroxy-4-methylcyclohex-3-enyl)propyl 2,2-dimethyl propanoate (542.7 mg, 1.47 mmol). ¹H NMR (500 MHz, C₆D₆) δ 5.54–5.48 (m, 1 H), 4.24–4.18 (m, 1 H), 3.54–3.47 (m, 2 H), 1.84–1.59 (m, 4 H), 1.53 (s, 3 H), 1.50–1.43 (m, 1 H), 1.34–1.25 (m, 1 H), 1.17 (br s, 1 H), 0.99 (obs d, 3 H), 0.98 (s, 9 H), 0.11 (s, 3 H), 0.10 (s, 3H); ¹³C NMR (125 MHz, C₆D₆) δ 138.1, 124.7, 67.2, 66.2, 42.1, 36.5, 31.4, 26.2, 23.3, 20.7, 18.5, 15.3, −2.9, −4.2; HR-ESI-TOF: m/z: 307.2062, [M+Na⁺] for the compound C₁₆H₃₂O₂Si requires 307.2069; Optical rotation: [α]²³D −146 (c 0.16, acetone).

(−)-(R)-2-[(1R,2S)-2-[(1,1-Dimethylethyl)dimethylsilyloyl]-4-methylcyclohex-3-enyl]propanal (30)
248.6 mg (0.88 mmol, 85% yield) of aldehyde 30 was obtained as a clear oil applying the literature procedure\(^7\) on (−)-29 (293.0 mg, 1.03 mmol). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 9.75 (d, \(J = 2.1\) Hz, 1 H), 5.43–5.38 (m, 1 H), 4.26–4.22 (m, 1 H), 2.49 (dqd, \(J = 7.1, 7.1, 1.9\) Hz, 1 H), 2.01–1.88 (m, 2 H), 1.87–1.75 (m, 2 H), 1.67 (s, 3 H), 1.63–1.57 (m, 1 H), 1.09 (d, \(J = 7.1\) Hz, 3 H), 0.86 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 204.9, 137.4, 124.1, 66.9, 46.4, 42.0, 29.8, 26.0, 23.2, 21.5, 18.2, 12.2, −3.7, −4.3; Spectral data are in agreement with the ones reported in the literature for (±)-30.\(^7\) HR-ESI-TOF-MS: \(m/z\): 305.1906, [M+Na\(^+\)] for the compound \(C_{16}H_{30}O_2Si\) requires 305.1913; Optical rotation: \([\alpha]\)\(^{23}\)D −101 (c 0.50, acetone).

**Construction of the fully functionalized carbon skeleton and synthesis completion.**

\((1S,6R)-1\)-[(1,1-Dimethylethyl)dimethylsilyloxy]-3-methyl-6-((2R)-3-hydroxy-4-((1R,2R,3R,4S)-1,3,4-trimethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl)butan-2-yl]-cyclohex-2-ene (31)

To a stirred solution of iodide 19 (240.0 mg, 0.857 mmol) in pentane:diethyl ether (3:4, 70 mL) at −78 °C was added a solution of \(t\)-butyl lithium (1.6 M in pentane, 1.2 mL, 1.9 mmol). The mixture was stirred for 30 min at this temperature and diethyl ether (20 mL) was slowly added. To this mixture and at −100 °C was slowly cannulated a solution of aldehyde 30 (122.0 mg, 0.432 mmol) in diethyl ether (20 mL). The mixture was stirred for 45 min at −100 °C and then methanol (1 mL) was added. The mixture was allowed to warm to ambient temperature before the addition of saturated aqueous NaHCO\(_3\) solution (100 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Flash column chromatography (9:1 to 7:3 hexane-ethyl acetate) of the residue thus obtained provided the starting aldehyde 30 (54.9 mg, 0.194 mmol, 45%) followed by alcohols 31 (56.6 mg, 0.130 mmol, 30% yield). A small fraction of the mixture of alcohols was subjected to a second flash column chromatography (9:1 hexane-ethyl acetate) to afford pure alcohols 31a and 31b for spectroscopic characterization.

31a: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.54–5.50 (m, 1 H), 4.31–4.27 (m, 1 H), 3.90–3.84 (m, 1 H), 2.64–2.54 (br s, 1 H), 2.05–1.89 (m, 2 H), 1.89–1.77 (m, 1 H), 1.76–1.60 (m, 3 H), 1.66 (s, 3 H), 1.60–1.35 (m, 7 H), 1.35 (s, 3 H), 1.28 (s, 3 H), 1.29–1.21 (m, 1 H), 0.95 (d, \(J = 6.7\) Hz, 3 H), 0.93 (d, \(J = 7.1\) Hz, 3 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 138.4, 124.2, 85.8, 84.9, 70.9, 66.7, 56.3, 48.7, 43.1, 39.0, 39.1, 38.9, 37.5, 32.2, 31.3, 26.1, 23.3, 21.4, 20.5, 18.7, 18.2, 10.6, −3.2, −3.9; HR-ESI-TOF-MS: \(m/z\): 459.3264, [M+Na\(^+\)] for the compound \(C_{26}H_{48}O_3Si\) requires 459.3270.
31b: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.52–5.46 (m, 1 H), 4.10–4.04 (m, 1 H), 3.86 (br d, $J = 9.1$ Hz, 1 H), 2.02–1.86 (m, 2 H), 1.84–1.74 (m, 2 H), 1.67 (s, 3 H), 1.66–1.52 (m, 4 H), 1.52–1.15 (m, 7 H), 1.37 (s, 3 H), 1.29 (s, 3 H), 0.98 (d, $J = 6.9$ Hz, 3 H), 0.92 (d, $J = 7.0$ Hz, 3 H), 0.87 (s, 9 H), 0.07 (s, 3 H), 0.04 (s, 3 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 138.4, 124.1, 85.7, 84.8, 71.2, 66.5, 53.7, 48.6, 42.2, 40.3, 39.1, 33.8, 32.3, 31.4, 26.0, 23.4, 20.9, 20.2, 19.5, 18.1, 11.9, –3.2, –4.5; HR-ESI-TOF-MS: m/z: 459.3264, [M+Na$^+$] for the compound C$_{26}$H$_{48}$O$_3$Si requires 459.3270.

((1S,6R)-1-[(1,1-Dimethylethyl)dimethylsilyloxy]-3-methyl-6-((2S)-4-((1R,2R,3R,4S)-1,3,4-trimethyl-7-oxa-bicyclo[2.2.1]heptan-2-yl)butan-2-yl)cyclohex-2-ene (34)

The mixture of alcohols 31 (15.1 mg, 34.5 µmol) was dissolved in THF (0.5 mL) and 1.0 M solution of NaHMDS in THF (0.35 mL, 0.35 mmol) was added at –78 °C. The mixture was stirred at this temperature for 30 min and then CS$_2$ (0.42 mL, 7.0 mmol) was added. The mixture was allowed to slowly (1.5 h) warm up to –20 °C and Mel (50 µL, 0.8 mmol) was added. After 15 min, the mixture was poured into saturated aqueous NaHCO$_3$ (5 mL) and extracted with Et$_2$O (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Flash column chromatography (100% hexane to 7:3 hexane-ethyl acetate) of the residue thus obtained provided a mixture of xanthates 32 as light yellow oil that was used without further purification in the next step.

To a stirred solution of the xanthates mixture 32 obtained above in toluene (2 mL) at ambient temperature were added sequentially tributyltin hydride (0.1 mL, 0.4 mmol) and 1.0 M solution of Et$_3$B in hexane (0.02 mL, 0.02 mmol). The mixture was stirred for 1 h and was then diluted with Et$_2$O (10 mL). The mixture was poured in a 10% aqueous solution of NaOH (10 mL) and extracted with Et$_2$O (2 × 10 mL). The combined organic phases were washed sequentially with water (2 × 10 mL) and brine (10 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Flash column chromatography (100% hexane to 95:5 hexane-ethyl acetate) of the residue thus obtained provided an inseparable 2:1 mixture of reduced product 34 and a by-product that was tentatively assigned the structure 33 (11.6 mg, 27.6 mmol; 80% yield from 31) as an oil. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.49 (br d, $J = 3.4$ Hz, 2 H), 4.16–4.12 (m, 2 H), 3.59–3.57 (m, 1 H), 2.14–2.04 (m, 1 H), 2.01–1.80 (m, 7 H), 1.78–1.69 (m, 2 H), 1.66 (s, 6 H), 1.64–1.46 (m, 15 H), 1.46–1.12 (m, 24 H), 1.36 (s, 3 H), 1.34 (s, 6 H), 1.29 (s, 3 H), 1.28 (s, 6 H), 1.08 (d, $J = 6.9$ Hz, 3 H), 1.02 (d, $J = 7.3$ Hz, 3 H), 0.94 (d, $J = 6.9$ Hz, 3 H), 0.92 (d, $J = 6.7$ Hz, 6 H), 0.91 (d, $J = 5.7$ Hz, 6 H), 0.87 (s, 9 H), 0.86 (s, 18 H), 0.05 (s, 6 H), 0.03 (s, 3 H), 0.03 (s, 6 H), 0.02 (s, 3 H).
(−)-Laurenditerpenol (1)

At ambient temperature, 1.0 M solution of TBAF in THF (1 mL, 1 mmol) was added to the mixture of 33 and 34 (8.2 mg, 19.5 μmol). The flask was sealed and the solution was stirred at 40 °C for 16 h. At ambient temperature it was then diluted with CH₂Cl₂ (5 mL) and silica gel was added. Solvents were removed under reduced pressure and the solid thus obtained was loaded on top of a silica gel column packed with 10% ethyl acetate in hexane. Elution with 10% to 30% ethyl acetate in hexane provided a mixture of 1 and 35 (4.6 mg, 15.0 μmol; 77% yield). Repeated, careful purification of this mixture by flash column chromatography (2% i-PrOH in hexane) provided (−)-laurenditerpenol (1) (1.5 mg), alcohol 35 (1.7 mg) and their non-separated mixture (1.4 mg).

(−)-1: ¹H NMR (500 MHz, CDCl₃) δ 5.64 (d, J = 4.1 Hz, 1 H), 4.12 (br s, 1 H), 2.06–1.91 (m, 2 H), 1.86 (ddd, J = 12.4, 9.1, 3.9 Hz, 1 H), 1.70 (s, 3 H), 1.65–1.49 (m, 6 H), 1.45–1.10 (m, 7 H), 1.36 (s, 3 H), 1.28 (s, 3 H), 1.02 (br d, 1 H), 0.95 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.9 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 139.8, 123.8, 85.8, 84.7, 65.3, 58.3, 48.9, 44.2, 39.1, 33.5, 33.3, 32.2, 31.6, 29.1, 23.4, 20.7, 20.5, 19.3, 18.1, 17.2; HR-ESI-TOF-MS: m/z: 289.2526, [M–H₂O+H⁺] for the compound C₂₀H₃₄O₂ requires 289.2531; Optical rotation: [α]D²³ −86.7 (c 0.15, CHCl₃). Spectral data and optical rotation are in agreement with the ones reported in the literature for (−)-laurenditerpenol.⁸

35: ¹H NMR (500 MHz, CDCl₃) δ 4.73 (s, 1 H), 2.12–2.03 (m, 1 H), 2.01–1.94 (m, 1 H), 1.94–1.85 (m, 1 H), 1.84–1.68 (m, 2 H), 1.68–1.15 (m, 13 H), 1.37 (s, 3 H), 1.29 (s, 3 H), 1.12 (d, J = 6.9 Hz, 3 H), 1.05 (d, J = 7.2 Hz, 3 H), 0.97 (d, J = 6.9 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 85.5, 56.2, 50.8, 49.3, 48.8, 48.5, 42.5, 39.6, 37.5, 32.7, 31.4, 27.3, 22.8, 22.1, 21.1, 20.0, 18.6; HR-ESI-TOF-MS: m/z: 307.2629, [M+H⁺] for the compound C₂₀H₃₄O₂ requires 307.2637.