Toward the Total Synthesis of Divergolides C and D

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Supporting Information

Contents

General Experimental Section ................................................................................................................................. 2
Experimental Procedures ........................................................................................................................................ 3
Single-Crystal X-Ray Analysis ............................................................................................................................. 19
$^1$H and $^{13}$C NMR Spectra .................................................................................................................................. 25
Literature ............................................................................................................................................................... 46
General Experimental Section

All reactions were performed under an atmosphere of argon and in oven-dried glassware (200 °C oven temperature) unless specified otherwise. Tetrahydrofuran (THF) was distilled prior to use from sodium and benzophenone, triethylamine (NEt$_3$) and N,N-Diisopropylethylamine (DIPEA) from calcium hydride. N,N-dimethylformamide (DMF), dichloromethane (CH$_2$Cl$_2$), chloroform (CHCl$_3$), toluene, benzene, and methanol (MeOH) were purchased from Acros Organics as 'extra dry' reagents under inert gas atmosphere and over molecular sieves. All other reagents were purchased from commercial sources and were used without further purification. Hexanes refers to fractions of isohexanes, which boil between 40 and 80 °C.

Analytical thin-layer chromatography (TLC) was carried out using pre-coated glass plates (silica gel 60 F$_{254}$) from Merck, and visualized by exposure to ultraviolet light (UV, 254 nm) and by staining with aqueous acidic ceric ammonium molybdate(IV) (CAM) solution. Flash column chromatography was performed using Merck silica gel 60 (40–63 µm particle size).

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian 300, Varian 400, Inova 400 or Varian 600 spectrometer. Chemical shifts (δ scale) are expressed in parts per million (ppm) and are calibrated using residual protic solvent as an internal reference (CHCl$_3$: δ = 7.26 ppm, DMSO-d$_6$: δ = 2.50 ppm, CHDCl$_2$: δ = 5.32 ppm). Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constants (Hz), integration). Couplings are expressed as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, or combinations thereof. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were recorded on the same spectrometers at 75, 100 and 150 Hz, respectively. Carbon chemical shifts (δ scale) are also expressed in parts per million (ppm) and are referenced to the central carbon resonances of the solvents (CDCl$_3$: δ = 77.16 ppm, DMSO-d$_6$: δ = 39.52 ppm, CD$_2$Cl$_2$: δ = 53.84 ppm). In order to assign the $^1$H and $^{13}$C NMR spectra, a range of 2D NMR experiments (COSY, HSQC, HMBC, NOESY) were used as appropriate.

Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum BX II (FTIR System) equipped with an attenuated total reflection (ATR) measuring unit. IR data is reported in frequency of absorption (cm$^{-1}$).

Mass spectrometry (MS) experiments were performed on a Thermo Finnigan MAT 95 (electron ionization, EI) or on a Thermo Finnigan LTQ FT (electrospray ionization, ESI) instrument.

Melting points (mp) were measured on a Büchi Melting Point B-540 or SRS MPA120 EZ-Melt apparatus and are uncorrected.

Optical rotations were measured at the given temperature (T in [°C]) on a Perkin-Elmer 241 or Krüss P8000-T polarimeter using a sodium lamp (λ = 589 nm, D-line). Measurements were carried out in a cell with a path length (l) of 0.5 dm. Concentrations (c) are expressed in g/(100 mL). Specific rotations ([α]$_D^0$) were calculated using the equation [α]$_D^0$ = 100·α/(c·l) and are reported in 10$^{-1}$ deg cm$^2$ g$^{-1}$.

High performance liquid chromatography (HPLC) was performed with HPLC grade solvents and deionized water that was purified on a TKA MicroPure water purification system. All solvents were degassed with helium gas prior to use. Unless noticed otherwise, all experiments were carried out at room temperature; the column used is specified as appropriate. Analytical HPLC spectra were recorded on an ultra high performance liquid
chromatography (UHPLC) system from the Agilent 1260 Infinity series (1260 degasser, 1260 Binary Pump VL, 1260 ALS auto sampler, 1260 TCC thermostatted column compartment, 1260 DAD diode array detector), which was computer-controlled through Agilent ChemStation software. Preparative HPLC was performed on a computer-operated Varian system (Galaxie Chromatography Software, two PrepStar pumps Model SD-1, manual injection, ProStar 335 Photo Diode Array Detector, 380-LC Evaporative Light Scattering Detector).

**Experimental Procedures**

**Preparation of alcohol 12**

(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-ol (12). To a magnetically stirred solution of methoxymethyl allyl ether 10 ([S2] (9.00 g, 88.1 mmol) in dry THF (36 mL) was added slowly sec-BuLi solution (1.4 M in cyclohexane, 62.9 mL, 88.1 mmol) at −78 °C. After the resulting orange-yellow mixture was stirred at −78 °C for 1 h, a solution of (+)-B-methoxydiisopinocamphenylborane (23.2 g, 73.4 mmol) in dry THF (73 mL) was added via cannula. Then, the mixture was stirred at −78 °C for an additional 1 h and subsequently, boron trifluoride etherate (13.6 g, 95.5 mmol, 12.1 mL) followed by 3-methylcrotonaldehyde (11) (6.17 g, 73.4 mmol, 7.10 mL) were added dropwise. The mixture was slowly warmed to room temperature over the time course of 12 h, before aqueous saturated NaHCO₃ solution (160 mL) and aqueous H₂O₂ solution (30 wt%, 100 mL) were added at 0 °C and the reaction was stirred for an additional 30 min at room temperature. After addition of Et₂O (160 mL), the layers were separated and the aqueous phase was extracted with Et₂O (2 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuo. Thus obtained crude material was subjected to flash column chromatography (EtOAc/hexanes 1:10 → 1:7 → 1:3 → 1:1, gradient elution) providing 9.31 g (50.0 mmol, 68%, er = 92:8) of alcohol 12 as a colorless oil.

The enantiomeric ratio (er) was determined by chiral HPLC analysis (Nucleocel DELTA S, 250 x 4.6 mm, isocratic elution, hexanes (A)/i-propanol (B), 95% A, flow rate: 1 mL/min, detection at 210 nm, tᵣ(12) = 5.65 min, tᵣ(ent-12) = 6.48 min).

Rᵣ = 0.31 (EtOAc/hexanes 1:3).

[α]D²¹ = +102.4 (c = 1.3, CHCl₃).

¹H NMR (300 MHz, CDCl₃): δ = 5.66 (ddd, J = 17.6, 10.3, 7.3 Hz, 1H), 5.32–5.27 (m, 1H), 5.26–5.24 (m, 1H), 5.18–5.15 (m, 1H), 4.75 (d, J = 6.6 Hz, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.31–4.25 (m, 1H), 3.90 (dd, J = 7.4, 7.3 Hz, 1H), 3.41 (s, 3H), 2.62 (d, J = 2.7 Hz, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.69 (d, J = 1.3 Hz, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 138.1, 134.6, 123.1, 119.3, 94.6, 81.7, 70.8, 55.9, 26.1, 18.9 ppm.
IR (ATR): $\bar{\nu} = 3432, 2912, 1677, 1443, 1376, 1257, 1214, 1150, 1098, 1030, 920 \text{ cm}^{-1}$.


**Preparation of acid 14**

(E)-5-Hydroxy-2-methylpent-2-enoic acid (14). A solution of ethyl ester 13$_{[^{[53]}]}$ (1.47 g, 9.29 mmol) and KOH (1.09 g, 19.5 mmol) in methanol/water (1:1, 88 mL) was stirred at 80 °C for 3 h. After being cooled to room temperature, the mixture was washed with EtOAc (2 x 100 mL) and the organic phase was discarded. The aqueous phase was acidified with aqueous HCl solution (1 M) to pH = 1 and extracted with EtOAc (4 x 150 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo providing 1.19 g (9.14 mmol, 98%) of acid 14 as a white solid.

$R_f = 0.10$ (EtOAc/hexanes 1:1).

mp: 55–57 °C.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 6.92$ (tq, $J = 7.4, 1.4$ Hz, 1H), 3.78 (t, $J = 6.4$ Hz, 2H), 2.49 (td, $J = 7.3, 0.8$ Hz, 2H), 1.87–1.86 (m, 3H) ppm.

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 172.9, 140.8, 129.6, 61.4, 32.4, 12.4$ ppm.

IR (ATR): $\bar{\nu} = 3450, 2953, 2632, 1680, 1375, 1241, 1139, 1041 \text{ cm}^{-1}$.

HRMS (EI): calculated for $\text{C}_{6}\text{H}_{10}\text{O}_{3}^+ [M]^+$ 130.0624, found 130.0625.

**Preparation of TBS ether 16**

(E)-5-(((Tert-butyldimethylsilyl)oxy)-2-methylpent-2-enoic acid (16). To a magnetically stirred solution of hydroxyacid 14 (3.23 g, 24.7 mmol) and 2,6-lutidine (7.42 g, 69.3 mmol, 8.07 mL) in dry CH$_2$Cl$_2$ (320 mL) was added dropwise tert-butyldimethylsilyl triflate (15.7 g, 59.4 mmol, 13.7 mL) at 0 °C. The reaction was stirred for 10 min and then warmed to room temperature. Stirring was continued for an additional 10 min. After addition of EtOAc (600 mL), the organic phase was washed with aqueous HCl solution (1 M, 400 mL) and brine (300 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. Thus obtained crude TBS ester 15 was dissolved in MeOH (100 mL) and after being cooled to 0 °C, potassium carbonate (3.76 g, 27.2 mmol) was added in one portion. Then, the mixture was stirred at 0 °C for 10 min, warmed to room temperature, and stirring was continued for an additional 1 h. After addition of EtOAc, the mixture was washed with aqueous HCl solution
(1 M, 300 mL) and brine (300 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated in vacuo providing 6.02 g (24.7 mmol, quant.) of acid 16 as colorless oil.

\[(E)\text{-Tert-butyl(dimethyl)silyl 5-([(\text{tert-butyl(dimethyl)silyl})oxy]-2-methylpent-2-enoate (15).}\]

Colorless oil.

\[R_f = 0.90\text{ (EtOAc/hexanes 1:1).} \]

\[^1H\text{ NMR (300 MHz, CDCl}_3\text{: } \delta = 6.82 \text{ (tq, } J = 7.4, 1.4 \text{ Hz, 1H)}, 3.70 \text{ (t, } J = 6.5 \text{ Hz, 2H), 2.43–2.36 \text{ (m, 2H), 1.83 (d, } J = 1.3 \text{ Hz, 3H), 0.95 (s, 9H), 0.88 (s, 9H), 0.28 (s, 6H), 0.05 (s, 6H) ppm.}\]

\[^{13}C\text{ NMR (75 MHz, CDCl}_3\text{: } \delta = 168.3, 139.9, 130.5, 61.8, 32.7, 26.0 \text{ (3 x C), 25.8 (3 x C), 18.4, 17.9, 12.8, –4.7 (2 x C), –5.2 (2 x C) ppm.}\]

\[\text{IR (ATR): } \tilde{\nu} = 2956 \text{ (w), 2859 (w), 1690 (m), 1472 (w), 1288 (m), 1252 (s), 1099 (s) cm}^{-1}.\]

\[\text{HRMS (EI): calculated for C}_{18}\text{H}_{38}\text{O}_2\text{Si}_2^+ [M–O+H]^+ 343.2483, found 343.2410.}\]

\[(E)-5-((\text{tert-butyl(dimethyl)silyl)}oxy)-2-methylpent-2-enoic acid (16).\]

Colorless oil.

\[R_f = 0.46 \text{ (EtOAc/hexanes 1:1).} \]

\[^1H\text{ NMR (600 MHz, CDCl}_3\text{: } \delta = 6.93 \text{ (tq, } J = 7.4, 1.4 \text{ Hz, 1H)}, 3.72 \text{ (t, } J = 6.6 \text{ Hz, 2H), 2.43–2.41 \text{ (m, 2H), 1.86 (d, } J = 1.4 \text{ Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H) ppm.}\]

\[^{13}C\text{ NMR (75 MHz, CDCl}_3\text{: } \delta = 173.4, 141.7, 128.6, 61.7, 32.8, 26.0 \text{ (3 x C), 18.5, 12.4, –5.2 (2 x C) ppm.}\]

\[\text{IR (ATR): } \tilde{\nu} = 2956, 2858, 1687, 1421, 1288, 1257, 1100, 905 \text{ cm}^{-1}.\]

\[\text{HRMS (ESI): calculated for C}_{12}\text{H}_{23}\text{O}_3\text{Si}^+ [M–H]^+ 243.1422, found 243.1422.}\]

**Preparation of ester 17**

\[
\text{(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-((tert-butyl(dimethyl)silyl)oxy)-2-methylpent-2-enoate (17).}\]

To a magnetically stirred solution of acid 16 (100 mg, 409 \(\mu\)mol) in dry toluene (12 mL) were added 2,4,6-trichlorobenzoyl chloride (TCBC) (149 mg, 614 \(\mu\)mol, 96.9 \(\mu\)L) and triethylamine (83.0 mg, 818 \(\mu\)mol, 120 \(\mu\)L). After the resulting mixture was stirred at room temperature for 1.5 h, a solution of
alcohol 12 (76.0 mg, 409 μmol) and DMAP (89.9 mg, 736 μmol) in dry toluene (17 mL) was added via cannula. The reaction was stirred for 6 h at room temperature before EtOAc (50 mL) and aqueous pH-7-phosphate buffer (0.1 M, 30 mL) were added. Then, the layers were separated and the aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Thus obtained crude material was subjected to flash column chromatography (EtOAc/hexanes 1:20, isocratic elution) providing 132 mg (320 μmol, 78%) of ester 17 as a colorless oil.

Rᵣ = 0.65 (EtOAc/hexanes 1:3).

[α]晶体⁻¹ = +2.5 (c = 1.0, CHCl₃).

¹H NMR (600 MHz, CDCl₃): δ = 6.79 (ddq, J = 7.4, 7.4, 1.4 Hz, 1H), 5.70 (ddd, J = 17.4, 10.5, 7.1 Hz, 1H), 5.64 (dd, J = 9.4, 6.5 Hz, 1H), 5.32–5.25 (m, 2H), 5.17–5.15 (m, 1H), 4.68 (d, J = 6.7 Hz, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.17 (dd, J = 6.8, 6.8 Hz, 1H), 3.70–3.68 (m, 2H), 3.35 (s, 3H), 2.41–2.37 (m, 2H), 1.85 (d, J = 1.3 Hz, 3H), 1.76 (d, J = 1.3 Hz, 3H), 1.73 (d, J = 1.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H) ppm.

¹³C NMR (150 MHz, CDCl₃): δ = 167.2, 139.3, 138.8, 134.2, 129.5, 120.1, 119.1, 94.3, 78.4, 72.6, 61.9, 55.6, 32.6, 26.1, 26.1 (3 x C), 18.9, 18.5, 12.8, −5.2 (2 x C) ppm.

IR (ATR): ν = 2956, 2859, 1740, 1710, 1580, 1446, 1373, 1230, 1151, 1044 cm⁻¹.


Preparation of alcohol 18

(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-hydroxy-2-methylpent-2-enoate (18). To a magnetically stirred solution of TBS ether 17 (600 mg, 1.45 mmol) in dry THF (25 mL) was added tetra-n-butyrammonium fluoride solution (1 M in THF, 3.18 mmol, 3.18 mL) at 0 °C. The reaction was stirred for 1 h at room temperature before pH-7-phosphate buffer (0.1 M, 30 mL) was added. Then, the mixture was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with brine (70 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. Thus obtained crude material was subjected to flash column chromatography (EtOAc/hexanes 1:4→1:1, gradient elution) providing 363 mg (1.22 mmol, 84%) of alcohol 18 as a colorless oil.

Rᵣ = 0.25 (EtOAc/hexanes 1:3).

[α]晶体⁻¹ = +19.2 (c = 0.50, CHCl₃).
1H NMR (600 MHz, CDCl3): δ = 6.79 (ddq, J = 7.4, 7.4, 1.3 Hz, 1H), 5.69 (ddd, J = 17.5, 10.4, 7.2 Hz, 1H), 5.64 (dd, J = 9.5, 6.7 Hz, 1H), 5.32–5.26 (m, 2H), 5.17–5.15 (m, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.17 (dd, J = 6.9, 6.9 Hz, 1H), 3.76–3.73 (m, 2H), 3.35 (s, 3H), 2.47–2.44 (m, 2H), 1.87 (s, 3H), 1.77 (d, J = 1.0 Hz, 3H), 1.74 (s, 3H) ppm.

13C NMR (150 MHz, CDCl3): δ = 167.1, 139.5, 138.0, 134.1, 130.5, 120.0, 119.2, 94.2, 78.4, 72.8, 61.6, 55.6, 32.4, 26.1, 18.9, 12.8 ppm.

IR (ATR): ʋ = 3454, 2933, 2888, 1820, 1707, 1649, 1442, 1324, 1265, 1150, 1099, 1026 cm\(^{-1}\).

HRMS (ESI): calculated for C\(_{16}\)H\(_{26}\)O\(_5\)Na\(^+\) \([M+Na]^+\) 321.1672, found 321.1672.

Preparation of acid 8

\((E)-5-((3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl)oxy)-4-methyl-5-oxopent-3-enoic\) acid (8). To a magnetically stirred solution of alcohol 18 (105 mg, 352 \(\mu\)mol) in acetone (5 mL) was added dropwise as much of freshly prepared Jones reagent (8 N) at 0 °C until the reaction mixture maintained an orange color (ca. 1.4 mL). After the mixture was stirred at 0 °C for 30 min, water (20 mL) was added and the solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated \(\text{in vacuo}\) providing 101 mg (323 \(\mu\)mol, 92%) of acid 8 as a colorless oil. The product is sensitive to silica and could not be purified any further using flash column chromatography.

\(R_f = 0.33\) (EtOAc/hexanes 1:1).

\([\alpha]_D^{25} = +18.3\) (c = 0.50, CHCl\(_3\)).

1H NMR (600 MHz, CDCl3): δ = 6.90 (dd, J = 6.6, 6.6 Hz, 1H), 5.71–5.63 (m, 2H), 5.33–5.26 (m, 2H), 5.18–5.15 (m, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 6.8 Hz, 1H), 4.18 (dd, J = 6.9, 6.9 Hz, 1H), 3.35 (s, 3H), 3.27–3.26 (m, 2H), 1.86 (s, 3H), 1.75 (d, J = 1.1 Hz, 3H), 1.72 (d, J = 1.1 Hz, 3H) ppm.

13C NMR (150 MHz, CDCl3): δ = 175.9, 166.6, 139.7, 133.9, 131.9, 131.5, 119.8, 119.4, 94.1, 78.3, 73.1, 55.6, 33.9, 26.1, 18.9, 13.0 ppm.

IR (ATR): ʋ = 2935, 1708, 1441, 1386, 1250, 1118, 1025 cm\(^{-1}\).

HRMS (ESI): calculated for C\(_{16}\)H\(_{25}\)O\(_6\)^-- \([M-H]^–\) 311.1500, found 311.1502.
Preparation of imide 20

(5R)-1-[(2E)-pent-2-enoyl]-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (20). A solution of auxiliary\[^{[S4]}\] 19 (16.7 g, 46.7 mmol) in dry THF (200 mL) was cooled to −78 °C and a solution of n-butyllithium (2.5 M in hexanes, 23.4 mL, 58.4 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min. In a separate flask, a solution of trans-2-pentenoic acid (5.90 mL, 58.4 mmol) and triethylamine (11.4 mL, 81.7 mmol) was cooled to 0 °C and pivaloyl chloride (7.90 mL, 64.1 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min, and then added slowly via cannula to the previously prepared amide anion solution at −78 °C. The reaction was allowed to warm to room temperature over a period of 2 h, and then quenched with aqueous saturated NH₄Cl solution (500 mL). The mixture was extracted with EtOAc (3 x 300 mL) and the combined organic fractions were washed with aqueous saturated NaHCO₃ solution (400 mL), water (400 mL) and brine (400 mL), dried over MgSO₄ and concentrated \textit{in vacuo}. Flash column chromatography (EtOAc/hexanes 1:9→1:6→1:4, gradient elution) afforded 17.6 g (40.0 mmol, 86%) of imide 20 as a white solid.

R\(_f\) = 0.50 (EtOAc/hexanes 1:3)

\([\alpha]_{D}^{23} = +84.7 \ (c = 1.0, \text{CH}_2\text{Cl}_2)\).

\text{mp: } 107–108 °C.

\(^1\text{H NMR (300 MHz, CDCl}_3\): } \delta = 7.40–7.33 \ (6 \mathrm{H}), 7.32–7.19 \ (10 \mathrm{H}), 7.13 \ (3 \mathrm{ddd}, J = 15.4, 6.4, 6.4 \mathrm{Hz}), 4.60–4.50 \ (1 \mathrm{H}), 3.57 \ (2 \mathrm{dd}, J = 9.7, 4.0 \mathrm{Hz}), 3.16 \ (2 \mathrm{dd}, J = 9.7, 2.7 \mathrm{Hz}), 2.97 \ (2 \mathrm{ddd}, J = 17.9, 11.0, 10.0 \mathrm{Hz}), 2.50 \ (2 \mathrm{dd}, J = 17.9, 9.7, 2.2 \mathrm{Hz}), 2.39–2.27 \ (2 \mathrm{H}), 2.17–1.91 \ (2 \mathrm{H}), 1.14 \ (2 \mathrm{ddd}, J = 7.4, 7.4 \mathrm{Hz}, 3 \mathrm{H}) \mathrm{ppm}.

\(^{13}\text{C NMR (75 MHz, CDCl}_3\): } \delta = 176.5, 166.2, 152.0, 143.8 \ (3 \mathrm{C}), 128.7 \ (6 \mathrm{C}), 128.0 \ (6 \mathrm{C}), 127.2 \ (3 \mathrm{C}), 121.9, 87.2, 64.3, 56.9, 33.5, 26.0, 21.2, 12.6 \mathrm{ppm}.

IR (ATR): \(\tilde{\nu} = 3100, 2967, 2929, 1728, 1675, 1621, 1490, 1356, 1291, 1193, 1151, 1080 \ \text{cm}^{-1} \).

HRMS (ESI): calculated for C\(_{29}\)H\(_{28}\)NO\(_3\)Na\(^+\) [M+Na\(^+\)] \ 462.2040, found 462.2035.

Preparation of alkene 21
(5R)-1-[(3R)-3-ethylpent-4-enoyl]-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (21). To a suspension of copper(I) bromide dimethyl sulfide complex (9.40 g, 45.7 mmol) and dimethyl sulfide (135 mL, 1.83 mol) in dry THF (770 mL) was added activated molecular sieve (12 g, pellets, 3Å), and the resulting mixture was cooled to −45 °C. A solution of vinylmagnesium bromide (1.0 M in THF, 91.5 mL, 91.5 mmol) was added dropwise and the solution stirred at −45 °C for 20 min. Then, a solution of imide 20 (13.4 g, 30.5 mmol) in dry THF (130 mL) was added via cannula, and the reaction mixture was stirred at −45 °C for an additional 60 min. The reaction was quenched with aqueous saturated NH₄Cl solution (300 mL), warmed to room temperature and diluted with water (200 mL). The mixture was extracted with EtOAc (3 x 500 mL), and the combined organic fractions were divided into two parts. Each part (∼750 mL) was washed with water (2 x 500 mL) and brine (500 mL), then dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (EtOAc/hexanes 1:8, isocratic elution) afforded 12.1 g (25.9 mmol, 85%) of alkene 21 as a white solid.

R f = 0.31 (EtOAc/hexanes 1:5).

[α]D²⁴ = +64.7 (c = 1.0, CH₂Cl₂).

mp: 108–109 °C.

¹H NMR (300 MHz, CDCl₃): δ = 7.38–7.33 (m, 6H), 7.32–7.19 (m, 9H), 5.67 (ddd, J = 17.2, 10.2, 8.4 Hz, 1H), 5.05–4.93 (m, 2H), 4.51–4.42 (m, 1H), 3.52 (dd, J = 9.7, 4.1 Hz, 1H), 3.16 (dd, J = 9.7, 2.7 Hz, 1H), 3.08–2.83 (m, 3H), 2.57–2.39 (m, 2H), 2.14–1.85 (m, 2H), 1.57–1.23 (m, 2H), 0.87 (dd, J = 7.4, 7.4 Hz, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 176.3, 172.9, 143.8 (3 x C), 141.5, 128.7 (6 x C), 128.0 (6 x C), 127.3 (3 x C), 115.0, 87.2, 64.1, 56.9, 42.1, 41.3, 33.4, 27.5, 21.5, 11.7 ppm.

IR (ATR): υ = 2959, 2876, 1733, 1691, 1489, 1370, 1280, 1219, 1198, 1074 cm⁻¹.


Preparation of ester 22

(R)-Methyl 4-((R)-3-ethylpent-4-enamido)-5-(trityloxy)pentanoate (22). To a magnetically stirred solution of dry methanol (174 mg, 5.43 mmol, 0.22 mL) in dry THF (2.75 mL) was added dropwise a solution of n-butyllithium (2.5 M in hexanes, 3.68 mmol, 1.47 mL) at 0 °C and the mixture was stirred at room temperature for 10 min. The freshly prepared lithium methoxide solution was added to a solution of imide 21 (250 mg, 534 μmol) in dry THF (2.5 mL) and the mixture was stirred at room temperature for 36 h before aqueous saturated NH₄Cl solution (10 mL) was added. The layers were separated and the aqueous layer was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in
vacuo. Thus obtained crude product was subjected to flash column chromatography (Et$_2$O/n-pentane 1:6→1:0, gradient elution) providing 120 mg (240 μmol, 45%) of ester 22 as a white solid.

$R_f = 0.20$ (EtOAc/hexanes 1:5).

mp: 107–109 °C.

$[α]^2_0 = +84.7$ ($c = 1.0$, CH$_2$Cl$_2$).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.41–7.38$ (m, 6H), 7.32–7.27 (m, 6H), 7.25–7.21 (m, 3H), 5.68 (d, $J = 9.0$ Hz, 1H), 5.55 (ddd, $J = 17.2$, 10.2, 8.4 Hz, 1H), 4.99–4.91 (m, 2H), 4.13–4.05 (m, 1H), 3.66 (s, 3H), 3.18 (ddd, $J = 9.3$, 3.6 Hz, 1H), 3.10 (dd, $J = 9.3$, 4.2 Hz, 1H), 2.42–2.29 (m, 3H), 2.19 (dd, $J = 14.2$, 5.9 Hz, 1H), 2.11–2.02 (m, 1H), 1.97–1.91 (m, 2H), 1.49–1.36 (m, 1H), 1.35–1.20 (m, 1H), 0.85 (dd, $J = 7.4$, 7.4 Hz, 3H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 174.1$, 171.5, 143.8 (3 x C), 141.1, 128.7 (6 x C), 128.0 (6 x C), 127.3 (3 x C), 115.6, 86.7, 65.1, 51.8, 48.9, 42.5, 42.4, 31.0, 27.6, 27.5, 11.6 ppm.

IR (ATR): $\tilde{\nu} = 3275$, 2924, 1738, 1643, 1552, 1448, 1344, 1287, 1169, 1070 cm$^{-1}$.

HRMS (ESI): calculated for C$_{32}$H$_{37}$NO$_4$Na$^+$ [M+Na]$^+$ 522.2615, found 522.2608.

Preparation of bromide 9

(3R)-5-bromo-3-ethylpent-1-ene (9). A solution of dry methanol (3.12 mL, 77.0 mmol) in dry THF (2 mL) was cooled to 0 °C and a solution of $n$-butyllithium (2.35 M in hexanes, 21.8 mL, 51.3 mmol) was added carefully. The resulting mixture was allowed to warm to room temperature and stirred at this temperature for 15 min. A solution of alkene 21 (4.00 g, 8.55 mmol) in dry THF (8 mL) was added via cannula, and the reaction mixture was stirred at room temperature for 20 h. Then, the solution was cooled to 0 °C and lithium aluminum hydride (973 mg, 25.7 mmol) was added. The mixture was stirred at 0 °C for 10 min, then allowed to warm to room temperature and stirred at this temperature for an additional 5.5 h. The reaction was quenched by adding carefully aqueous saturated Rochelle salt solution (30 mL), followed by dilution with water (30 mL) and stirred at room temperature for 1 h. The mixture was extracted with Et$_2$O (3 x 20 mL), and the combined organic fractions were washed with brine (20 mL), then dried over MgSO$_4$ and concentrated to a volume of ca. 20 mL by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 45–80 °C oil bath temperature). The distillation residue was subjected to flash column chromatography [Et$_2$O/n-pentane 1:7, isocratic elution] and the resulting fraction were concentrated by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 50 °C oil bath temperature) to yield 1.76 g of a mixture of volatile alcohol 23, Et$_2$O and $n$-pentane (1:2:0.4, as determined by $^1$H-NMR spectroscopy, 7.71 mmol of 23, 90%). The mixture was diluted with dry CH$_2$Cl$_2$ (10 mL), then
triphenylphosphine (2.70 g, 10.3 mmol) was added and the solution cooled to 0 °C. N-Bromosuccinimide (1.83 g, 10.3 mmol) was added in one portion and the resulting mixture cooled at 0 °C for 15 min. The reaction was quenched with water (20 mL) and the mixture was extracted with Et₂O (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), then dried over MgSO₄ and concentrated to a volume of ca. 15 mL by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 45 °C oil bath temperature). The distillation residue was subjected to flash column chromatography [n-pentane, isocratic elution] and the product containing fractions were concentrated by removing the solvent through careful distillation (20 cm vacuum isolated Vigreux condenser, 1000 mbar, 50–80 °C oil bath temperature) to yield 1.13 g of a mixture of volatile bromide 9 and n-pentane (2:1, as determined by ¹H-NMR spectroscopy, 5.33 mmol of 9, 62% over 2 steps) as a colorless liquid. A stock solution of bromide 9 in dry THF (0.36 M) was prepared and stored over molecular sieve (pellets, 3Å).

(3R)-5-bromo-3-ethylpent-1-ene (9).

Colorless liquid.

Rᶠ = 0.80 (n-pentane).

[α]²⁵D = −46.0 (c = 0.45, n-pentane).

¹H NMR (300 MHz, CDCl₃): δ = 5.52–5.41 (m, 1H), 5.09–5.02 (m, 2H), 3.48–3.41 (m, 1H), 3.33 (ddd, J = 9.8, 8.3, 7.3 Hz, 1H), 2.16–2.05 (m, 1H), 1.99–1.89 (m, 1H), 1.82–1.71 (m, 1H), 1.48–1.37 (m, 1H), 1.36–1.23 (m, 1H), 0.88 (dd, J = 7.4, 7.4 Hz, 3H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 141.1, 116.2, 44.6, 37.6, 32.2, 27.7, 11.6 ppm.

IR (ATR): ν = 3078, 2964, 1641, 1461, 1252, 1100, 996, 915, 756, 676 cm⁻¹.


(3R)-3-ethylpent-4-en-1-ol (23).

For the purpose of full characterization of volatile alcohol 23, an analytical sample was concentrated in vacuo.

Rᶠ = 0.70 [EtOAc/hexanes 1:3].

[α]²⁵D = −11.1 (c = 0.50, Et₂O).

¹H NMR (400 MHz, CD₂Cl₂): δ = 5.63–5.52 (m, 1H), 5.04–4.96 (m, 2H), 3.67–3.53 (m, 2H), 2.08–1.97 (m, 1H), 1.70–1.60 (m, 1H), 1.52–1.39 (m, 2H), 1.32–1.23 (m, 1H), 0.86 (dd, J = 7.4, 7.4 Hz, 3H) ppm.

¹³C NMR (100 MHz, CD₂Cl₂): δ = 143.3, 114.9, 61.5, 43.2, 38.0, 28.3, 11.7 ppm.

IR (ATR): ν = 3319, 2960, 2924, 1640, 1463, 1420, 1379, 1057, 994 cm⁻¹.

Preparation of naphthoquinone 26.

**Tert-butyl (6-hydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (26).** A pressure tube was charged with diene\(^{[55]}\) 24 (1.31 g, 7.00 mmol), quinone\(^{[56]}\) 25 (1.56 g, 7.00 mmol) and dry benzene (10 mL), sealed and heated to 75 °C for 3 h. The yellow reaction mixture was cooled to room temperature and washed with aqueous HCl solution (1 M, 10 mL). The organic layer was separated, dried over Na\(_2\)SO\(_4\), filtered and the solvent was removed under reduced pressure. The crude residue was dissolved in CHCl\(_3\)/acetone (1:1, 50 mL) and oven-dried silica gel (5 g) was added. The suspension was stirred under ambient atmosphere for 24 h and subsequently concentrated \textit{in vacuo}. The crude material was purified by flash column chromatography (CHCl\(_3\)/acetone 30:1→10:1→5:1→2:1→1:1, gradient elution) to afford 1.48 g (4.88 mmol, 70%) of naphthoquinone 26 as an orange solid.

R\(_f\) = 0.26 (CHCl\(_3\)/acetone 20:1).

mp: 320 °C, decomposition.

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 11.07\) (s, 1H), 8.51 (s, 1H), 7.77 (d, \(J = 0.8\) Hz, 1H), 7.30 (s, 1H), 7.11 (s, 1H), 2.22 (d, \(J = 0.5\) Hz, 3H), 1.48 (s, 9H) ppm.

\(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 184.4, 178.5, 161.8, 151.5, 141.8, 131.9, 130.2, 129.6, 121.7, 113.3, 110.7, 81.7, 27.7\) (3 x C), 15.9 ppm.

IR (ATR): \(\tilde{\nu} = 3326, 1737, 1664, 1632, 1609, 1578, 1496, 1335, 1225, 1202, 1143, 1079, 1042, 1014, 962, 915, 876, 810, 802, 768, 736\) cm\(^{-1}\).

HRMS (ESI): calculated for C\(_{16}\)H\(_{18}\)NO\(_5\)\([\text{M+H}]^+\) 304.1179, found 304.1181.
Preparation of Bromo-naphthoquinone 27.

![Chemical structure of 26 and 27](image)

Tert-butyl (5-bromo-6-hydroxy-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (27). To a solution of naphthoquinone 26 (1.20 g, 3.94 mmol) in CHCl₃ (300 mL) was added N-bromosuccinimide (841 mg, 4.72 mmol) and the orange reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (EtOAc/hexanes 1:10→1:5→1:2) to provide 1.36 g (3.56 mmol, 90%) of the target compound 27 as a yellow solid.

Rₓ = 0.78 (CHCl₃/acetone 10:1).

mp: 173 °C.

¹H NMR (300 MHz, CDCl₃): δ = 7.93 (s, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.02 (s, 1H), 2.41 (s, 3H), 1.53 (s, 9H) ppm.

¹³C NMR (75 MHz, CDCl₃): δ = 183.3, 179.2, 156.9, 151.2, 139.7, 130.0, 129.7, 127.8, 124.9, 115.6, 109.1, 82.6, 28.1 (3 x C), 17.1 ppm.

IR (ATR): ν = 3376, 2983, 1740, 1657, 1647, 1622, 1581, 1507, 1457, 1327, 1271, 1231, 1206, 1181, 1144, 1094, 1042, 1011, 967, 886, 867, 816, 680 cm⁻¹.


Preparation of protected naphthoquinone S1.

![Chemical structure of 27 and S1](image)

Tert-butyl (5-bromo-6-(methoxymethoxy)-7-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)carbamate (S1). Naphthoquinone 27 (1.32 g, 3.45 mmol) was dissolved in dry CH₂Cl₂ (100 mL) and the clear orange solution was cooled to 0 °C. N,N-Diisopropylethylamine (1.21 mL, 6.92 mmol) was added dropwise, upon which the solution rapidly turned dark purple. Bromomethyl methyl ether (367 μL, 4.50 mmol) was added dropwise and the reaction mixture was allowed to stir for 45 min at 0 °C. Aqueous saturated NaHCO₃ solution (50 mL) was then added and the layers were separated. The aqueous layer was extracted with CHCl₃ (3 x 100 mL), the combined organic phases were dried over sodium sulfate, filtered and the solvent was removed in vacuo. Purification of the residue by flash column chromatography (CHCl₃/acetone 40:1→30:1, gradient elution) afforded 1.40 g (3.28 mmol, 95%) of protected naphthoquinone S1 as a yellow solid.
R_f = 0.63 (CHCl_3/acetone 20:1).

mp: 42 °C.

^1^H NMR (300 MHz, CDCl_3): δ = 7.99 (d, J = 0.7 Hz, 1H), 7.59 (br s, 1H), 7.43 (s, 1H), 5.18 (s, 2H), 3.67 (s, 3H), 2.49 (d, J = 0.7 Hz, 3H), 1.53 (s, 9H) ppm.

^1^3^C NMR (75 MHz, CDCl_3): δ = 183.2, 179.6, 160.5, 151.2, 139.3, 138.4, 129.7, 129.1, 128.4, 118.0, 116.7, 100.4, 82.6, 58.0, 28.1 (3 x C), 17.9 ppm.

IR (ATR): \( \tilde{\nu} = 3384, 2977, 2931, 1735, 1666, 1646, 1629, 1582, 1501, 1454, 1392, 1368, 1327, 1271, 1239, 1208, 1140, 1078, 1040, 1005, 971, 918, 884, 864, 804, 751, 726 \text{ cm}^{-1} \).

HRMS (ESI): calculated for C_{18}H_{21}BrNO_6 \[ \text{[M+H]}^+ \] 426.0547, found 426.0549.

Preparation of hydroquinone dimethyl ether 28.

\[ \text{S1} \quad \xrightarrow{\text{NaBH}_4, \text{CeCl}_3, \text{KOH, Me}_2\text{SO}_4, \text{THF/H}_2\text{O}} \quad \text{28} \]

**Tert-butyl (5-bromo-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-yl)carbamate (28).** Naphthoquinone S1 (1.40 g, 3.28 mmol) was dissolved in a 2:1 mixture of THF (80 mL) and water (40 mL) and cerium(III)-chloride heptahydrate (1.80 g, 4.94 mmol) was added. The reaction mixture was cooled to 0 °C and NaBH_4 (250 mg, 6.58 mmol) was added in two portions over 5 min. After 20 min, a solution of KOH (3.70 g, 65.8 mmol) in water (15 mL) was added dropwise to the white reaction mixture, which turned immediately black-brown. Me_2SO_4 (9.30 mL, 98.7 mmol) was next added dropwise and the resulting solution was stirred at 0 °C for 35 min, after which aqueous saturated NH_4OH solution (50 mL) and H_2O (15 mL) were added. The reaction mixture was warmed to room temperature, extracted with EtOAc (3 x 250 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated \textit{in vacuo}. Purification of the residue by flash column chromatography (EtOAc/hexanes 1:20→1:10→1:5, gradient elution) afforded 1.33 g (2.92 mmol, 89%) of hydroquinone dimethyl ether 28 as a white solid.

R_f = 0.77 (hexanes/EtOAc 2:1).

mp: 100 °C.

^1^H NMR (600 MHz, CDCl_3): δ = 7.87 (br s, 1H), 7.70 (d, J = 1.0 Hz, 1H), 7.11 (br s, 1H), 5.16 (s, 2H), 3.96 (s, 3H), 3.68 (s, 3H), 2.53 (d, J = 0.9 Hz, 3H), 1.56 (s, 9H) ppm.

^1^3^C NMR (150 MHz, CDCl_3): δ = 152.7, 152.5, 152.3, 134.8, 133.0, 128.2, 127.3, 122.0, 120.0, 111.8, 100.5, 100.1, 80.9, 61.3, 57.8, 56.0, 28.4 (3 x C), 18.4 ppm.
IR (ATR): $\tilde{\nu} = 3308, 2977, 2928, 1718, 1626, 1614, 1573, 1512, 1448, 1362, 1315, 1264, 1243, 1221, 1148, 1112, 1043, 984, 940, 916, 874, 830, 783, 769, 761, 669\text{ cm}^{-1}$.

HRMS (EI): calculated for C$_{20}$H$_{26}$BrNO$_6^+$ [M$^+$] 455.0938, found 455.0942.

**Preparation of aldehyde 7**

*Tert-butyl N-[5-formyl-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-yl] carbamate (7).* A solution of bromide 28 (250 mg, 0.548 mmol) in dry THF (12 mL) was cooled to $-78^\circ\text{C}$, and a solution of methylolithium (1.6 M in Et$_2$O, 688 $\mu$L, 1.10 mmol) was added dropwise. The resulting mixture was stirred at $-78^\circ\text{C}$ for 30 min, and then a solution of $n$-butyllithium (2.35 M in hexanes, 515 $\mu$L, 1.21 mmol) was added. After additional 30 min at $-78^\circ\text{C}$, dry dimethylformamide (424 $\mu$L, 5.48 mmol) was added and the reaction mixture was stirred further at $-78^\circ\text{C}$ for 30 min, then allowed to warm to room temperature within 10 min. The reaction was quenched with aqueous saturated NH$_4$Cl solution (10 mL) and the mixture extracted with Et$_2$O (3 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried over MgSO$_4$ and concentrated *in vacuo*. Flash column chromatography (EtOAc/hexanes 1:9 $\rightarrow$ 1:6, gradient elution) afforded 190 mg (0.469 mmol, 86%) of aldehyde 7 as a yellowish solid and 21.3 mg (56.4 $\mu$mol, 10%) protodemetallated naphthalene S2 as a white solid.

*Tert-butyl N-[5-formyl-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-yl] carbamate (7).*

R$_f$ = 0.40 (EtOAc/hexanes 1:3).

mp: 107–108 $^\circ\text{C}$.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 10.64$ (s, 1H), 7.83 (br s, 1H), 7.80 (s, 1H), 7.14 (br s, 1H), 5.06 (s, 2H), 3.94 (s, 3H), 3.84 (s, 3H), 3.58 (s, 3H), 2.48 (s, 3H), 1.56 (s, 9H) ppm.

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 194.3, 152.9, 152.0, 151.1, 135.6, 133.2, 128.7, 128.4, 125.5, 124.8, 119.1, 102.2, 99.3, 81.1, 61.7, 57.7, 56.3, 28.5 (3 x C), 17.9 ppm.

IR (ATR): $\tilde{\nu} = 3301, 2941, 1722, 1694, 1625, 1364, 1231, 1149, 966, 876, 706\text{ cm}^{-1}$.

HRMS (ESI): calculated for C$_{21}$H$_{27}$NNaO$_7^+$ [M+Na$^+$] 428.1680, found 428.1679.
**Tert-butyl N-[1,4-dimethoxy-6-(methoxym ethoxy)-7-methyl-naphthalen-2-yl]carbamate (S2).**

R<sub>f</sub> = 0.62 (EtOAc/hexanes 1:3).

mp: 109–111 °C.

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>): δ = 7.70 (br s, 1H), 7.67 (s, 1H), 7.64 (s, 1H), 7.10 (br s, 1H), 5.33 (s, 2H), 3.99 (s, 3H), 3.85 (s, 3H), 3.53 (s, 3H), 2.42 (s, 3H), 1.56 (s, 9H) ppm.

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 153.0, 152.9, 151.3, 135.4, 129.6, 126.3, 123.3, 122.0, 121.8, 103.5, 97.3, 94.4, 80.4, 61.4, 56.2, 55.7, 28.4 (3 x C), 17.3 ppm.

IR (ATR): ν = 3299, 2974, 2924, 1725, 1613, 1502, 1461, 1410, 1331, 1216, 1151, 1045, 987, 880, 726 cm<sup>−1</sup>.

HRMS (ESI): calculated for C<sub>20</sub>H<sub>27</sub>NaO<sub>6</sub> [M+Na]<sup>+</sup> 400.1731, found 400.1730.

**Preparation of ketone 29**

**Tert-butyl N-[5-[(4R)-4-ethylhex-5-enoyl]-1,4-dimethoxy-6-(methoxym ethoxy)-7-methyl-naphthalen-2-yl]carbamate (29).** A solution of bromide 9 (0.36 M in THF, 494 μL, 0.178 mmol) was diluted with dry THF (0.5 mL) and cooled to −78 °C. A solution of tert-butyllithium (1.7 M in pentane, 209 μL, 0.355 mmol) was added dropwise and the resulting mixture was stirred at −78 °C for 30 min. The reaction mixture was warmed to 0 °C and stirred at this temperature for an additional 30 min. After cooling to −78 °C, a solution of aldehyde 7 (14.4 mg, 35.5 μmol) in dry THF (1.5 mL) was added via cannula and the reaction mixture was stirred at −78 °C for an additional 30 min. The reaction mixture was quenched with aqueous saturated NH<sub>4</sub>Cl solution (5 mL), allowed to warm to room temperature and then extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. The crude product was immediately dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), and NaHCO<sub>3</sub> (44.7 mg, 0.533 mmol) was added followed by Dess-Martin periodinane (30.1 mg, 71.0 μmol). The resulting suspension was stirred at room temperature for 60 min. Then, the reaction was quenched with a mixture (1:1, 5 mL) of aqueous saturated NaHCO<sub>3</sub> solution and aqueous saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution, and the mixture was extracted with Et<sub>2</sub>O (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried over MgSO<sub>4</sub> and concentrated in vacuo. Flash column chromatography (EtOAc/hexanes 1:9, isocratic elution) afforded 11.7 mg (23.3 μmol, 67% over two steps) of ketone 29 as a white solid consisting of two atropisomers (dr 1:1, as determined by <sup>1</sup>H-NMR spectroscopy) as an inseparable mixture.

R<sub>f</sub> = 0.44 (EtOAc/hexanes 1:3).
$^1$H NMR (400 MHz, CDCl$_3$) (mixture of isomers, both isomers quoted): $\delta = 7.76$ (s, 2H), 7.72–7.70 (m, 2H), 7.13 (br s, 2H), 5.58–5.44 (m, 2H), 5.04–4.89 (m, 8H), 3.87 (s, 3H), 3.86 (s, 3H), 3.83 (br s, 6H), 3.57 (s, 3H), 3.56 (s, 3H), 2.97–2.86 (m, 1H), 2.84–2.74 (m, 1H), 2.72–2.62 (m, 1H), 2.61–2.51 (m, 1H), 2.50–2.47 (m, 6H), 2.03–1.93 (m, 1H), 1.93–1.83 (m, 2H), 1.83–1.73 (m, 2H), 1.66–1.58 (m, 1H), 1.55 (br s, 8H), 1.50–1.38 (m, 2H), 1.38–1.24 (m, 2H), 0.89–0.84 (m, 6H) ppm.

$^{13}$C-NMR (100 MHz, CDCl$_3$) (mixture of isomers, both isomers quoted): $\delta = 207.0, 207.0, 153.0$ (2 x C), 151.3, 151.3, 149.1, 149.1, 142.6, 142.6, 135.6, 135.6, 132.9, 132.9, 131.6, 131.6, 128.2 (2 x C), 125.7 (2 x C), 123.1, 123.0, 118.2, 118.2, 115.1, 115.0, 101.7, 101.6, 99.0, 98.9, 81.0 (2 x C), 61.6 (2 x C), 57.8 (2 x C), 56.4, 56.4, 45.5, 45.4, 43.2, 43.2, 28.5 (6 x C), 28.2, 28.2, 27.9, 27.7, 17.8, 17.8, 11.8, 11.8 ppm.

IR (ATR): $\tilde{\nu} = 3431, 2955, 1707, 1626, 1605, 1495, 1456, 1366, 1229, 1146, 1046, 986, 930, 880, 753$ cm$^{-1}$.

HRMS (ESI): calculated for C$_{28}$H$_{40}$NO$_7$ $^{[M+H]^+}$ 502.2799, found 502.2796.

Preparation of aminonaphthalene 30

1-(6-Amino-2-hydroxy-5,8-dimethoxy-3-methylnaphthalen-1-yl)-4-ethylhex-5-en-1-one (30). To a solution of protected naphthalene 29 (21.7 mg, 43.3 $\mu$mol) in dry MeOH (1 mL) was added dropwise a solution of HCl in dry MeOH (1 mL), prepared by bubbling HCl gas (NaCl, conc. H$_2$SO$_4$) through dry MeOH for 30 min, and the resulting mixture was stirred at room temperature for 1.5 h. The reaction was quenched with aqueous saturated NaHCO$_3$ solution (10 mL) and the mixture extracted with Et$_2$O (3 x 10 mL). The combined organic fractions were dried over MgSO$_4$ and concentrated in vacuo. Flash column chromatography (EtOAc/hexanes 1:3, isocratic elution) afforded 15.5 mg (43.3 $\mu$mol, quant.) of aminonaphthalene 30 as a yellow oil.

$\text{R}_f = 0.59$ (EtOAc/hexanes 1:1).

[\alpha]$_D^{21} = +7.1$ (c = 0.20, CHCl$_3$).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.70$ (d, $J = 1.0$ Hz, 1H), 6.39 (s, 1H), 5.42 (ddd, $J = 17.2, 10.1, 8.8$ Hz, 1H), 4.88 (dd, $J = 10.2, 1.8$ Hz, 1H), 4.83–4.73 (m, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.52–2.43 (br m, 2H), 2.38 (d, $J = 1.0$ Hz, 3H), 1.76 (br s, 2H), 1.58 (br s, 1H), 1.40–1.32 (m, 1H), 1.27–1.19 (m, 1H), 0.81 (dd, $J = 7.4, 7.4$ Hz, 3H) ppm.

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta = 210.3, 151.7, 150.9, 142.4, 134.3, 128.7, 125.2, 124.4, 116.7, 116.3, 115.1, 99.5, 60.5, 56.0, 45.8, 42.8, 30.3, 27.8, 17.1, 11.8, one aromatic carbon not observed.

IR (ATR): $\tilde{\nu} = 3362, 2927, 1688, 1626, 1442, 1391, 1228, 992, 753$ cm$^{-1}$.
HRMS (ESI): calculated for C_{21}H_{28}NO_{4}^{+} [M+H]^+ 358.2013, found 358.2008.

**Preparation of amide 31**

(3S,4S)-3-(methoxymethoxy)-6-methylhepta-1,5-dien-4-yl-(2E)-4-((5-[4R]-4-ethylhex-5-enoyl)-6-hydroxy-1,4-dimethoxy-7-methylnaphthalen-2-yl)carbamoyl)-2-methylbut-2-enoate (31). To a solution of carboxylic acid 8 (12.5 mg, 40.1 μmol) in dry DMF (0.35 mL) was added 1-hydroxybenzotriazole hydrate (86 wt%, 10.4 mg, 66.8 μmol), and the mixture was cooled to 0 °C. N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (11.8 μL, 66.8 μmol) was added followed by a solution of aminonaphthalene 30 (11.9 mg, 33.4 μmol) in dry DMF (0.50 mL). The reaction mixture was stirred at 0 °C for 1 h and was then allowed to warm to room temperature. After stirring at this temperature for an additional 19 h, the reaction was diluted with Et₂O (10 mL). The organic phase was washed with aqueous LiCl solution (10 wt%, 3 x 10 mL) and brine (10 mL), dried over MgSO₄ and concentrated in vacuo. Flash column chromatography (EtOAc/hexanes 1:3, isocratic elution) afforded 14.0 mg (21.5 μmol, 64%) of amide 31 as a yellow oil.

Due to the instability of compound 31 the characterization was limited to NMR analysis and mass spectrometry. 

R_f = 0.83 (EtOAc/hexanes 1:1).

$^{1}$H NMR (600 MHz, CDCl₃): δ = 7.96 (s, 1H), 7.89 (br s, 1H), 7.74 (s, 1H), 7.34 (s, 1H), 7.07–7.02 (m, 1H), 5.74–5.66 (m, 2H), 5.45–5.37 (m, 1H), 5.35–5.26 (m, 2H), 5.21–5.16 (m, 1H), 4.90–4.84 (m, 1H), 4.81–4.71 (br m, 1H), 4.69 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.21–4.17 (m, 1H), 3.87 (s, 3H), 3.82 (s, 3H), 3.42–3.37 (m, 2H), 3.35 (s, 3H), 2.88–2.28 (br m, 2H), 2.40 (d, J = 1.0 Hz, 3H), 1.99 (s, 3H), 1.78 (d, J = 1.4 Hz, 3H), 1.74 (d, J = 1.4 Hz, 3H), 1.79–1.71 (m, 2H), 1.59–1.53 (m, 1H), 1.39–1.32 (m, 1H), 1.26–1.20 (m, 1H), 0.80 (dd, J = 7.4, 7.4 Hz, 3H) ppm.

$^{13}$C NMR (150 MHz, CDCl₃): δ = 210.1, 167.5, 166.5, 153.6, 150.4, 142.2, 139.7, 137.3, 134.0, 132.9, 132.6, 129.3, 126.4, 125.8, 122.7, 119.8, 119.9, 119.6, 119.4, 116.4, 115.2, 100.8, 94.3, 78.3, 73.2, 62.0, 56.2, 55.7, 45.8, 42.9, 37.9, 29.9, 26.1, 18.9, 17.1, 13.1, 11.7 ppm.

HRMS (ESI): calculated for C$_{37}$H$_{49}$NNaO$_{9}$ $^{+}$ [M+Na]$^{+}$ 674.3300, found 674.3293.
Single-Crystal X-Ray Analysis

Single-Crystal X-Ray Analysis for Compounds 20, 21 and 22

The data collections were performed on an Oxford Diffraction Xcalibur or KappaCCD diffractometers at 173 K using MoKα-radiation (λ = 0.71073 Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 and refined by least-squares methods against F² with SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table C. The corresponding Cambridge Crystallographic Data Center (CCDC) storage numbers for the compounds 20, 21, and 22 are 894000, 894001 and 894002, respectively.

Figure A. Crystal structure of acylated auxiliary 20.

Figure B. Crystal structure of alkene 21.
**Figure C.** Crystal structure of open auxiliary 22.

**Table A.** Crystallographic data of auxiliary 20, amide 21 and alkene 22.

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<td>C_{29}H_{27}NO_{4}</td>
<td>C_{31}H_{33}NO_{3}</td>
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<td>MoKα</td>
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<td>'KappaCCD'</td>
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<td>P(_{2_1}2_1)</td>
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<td>Value</td>
<td>Value</td>
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<td>90</td>
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<td>3483</td>
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<td>1</td>
<td>1</td>
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<td>$R(F_{obs})$</td>
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<td>0.0473</td>
<td>0.0469</td>
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<td>min electron density/e Å$^{-3}$</td>
<td>−0.177</td>
<td>−0.189</td>
<td>−0.217</td>
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</table>

$m$ Methoxy group disordered over three sites, split model applied, sof ratio 0.36/0.40/0.24, Split atoms refined isotropically.

$^b$ Flack parameter meaningless, correct structure derived from synthesis.
Single-Crystal X-Ray Analysis for Compounds 26 and 27

The data collections were performed on a KappaCCD diffractometer at 173 K using MoKα-radiation ($\lambda = 0.71073$ Å, graphite monochromator). The CrysAlisPro software (version 1.171.33.41) was applied for the integration, scaling and multi-scan absorption correction of the data. The structures were solved by direct methods with SIR97 and refined by least-squares methods against $F^2$ with SHELXL-97. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed in ideal geometry riding on their parent atoms. Further details are summarized in Table C. The corresponding Cambridge Crystallographic Data Center (CCDC) storage numbers for the compounds 26 and 27 are 933387 and 933388, respectively.

**Figure D.** Crystal structure of compound 26.

**Figure E.** Crystal structure of compound 27.
Table B. Crystallographic data of compounds 26 and 27.

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</table>

$^1$H and $^{13}$C NMR Spectra

$(3S,4S)$-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-ol (12) ($^1$H, $^{13}$C)
(E)-5-Hydroxy-2-methylpent-2-enoic acid (14) (\(^1\)H, \(^{13}\)C)
(E)-\textit{Tert}-butyldimethylsilyl 5-\textit{((tert}-butyldimethylsilyl)oxy)-2-methylpent-2-enoate (15) ($^1$H, $^{13}$C)
(E)-5-((Tert-butyldimethylsilyloxy)-2-methylpent-2-enoic acid (16) ($^1$H, $^{13}$C)
(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-((t-Butyldimethylsilyl) oxy)-2-methylpent-2-enoate (17) (^1H, ^13C)
(E)-(3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl 5-hydroxy-2-methylpent-2-enoate (18) (\(^1\)H, \(^{13}\)C)
(E)-5-(((3S,4S)-3-(Methoxymethoxy)-6-methylhepta-1,5-dien-4-yl)oxy)-4-methyl-5-oxopent-3-enoic acid (8) 
\( ^1H, ^{13}C \)
(R,E)-1-pent-2-enoyl-5-(trityloxymethyl)pyrrolidin-2-one (20) \(^{(1} \text{H}, \, ^{13} \text{C})\)
(R)-1-((R)-3-ethylpent-4-eno)-5-(trityloxymethyl)pyrrolidin-2-one (21) (\(^1\)H, \(^{13}\)C)
(R)-Methyl 4-((R)-3-ethylpent-4-enamido)-5-(trityloxy)pentanoate (22) \( (^1\text{H}, ^{13}\text{C}) \)
(R)-3-ethylpent-4-en-1-ol (23) \( (^{1}H, {^{13}C}) \)
(R)-5-bromo-3-ethylpent-1-ene (9) \( (^1H, ^13C) \)
tert-Butyl (6-hydroxy-7-methyl-1,4-dioxo-1,4-dihyronaphthalen-2-yl)carbamate (26) (\(^1\)H, \(^{13}\)C)
*tert*-Butyl (5-bromo-6-hydroxy-7-methyl-1,4-dioxo-1,4-dihyronaphthalen-2-yl)carbamate (27) ($^1$H, $^{13}$C)
**tert-Butyl (5-bromo-6-(methoxymethoxy)-7-methyl-1,4-dioxo-1,4-dihyronaphthalen-2-yl)carbamate (S1)**


tert-Butyl (5-bromo-6-(methoxymethoxy)-7-methyl-1,4-dioxo-1,4-dihyronaphthalen-2-yl)carbamate (S1) ($^1$H, $^{13}$C)
**tert-Butyl (5-bromo-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-yl)carbamate** (28) \(\left({}^1\!H, {}^{13}\!C\right)\)
tert-Butyl 5-formyl-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-ylcarbamate (7) ($^1$H, $^{13}$C)
**tert-Butyl 1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-ylcarbamate (S2) ($^1$H, $^{13}$C)**
(R)-tert-Butyl 5-(4-ethylhex-5-enoyl)-1,4-dimethoxy-6-(methoxymethoxy)-7-methylnaphthalen-2-ylcarbamate (29) (\textsuperscript{1}H, \textsuperscript{13}C)
(R)-1-(6-amino-2-hydroxy-5,8-dimethoxy-3-methylnaphthalen-1-y1)-4-ethylhex-5-en-1-one (30) $\left(^1H, ^{13}C\right)$
(E)-\((35,45)-3-(\text{methoxymethoxy})-6\text{-methylhepta}-1,5\text{-dien-4-yl})\quad 5-(5-((R)-4-\text{ethylhex-5-enoyl})-6\text{-hydroxy-1,4-dimethoxy-7-methynaphthalen-2-ylamino})-2\text{-methyl-5-oxopent-2-enoate (31)}\quad ^1\text{H,}^\text{13}\text{C}
Literature


