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Catalytic enantioselective total synthesis of (+)-eucomic acid

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ABSTRACT

A catalytic enantioselective synthesis of (+)-eucomic acid is reported. A palladium-catalyzed asymmetric allylic alkylation is employed to access the chiral tetrasubstituted α-hydroxyacid moiety found in the natural product. The protecting group strategy was investigated, and a protecting group manipulation was made without any appreciable deleterious effects in the allylic alkylation reaction. Non-natural (+)-eucomic acid is synthesized in a longest linear sequence of 13 steps.

1. Introduction

Cytochrome *c* oxidase plays a vital role in energy metabolism, functioning as a critical enzymatic constituent in the final step of the respiratory transport chain in the mitochondria. Impairment of this metabolic pathway in keratinocytes, the predominant cell type of the epidermis, causes a slowdown in skin rejuvenation and wound-healing processes.[1] Naturally occurring (−)-eucomic acid (**1**, Fig. 1) has been shown to be a global stimulus for cytochrome *c* oxidase activity and respiratory functions in the human keratinocyte cell line HaCaT, rendering it both a potential component for protective skin anti-aging therapies and an attractive target for total synthesis.[1] Eucomic acid (**1**) was first isolated in 1974 from the bulbs of *Eucomis punctata*.[2a] Since its initial isolation over 40 years ago, there has been only one published total synthesis of eucomic acid. The authors were able to access both enantiomers from *O*-benzyl-L-tyrosine in a stereoselective fashion.[2c] Herein, we report the first enantioselective total synthesis of non-natural (+)-eucomic acid (**(+)-1**) in a longest linear sequence of 13 steps from commercially available materials.

A central challenge in the enantioselective synthesis of eucomic acid is the construction of the tetrasubstituted α-hydroxyacid moiety in an enantioselective fashion. Such tetrasubstituted α-hydroxycarbonyl and α-alkoxycarbonyl functionalities can be found in numerous biologically active natural products (Fig. 1). Aspterric acid methyl ester (**2**) has demonstrated antiproliferative activity in human K562 chronic myelogenous leukemia cells.[3] Quinic acid (**3**) is a primary metabolite, which has been widely used as a synthon in small-molecule total synthesis.[4] In the case of the harringtonine alkaloids (**4a**–**f**), the individual antileukemic potencies are highly dependent on the presence of, and substitution about, a chiral α-hydroxyester fragment.[5]

The palladium-catalyzed enantioselective allylic alkylation of dioxanone substrates is a mild yet powerful method to access enantioenriched α-oxygenated carbonyl compounds.[6] In keeping with our group's long-standing interest and expertise in asymmetric allylic alkylation chemistry, we sought to employ this reaction in the enantioselective total synthesis of eucomic acid (**1**).

Retrosynthetically, we envisioned that the target compound would be accessed through phenolic ether deprotection and global saponification of diester **5** (Scheme 1). This diester would in turn be derived from α-tetrasubstituted dioxanone **6** via ketal removal and subsequent oxidative transformations. The enantioselective synthesis of dioxanone **6** would be achieved via a palladium-catalyzed enantioselective allylic alkylation of silyl enol ether **7**. We

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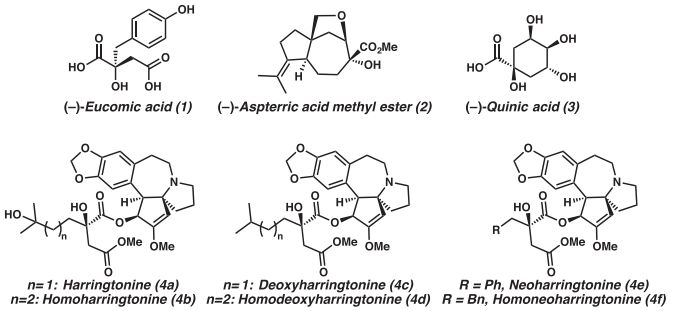
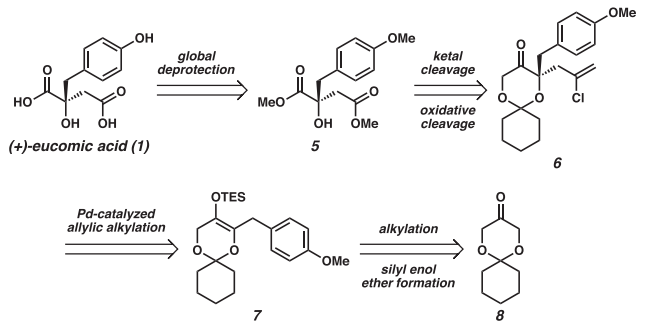


Fig. 1. Representative natural products containing chiral, tetrasubstituted α-hydroxyacid or α-hydroxyester moieties.

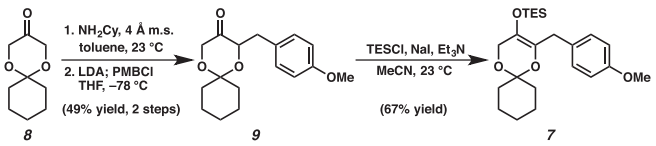
hypothesized that strategic incorporation of a 2-chloroallyl fragment during the alkylation event would enable smooth access to the carboxylic acid oxidation state found in the natural product. Silyl enol ether **7** would be synthesized from dioxanone **8**, which is available in three steps from commercially available compounds.[7]



Scheme 1. Retrosynthetic analysis of (+)-eucomic acid.

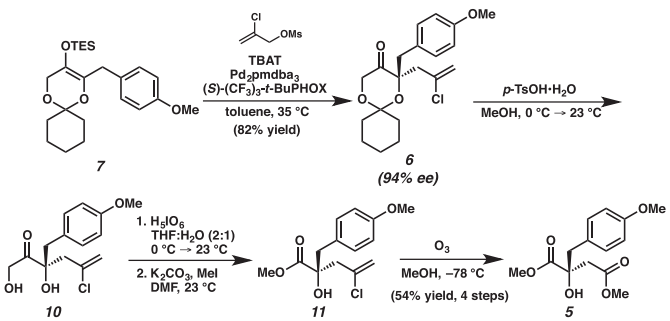
2. Results and discussion

Our synthetic efforts began with the development of a route to access silyl enol ether **7** in multi-gram quantities. This goal was accomplished by modifying procedures previously disclosed by our group.[7] To circumvent known challenges in selective *C*-alkylation of dioxanone substrates, we converted dioxanone **8** to its cyclohexyl imine derivative, which was smoothly mono-alkylated under standard conditions to give *C*-alkylated dioxanone **9** in 49% yield over two steps (Scheme 2). Formation of the silyl enol ether under thermodynamic conditions yielded tetrasubstituted enol ether **7** in 67% yield on 2-gram scale, positioning us to explore our key allylic alkylation reaction.



Scheme 2. Multi-gram synthesis of silyl enol ether **7**.

Gratifyingly, we found that treatment of silyl enol ether **7** with $Pd_2(pmdba)_3$ (1.5 mol %, pmdba=bis(4-methoxybenzylidene)acetone), (*S*)–$(CF_3)_3$–*t*-BuPHOX (3.5 mol %), $Bu_4NPh_3SiF_2$ (TBAT, 1.0 equiv), and 2-chloroallyl methanesulfonate (1.2 equiv) in toluene at 35 °C furnished the chloroallyl ketone product (**6**) in 82% yield and 94% ee (Scheme 3). Acid-catalyzed ketal removal, followed by regioselective periodic acid-mediated oxidative cleavage and subsequent carboxylate alkylation furnished α-tetrasubstituted methyl ester **11**. Ozonolysis of the 2-chloroallyl fragment with concomitant methanolysis afforded diester **5** in 54% yield over four steps from alkylation product **6**.

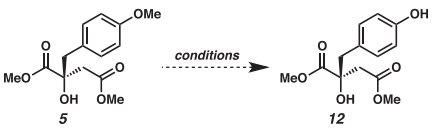


Scheme 3. Construction of diester **5**.

With late-stage diester **5** in hand, seemingly straightforward global demethylation stood as the lone remaining task. Unfortunately, we were unable to unveil the free phenol found in the natural product ((+)-**1**) under either Lewis acidic or nucleophilic conditions (Table 1).[8] In the case of boron tribromide (entry 1), we observed mono-demethylation, but were disappointed to find that the reaction proceeded with undesired chemoselectivity, cleaving one of the methyl esters instead.[9] Other typical demethylation conditions returned starting material (entries 2–5).

Following this unfortunate setback, we revisited our protecting group strategy. We opted to change the phenolic protecting group to a benzyl ether, thereby enabling an orthogonal deprotection event. We thus prepared benzyloxybenzyl silyl enol ether **14** (Scheme 4) and were pleased to find that this compound performed well in our asymmetric alkylation chemistry, forming α-tetrasubstituted dioxanone product **15** in 77% yield and 92% ee. Benzyl-protected diester **16** was synthesized from tertiary ether **15** in 60% yield over a four-step sequence analogous to that described above (cf. Schemes 3 and 4).[10] Our revised protecting group strategy proved fruitful, as hydrogenolysis of the benzyl ether smoothly yielded the free phenol. Subsequent saponification of both methyl esters furnished (+)-eucomic acid ((+)-**1**) in 76% yield over the final two steps.[11]

Table 1
Aryl–OMe deprotection attempts



Entry	Conditions	Result
1[a]	BBr_3, CH_2Cl_2, –78 °C	Mono ester demethylation
2[a,b]	TMSI·quinoline, MeCN, 23 °C→60 °C	No reaction
3[a]	$AlCl_3$, CH_2Cl_2, 0 °C→23 °C	No reaction
4	NaSEt, DMF, reflux	No reaction
5[c]	$AlBr_3$, EtSH, 0 °C→23 °C	No reaction

[a] Reactions performed using 15 equiv of Lewis acid.
[b] TMSI·quinoline complex was also examined in the absence of solvent, without success.
[c] Ethanethiol was used as solvent.

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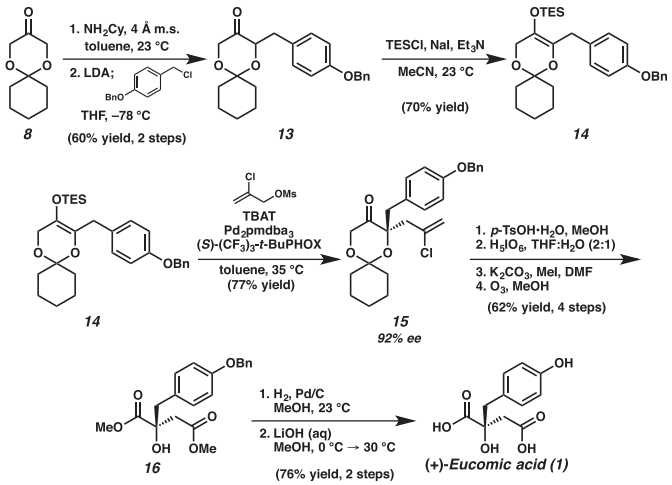

Scheme 4. Successful completion of the first enantioselective total synthesis of (+)-eucomic acid.

3. Conclusion

In summary, we have described an efficient total synthesis of non-natural (+)-eucomic acid. Our route affords the target compound in 14% yield over 13 linear steps from commercially available materials. A palladium-catalyzed asymmetric allylic alkylation reaction was used to generate the stereogenic tetrasubstituted oxygenated center at an early stage. The judicious incorporation of a 2-chloroallyl fragment enabled smooth chemo- and regioselective oxidation late in the synthesis. A surprisingly problematic phenolic deprotection step was circumvented by switching from a methyl ether to a benzyl ether. Efforts to further exploit this chemistry for the benefit of small-molecule synthesis are ongoing in our laboratory and will be reported in due course.

4. Experimental section

4.1. Materials and methods

Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried glassware under an argon atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina).[12] Commercially available reagents were used as received. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. (*S*)-*t*-BuPHOX[13] and tris(4,4′-methoxydibenzylideneacetone)dipalladium(0) ($Pd_2(pmdba)_3$)[14] were prepared by known methods. Et_3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Reagent grade acetone was obtained from Sigma–Aldrich and used as received. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system.[4] Å molecular sieves were oven-dried at 120 °C for a minimum of 24 h and cooled in a desiccator to ambient temperature immediately prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 500 (500 MHz and 126 MHz, respectively) and a Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively) and are reported in terms of chemical shift relative to $CHCl_3$ (δ 7.26 and 77.16, respectively) or MeOH (δ 3.31 and 49.00, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). Analytical chiral SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with Chiralpak AD-H column obtained from Daicel Chemical Industries, Ltd. High resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility using a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or from the Caltech Center for Catalysis and Chemical Synthesis using an Agilent 6200 series TOF with an Agilent G1978A Multimode source in mixed (Multimode ESI/APCI) ionization mode. Optical rotations were measured on a Jasco P-2000 polarimeter operating on the sodium D-line (589 nm), using a 100 mm path-length cell and are reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent).

4.2. 2-(4-Methoxybenzyl)-1,5-dioxaspiro[5.5]undecan-3-one (9)

To a solution of dioxanone **8** (6.0 g, 35.25 mmol, 1.00 equiv) in toluene (120 mL) were charged 4 Å molecular sieves (7.2 g, 1.20 equiv by mass) and cyclohexylamine (7.8 mL, 70.5 mmol, 1.94 equiv). After 13 h, the reaction mixture was filtered over Celite, rinsing with toluene, and concentrated in vacuo to give the crude cyclohexyl imine.

In a separate three-neck flask with an internal temperature probe, a solution of freshly prepared lithium diisopropylamide (LDA, 0.60 M in THF, 1.00 equiv) was cooled to −78 °C (dry ice/isopropanol bath). To the solution of LDA was added crude cyclohexyl imine as a solution in THF (35 mL) dropwise through a cannula with an overpressure of argon. After 5 min, the reaction flask was introduced to a −15 °C bath (ice/methanol) and after 1.75 h was cooled back to −78 °C. To the reaction mixture was then added *p*-methoxybenzyl chloride (PMBCl, 5.80 g, 37.0 mmol, 1.05 equiv) at a rate of 2.00 mL/h with a syringe pump, ensuring the internal temperature did not exceed −70 °C. Upon completion of addition, the reaction was allowed to stir for 30 min before being allowed to slowly warm to ambient temperature. Upon reaching ambient temperature, the reaction was quenched with saturated aqueous NH_4Cl (75 mL) and stirred for 14 h. The reaction mixture was then extracted with Et_2O (5×75 mL). Combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford an orange-tan oil. Flash column chromatography (15% Et_2O in hexanes eluent) afforded alkylated dioxanone **9** (5.04 g, 49% yield) as a light orange solid. R_f=0.4 (4:1 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J*=8.6 Hz, 2H), 6.82 (d, *J*=8.6 Hz, 2H), 4.37 (ddd, *J*=9.3, 3.3, 1.5 Hz, 1H), 4.27 (dd, *J*=17.1, 1.5 Hz, 1H), 4.00 (d, *J*=17.0 Hz, 1H), 3.79 (s, 3H), 3.17 (dd, *J*=14.7, 3.2 Hz, 1H), 2.74 (dd, *J*=14.7, 9.3 Hz, 1H), 1.85–1.78 (m, 1H), 1.63–1.52 (m, 5H), 1.45–1.39 (m, 2H), 1.36–1.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.5, 158.3, 130.5, 129.9, 113.7, 101.0, 75.7, 66.6, 55.4, 34.0, 33.6, 32.4, 25.4, 22.9, 22.7; IR (Neat Film, NaCl) 2935, 2860, 1746, 1612, 1584, 1513, 1463, 1449, 1365, 1300, 1278, 1247, 1177, 1163, 1115, 1035, 967, 929, 824 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{17}H_{22}O_4$ $[M]^+$: 290.1518, found 290.1528.

4.3. Triethyl((2-(4-methoxybenzyl)-1,5-dioxaspiro[5.5]undec-2-en-3-yl)oxy)silane (7)

A 100 mL round bottom was soaked in a 20:1 isopropanol:toluene bath saturated with KOH for 12 h, rinsed with deionized water, acetone, and allowed to dry. To a solution of alkylated dioxanone **9** (2.32 g, 8.0 mmol, 1.00 equiv) in CH_3CN (13.3 mL) in a flame-dried 100 mL base-bathed round bottom flask

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with stir bar were added sodium iodide (2.40 g, 16.0 mmol, 2.00 equiv) in a single portion and Et_3N (3.35 mL, 24.0 mmol, 3.00 equiv) dropwise with stirring. After 5 min, triethylsilyl chloride (TESCl, 2.7 mL, 16.0 mmol, 2.00 equiv) was added dropwise. After 18 h, consumption of starting material was complete as determined by TLC and the reaction mixture was extracted with pentane (3×80 mL). Combined organic layers were washed with water (40 mL), brine (40 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to produce a yellow oil. Flash column chromatography (3.0% Et_2O/0.5% Et_3N in hexanes eluent) on base-treated silica furnished silyl enol ether **7** (2.17 g, 67% yield) as a viscous yellow oil: R_f=0.35 (19:1 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 4.09 (t, J=1.2 Hz, 1H), 3.79 (s, 3H), 3.45 (s, 1H), 1.68–1.54 (m, 4H), 1.44–1.38 (m, 2H), 1.34–1.26 (m, 4H), 1.00 (t, J=7.9 Hz, 9H), 0.68 (q, J=7.8 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 136.6, 131.4, 129.9, 126.1, 113.6, 98.5, 60.4, 55.4, 32.9, 32.9, 25.6, 22.5, 6.9, 5.6; IR (Neat Film, NaCl) 2951, 2937, 2876, 2832, 1612, 1584, 1511, 1462, 1381, 1300, 1246, 1222, 1175, 1153, 1100, 1039, 1011, 974, 940, 864, 846, 827, 730 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{23}H_{35}O_4Si$ $[M-H_2+H]^+$: 403.2305, found 403.2298.

4.4. (*S*)-2-(2-Chloroallyl)-2-(4-methoxybenzyl)-1,5-dioxaspiro [5.5]undecan-3-one (6)

A 500 mL Schlenk flask was soaked in a 20:1 isopropanol:toluene bath saturated with KOH for 12 h, rinsed with deionized water, acetone, and allowed to dry. To a flame-dried 500 mL base-bathed Schlenk flask in a nitrogen-filled glovebox were charged $Bu_4NPh_3SiF_2$ (TBAT, 1.33 g, 2.47 mmol, 1.00 equiv), $Pd_2(pmdba)_3$ (41 mg, 37.1 μmol, 0.015 equiv), (*S*)–$(CF_3)_3$–*t*-BuPHOX (51 mg, 86.5 μmol, 0.035 equiv), and toluene (50 mL, 0.0015 M in Pd). The reaction vessel was immediately removed from the glovebox, introduced to an argon atmosphere, and placed in a pre-heated 35 °C oil bath with stirring. After 20 min, a dark purple solution was observed. 2-Chloroallyl mesylate (0.5 g, 2.96 mmol, 1.20 equiv) was added dropwise over 30 s. After 3 min, silyl enol ether **7** (1.0 g, 2.47 mmol, 1.00 equiv) was added dropwise over 3 min. The resultant brownish-yellow reaction mixture was allowed to stir for 20 h. The resultant clear yellow reaction was then filtered through a pad of SiO_2 using hexanes as the eluent to remove toluene, at which time separate fractions were collected, eluting with Et_2O, to isolate the volatile reaction products. The filtrate was concentrated in vacuo to a bright yellow crude oil. Flash column chromatography (10% Et_2O in hexanes eluent) afforded **6** (0.74 g, 82% yield) as a yellow oil. 94% ee, $[\alpha]_D^{25}$ +11.6 (*c* 1.08, $CDCl_3$); R_f=0.4 (4:1 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (d, J=8.8 Hz, 2H), 6.80 (d, J=8.7 Hz, 2H), 5.35 (d, J=1.1 Hz, 1H), 5.27 (q, J=0.8 Hz, 1H), 4.17 (d, J=18.3 Hz, 1H), 3.87 (d, J=18.3 Hz, 1H), 3.79 (s, 3H), 3.08 (d, J=13.9 Hz, 1H), 3.05 (d, J=13.9 Hz, 1H), 2.85 (dd, J=14.7, 0.8 Hz, 1H), 2.81 (d, J=14.4 Hz, 1H), 1.89–1.81 (m, 1H), 1.74–1.57 (m, 5H), 1.54–1.40 (m, 3H), 1.38–1.28 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6, 158.6, 136.9, 132.1, 127.5, 117.5, 113.4, 100.3, 84.6, 67.1, 55.3, 47.2, 43.0, 35.7, 35.4, 25.2, 23.0, 23.0; IR (Neat Film, NaCl) 2936, 2858, 1738, 1629, 1611, 1512, 1442, 1366, 1301, 1248, 1177, 1157, 1114, 1036, 983, 941, 890, 825 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{20}H_{26}O_4Cl$ $[M+H]^+$: 365.1520, found 365.1536; SFC conditions: 2% IPA, 2.5 mL/min, Chiralpak AD-H column, λ=210 nm, t_R (min): major=18.74, minor=24.78.

4.5. (*S*)-5-Chloro-1,3-dihydroxy-3-(4-methoxybenzyl)hex-5-en-2-one (10)

To a solution of chloroallyl ketal **6** (284 mg, 0.78 mmol, 1.00 equiv) in MeOH (15.5 mL, 0.05 M) was added *p*-toluenesulfonic acid monohydrate (30 mg, 0.156 mmol, 0.20 equiv) in a single portion at 0 °C (ice/water bath) with stirring. After 10 min, the reaction was removed from the ice bath and stirring was continued. After 24 h, consumption of starting material was complete as determined by TLC and the reaction was quenched by the addition of Et_3N (1.2 mL). The mixture was concentrated under reduced pressure and the crude residue was purified by column chromatography (30% EtOAc in hexanes eluent) to afford diol **10** (202 mg, 91% yield) as a white amorphous solid. $[\alpha]_D^{25}$ +26.2 (*c* 1.05, $CDCl_3$); R_f=0.3 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J=8.6 Hz, 2H), 6.83 (d, J=8.7 Hz, 2H), 5.34 (d, J=1.4 Hz, 1H), 5.24 (m, 1H), 4.47 (d, J=20.2 Hz, 1H), 4.05 (d, J=20.2 Hz, 1H), 3.78 (s, 3H), 3.05 (dd, J=14.6, 1.0 Hz, 1H), 3.04 (d, J=13.8 Hz, 1H), 2.82 (d, J=13.8 Hz, 1H), 2.69 (d, J=14.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.2, 159.1, 136.0, 131.4, 126.0, 118.2, 114.2, 81.1, 67.5, 55.3, 48.1, 44.9; IR (Neat Film, NaCl) 3447, 2914, 2836, 1718, 1631, 1611, 1513, 1247, 1179, 1033, 987, 894, 835 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{14}H_{17}O_4Cl$ $[M]^+$: 284.0815, found 284.0805.

4.6. Methyl (*S*)-4-chloro-2-hydroxy-2-(4-methoxybenzyl) pent-4-enoate (11)

To a solution of diol **10** (100 mg, 0.352 mmol, 1.00 equiv) in THF (7.4 mL) and water (3.7 mL) was added H_5IO_6 (127 mg, 0.50 mmol, 1.50 equiv) in one portion at 0 °C (ice/water bath). After 20 min, the reaction was removed from the ice/water bath and stirred for an additional 24 h. The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude white semi-solid which was used immediately without further purification.

To a suspension of the crude residue and K_2CO_3 (97 mg, 0.7 mmol, 2.00 equiv) in DMF (3.5 mL, 0.1 M) was added methyl iodide (44 μL, 0.7 mmol, 2.00 equiv) dropwise at 23 °C. After stirring for 1 h, water (5 mL) was added, and the reaction was extracted with Et_2O (3×40 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (15% EtOAc in hexanes eluent) to give methyl ester **11** (60 mg, 60% yield, two steps) as a white amorphous solid. $[\alpha]_D^{25}$ +1.6 (*c* 0.82, $CDCl_3$); R_f=0.65 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J=8.8 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 5.32 (d, J=1.2 Hz, 1H), 5.27 (dt, J=1.3, 0.7 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.27 (br s, 1H), 3.03 (d, J=13.6 Hz, 1H), 2.97 (dd, J=14.5, 0.9 Hz, 1H), 2.91 (d, J=13.6 Hz, 1H), 2.80 (dd, J=14.5, 0.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 158.8, 136.5, 131.3, 127.2, 117.2, 113.8, 77.0, 55.3, 52.8, 48.3, 44.8; IR (Neat Film, NaCl) 3520, 3000, 2953, 2836, 1738, 1732, 1633, 1612, 1513, 1442, 1248, 1178, 1141, 1115, 1034, 889, 839 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{14}H_{17}O_4Cl$ $[M]^+$: 284.0815, found 284.0824.

4.7. Dimethyl (*S*)-2-hydroxy-2-(4-methoxybenzyl)succinate (5)

A solution of methyl ester **11** (0.21 g, 0.74 mmol, 1.00 equiv) in 28 mL MeOH was cooled to −78 °C (dry ice/isopropanol bath) at which time ozone was bubbled through the solution (O_2 flow rate=1/4 L/min, seven setting on ozone generator) for 2 h. Complete consumption of starting material was determined by TLC, and Na_2SO_3 (0.93 g, 7.4 mmol, 10.00 equiv) was added in one portion. The flask was warmed to room temperature over 30 min. The reaction mixture was poured onto water (25 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash column chromatography (25% EtOAc in hexanes eluent) afforded diester **5** (206 mg, 99% yield) as a clear colorless oil. $[\alpha]_D^{25}$ +12.2 (*c* 0.3, $CDCl_3$); R_f=0.4 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 7.10 (d, *J*=8.6 Hz, 1H), 6.82 (d, *J*=8.6 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.01 (d, *J*=16.1 Hz, 1H), 2.97 (d, *J*=13.3 Hz, 1H) 2.88 (d, *J*=13.7 Hz, 1H), 2.70 (d, *J*=16.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 171.3, 158.9, 131.3, 126.9, 113.8, 76.1, 55.3, 52.9, 52.1, 44.6, 43.0; IR (Neat Film, NaCl) 3494, 2940, 2921, 2358, 1733, 1609, 1511, 1435, 1353, 1247, 1205, 1176, 1116, 1031, 818 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{14}H_{19}O_6$ $[M+H]^+$: 283.1182, found 283.1192.

4.8. 2-(4-(Benzyloxy)benzyl)-1,5-dioxaspiro[5.5]undecan-3-one (13)

Prepared using the same procedure for the synthesis of dioxanone **9**. Dioxanone **8** (2.86 g, 16.8 mmol, 1.00 equiv); 4 Å molecular sieves (5.87 g, 2.05 equiv by mass); cyclohexylamine (3.73 mL, 32.6 mmol, 1.94 equiv); LDA (0.6M in THF, 1.00 equiv); *p*-benzyloxybenzyl chloride (4.1 g, 17.64 mmol, 1.05 equiv). Flash column chromatography (15% Et_2O in hexanes eluent) afforded alkylated dioxanone **13** (3.71 g, 60% yield) as a faint orange oil. R_f=0.55 (7:3 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.38 (ddd, *J*=7.9, 6.9, 0.8 Hz, 2H), 7.36–7.28 (m, 1H), 7.23–7.15 (m, 2H), 6.92–6.88 (m, 2H), 5.06 (s, 2H), 4.37 (ddd, *J*=9.4, 3.3, 1.5 Hz, 1H), 4.28 (dd, *J*=17.0, 1.5 Hz, 1H), 4.01 (d, *J*=17.0 Hz, 1H), 3.18 (dd, *J*=14.7, 3.2 Hz, 1H), 2.74 (dd, *J*=14.6, 9.4 Hz, 1H), 1.87–1.80 (m, 1H), 1.65–1.54 (m, 5H), 1.46–1.39 (m, 2H), 1.37–1.21 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6, 157.5, 137.2, 130.5, 130.2, 128.7, 128.0, 127.6, 114.7, 101.1, 75.7, 70.1, 66.6, 34.0, 33.5, 32.4, 25.3, 22.9, 22.7; IR (Neat Film, NaCl) 3031, 2933, 2860, 1744, 1610, 1583, 1510, 1452, 1364, 1333, 1277, 1241, 1175, 1162, 1114, 1079, 1025, 967, 928, 736, 695 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{23}H_{26}O_4$ $[M]^+$: 366.1831, found 366.1833.

4.9. ((2-(4-(Benzyloxy)benzyl)-1,5-dioxaspiro[5.5]undec-2-en-3-yl)oxy) triethylsilane (14)

Prepared using the same procedure for the synthesis of silyl enol ether **7**. Dioxanone **13** (2.0 g, 5.46 mmol, 1.00 equiv); Et_3N (2.28 mL, 16.38 mmol, 3.00 equiv); TESCl (1.83 mL, 10.92 mmol, 2.00 equiv); NaI (1.63 g, 10.92 mmol, 2.00 equiv). Flash column chromatography (0.5% Et_3N/5.0% Et_2O in hexanes eluent) on base-treated silica furnished silyl enol ether **14** (1.83 g, 70% yield) as a light yellow oil. R_f=0.8 (7:3 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.42 (m, 2H), 7.40–7.36 (m, 2H), 7.34–7.30 (m, 1H), 7.19–7.15 (m, 2H), 6.90–6.87 (m, 2H), 5.06 (s, 2H), 4.09 (t, *J*=1.2 Hz, 2H), 3.45 (s, 2H), 1.71–1.61 (m, 2H), 1.62–1.55 (m, 2H), 1.46–1.37 (m, 2H), 1.35–1.25 (m, 4H), 1.00 (t, *J*=7.9 Hz, 9H), 0.68 (q, *J*=8.1 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.2, 137.4, 136.6, 131.7, 130.0, 128.7, 128.0, 127.6, 126.1, 114.7, 98.5, 70.1, 60.4, 32.9, 32.9, 25.6, 22.5, 6.9, 5.6; IR (Neat Film, NaCl) 3031, 2936, 2875, 1610, 1548, 1510, 1454, 1380, 1290, 1222, 1174, 1152, 1099, 1012, 973, 940, 863, 731, 695 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{29}H_{40}SiO_4$ $[M]^+$: 480.2696, found 480.2715.

4.10. (*S*)-2-(2-Chloroallyl)-2-(4-methoxybenzyl)-1,5-dioxaspiro[5.5]undecan-3-one (15)

Prepared using the same procedure for the synthesis of chloroallyl ketone **6**. Silyl enol ether **14** (500 mg, 1.04 mmol, 1.00 equiv); TBAT (561 mg, 1.04 mmol, 1.00 equiv); $Pd_2(pmdba)_3$ (18 mg, 15.6 μmol, 0.015 equiv); (*S*)–$(CF_3)_3$–*t*-BuPHOX (22 mg, 36.4 μmol, 0.035 equiv); 2-chloroallyl mesylate (213 mg, 1.25 mmol, 1.20 equiv). Flash column chromatography (12% Et_2O in hexanes eluent) afforded **15** (344 mg, 77%) as a light yellow oil. 92% ee $[\alpha]_D^{25}$ +7.1 (*c* 0.72, $CDCl_3$); R_f=0.55 (7:3 hexanes:Et_2O eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.41–7.36 (m, 2H), 7.35–7.30 (m, 1H), 7.13 (d, *J*=8.6 Hz, 1H), 6.87 (d, *J*=8.6 Hz, 1H), 5.36 (d, *J*=1.1 Hz, 1H), 5.27 (q, *J*=0.8 Hz, 1H), 5.04 (s, 2H), 4.17 (d, *J*=18.3 Hz, 1H), 3.88 (d, *J*=18.3 Hz, 1H), 3.09 (d, *J*=13.9 Hz, 1H), 3.04 (d, *J*=13.9 Hz, 1H), 2.85 (dd, *J*=14.6, 0.8 Hz, 1H), 2.83 (d, *J*=14.6 Hz, 1H), 1.90–1.82 (m, 1H), 1.75–1.39 (m, 8H), 1.38–1.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6, 157.9, 137.2, 136.9, 132.2, 128.7, 128.1, 127.9, 127.7, 117.6, 114.4, 100.3, 84.6, 70.1, 67.1, 47.3, 43.0, 35.7, 35.3, 25.2, 23.1, 23.0; IR (Neat Film, NaCl) 3035, 2936, 2858, 1737, 1630, 1610, 1510, 1453, 1366, 1242, 1177, 1158, 1114, 1026, 941, 888, 826, 735, 696 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{26}H_{28}O_4Cl$ $[M-H_2+H]^+$: 439.1676, found 439.1682; SFC conditions: 10% MeOH, 2.5 mL/min, Chiralpak AD-H column, λ=210 nm, t_R (min): major=11.38, minor=12.23.

4.11. (*S*)-3-(4-(Benzyloxy)benzyl)-5-chloro-1,3-dihydroxyhex-5-en-2-one (S1)

Prepared using the same procedure for the synthesis of diol **10**. Chloroallyl ketal **15** (1.38 g, 3.13 mmol, 1.00 equiv); *p*-TsOH•H_2O (124 mg, 0.65 mmol, 0.21 equiv). Flash column chromatography (25% EtOAc in hexanes eluent) afforded diol **S1** (982 mg, 87% yield) as a white solid. $[\alpha]_D^{25}$ +25.4 (*c* 0.82, $CDCl_3$); R_f=0.35 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44–7.37 (m, 4H), 7.36–7.30 (m, 1H), 7.06 (d, *J*=8.6 Hz, 2H), 6.91 (d, *J*=8.6 Hz, 2H), 5.36 (d, *J*=1.4 Hz, 1H), 5.25 (dt, *J*=1.5, 0.7 Hz, 1H), 5.04 (s, 2H), 4.48 (d, *J*=20.2 Hz, 1H), 4.07 (d, *J*=20.2 Hz, 1H), 3.06 (dd, *J*=14.6, 0.9 Hz, 1H), 3.05 (d, *J*=13.7 Hz, 1H), 2.83 (d, *J*=13.8 Hz, 1H), 2.71 (d, *J*=14.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 158.4, 136.9, 136.0, 131.4, 128.8, 128.2, 127.7, 126.3, 118.3, 115.1, 81.1, 70.1, 67.5, 48.1, 44.9; IR (Neat Film, NaCl) 3446, 3032, 2922, 2869, 1716, 1632, 1610, 1511, 1454, 1382, 1242, 1178, 1118, 1066, 1024, 987, 894, 834, 737, 696 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{20}H_{20}O_4Cl$ $[M-H_2+H]^+$: 359.1050, found 359.1060.

4.12. Methyl (*S*)-2-(4-(benzyloxy)benzyl)-4-chloro-2-hydroxypent-4-enoate (S2)

Prepared using the same procedure for the synthesis of methyl ester **11**. Diol **S1** (146 mg, 0.405 mmol, 1.00 equiv); H_5IO_6 (277 mg, 1.21 mmol, 3.00 equiv); K_2CO_3 (104 mg, 0.755 mmol, 1.85 equiv); MeI (107 mg, 0.755 mmol, 1.85 equiv). Flash column chromatography (15% EtOAc in hexanes eluent) afforded methyl ester **S2** (125 mg, 92% yield, two steps) as a white amorphous solid. $[\alpha]_D^{25}$ +4.6 (*c* 1.07, $CDCl_3$); R_f=0.65 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46–7.40 (m, 2H), 7.41–7.37 (m, 2H), 7.36–7.31 (m, 1H), 7.14–7.10 (m, 2H), 6.89 (d, *J*=8.6 Hz, 1H), 5.32 (d, *J*=1.2 Hz, 1H), 5.28 (dd, *J*=1.3, 0.7 Hz, 1H), 5.03 (s, 2H), 3.75 (s, 3H), 3.28 (br s, 1H), 3.04 (d, *J*=13.6 Hz, 1H), 2.97 (dd, *J*=14.6, 0.8 Hz, 1H), 2.91 (d, *J*=13.6 Hz, 1H), 2.80 (dd, *J*=14.6, 0.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 158.1, 137.1, 136.5, 131.3, 128.7, 128.1, 127.6, 127.5, 117.2, 114.7, 77.0, 70.1, 52.8, 48.3, 44.8; IR (Neat Film, NaCl) 3516, 3032, 2952, 2914, 2854, 2362, 1731, 1632, 1609, 1509, 1449, 1381, 1226, 1175, 1139, 1115, 1098, 1018, 890, 837, 803, 737, 696 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{20}H_{22}O_4Cl$ $[M+H]^+$: 361.1207, found 361.1206.

4.13. Dimethyl (*S*)-2-(4-(benzyloxy)benzyl)-2-hydroxysuccinate (16)

Prepared using the same procedure for the synthesis of diester **5**. Methyl ester **S2** (675 mg, 1.87 mmol, 1.00 equiv); Na_2SO_4 (2.36 g, 18.7 mmol, 10.00 equiv). Flash column chromatography (25% EtOAc in hexanes eluent) afforded diester **16** (542 mg, 78% yield) as a white amorphous solid. $[\alpha]_D^{25}$ +18.2 (*c* 0.93, $CDCl_3$); R_f=0.35 (7:3 hexanes:EtOAc eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.41 (m, 2H), 7.42–7.35 (m, 2H), 7.35–7.30 (m, 1H), 7.10 (d, *J*=8.6 Hz, 2H), 6.89 (d, *J*=8.7 Hz, 2H), 5.03 (s, 2H), 3.74 (s, 3H), 3.67 (s, 3H), 3.01 (d,

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J=16.2 Hz, 1H), 2.97 (d, J=13.7 Hz, 1H), 2.88 (d, J=13.6 Hz, 1H), 2.70 (d, J=16.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 171.4, 158.2, 137.1, 131.3, 128.7, 128.1, 127.6, 127.2, 114.7, 76.1, 70.1, 52.9, 52.1, 44.6, 43.0; IR (Neat Film, NaCl) 3506, 3031, 2949, 2858, 1735, 1609, 1582, 1509, 1437, 1352, 1220, 1175, 1119, 1013, 967, 839, 739, 696 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{20}H_{23}O_6$ $[M+H]^+$: 359.1495, found 359.1477.

4.14. Dimethyl (*S*)-2-hydroxy-2-(4-hydroxybenzyl)succinate (12)

A solution of **16** (220 mg, 0.61 mmol, 1.00 equiv) in MeOH (12 mL) was purged with H_2 (balloon) for 10 min. To this solution was added Pd/C (10 wt%, 63 mg, 0.06 mmol, 0.10 equiv) in one portion and the reaction mixture was stirred under H_2 atmosphere (balloon). After 1 h, consumption of starting material was determined by TLC analysis. The mixture was filtered through Celite, rinsing with MeOH. The filtrate was concentrated under reduced pressure and flash column chromatography (33% acetone in hexanes eluent) afforded phenol **12** (144 mg, 88% yield) as a white amorphous solid. $[\alpha]_D^{25}$ +25.7 (c 2.7, $CDCl_3$); R_f=0.5 (1:1 acetone:-hexane eluent). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J=8.7 Hz, 2H), 6.73 (d, J=8.5 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 3.02 (d, J=16.2 Hz, 1H), 2.96 (d, J=13.6 Hz, 1H), 2.88 (d, J=13.7 Hz, 1H), 2.72 (d, J=16.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 171.4, 155.0, 131.5, 126.9, 115.3, 76.1, 53.0, 52.1, 44.6, 43.0; IR (Neat Film, NaCl) 3423, 3018, 2961, 2919, 2847, 1735, 1613, 1594, 1515, 1439, 1351, 1263, 1215, 1170, 1116, 1000, 835 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{13}H_{17}O_6$ $[M+H]^+$: 269.1025, found 269.1020.

4.15. (+)-Eucomic acid ((+)-1)

To a solution of diester **12** (30 mg, 0.112 mmol, 1.00 equiv) in MeOH (1.50 mL) was added a 1.0 M aqueous solution of LiOH (1.00 mL, 1.00 mmol, 8.92 equiv) dropwise at 0 °C. After 15 min, the reaction was transferred to a preheated 30 °C oil bath. After 20 h, full conversion was determined by mass spectrometry analysis.[15] The crude reaction mixture was concentrated under reduced pressure to remove methanol. To the resulting aqueous solution was added 1 N aqueous HCl (4 mL), followed by extraction with EtOAc (9×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to afford (+)-eucomic acid (**1**) (23 mg, 86% yield) as a white solid. $[\alpha]_D^{25}$ +17.0 (c 1.15, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.06 (d, J=8.5 Hz, 2H), 6.68 (d, J=8.5 Hz, 2H), 2.95 (d, J=16.6 Hz, 1H), 2.94 (d, J=13.4 Hz, 1H), 2.86 (d, J=13.7 Hz, 1H), 2.56 (d, J=16.2 Hz, 1H); ^{13}C NMR (101 MHz, CD_3OD) δ177.7, 174.2, 157.4, 132.6, 127.6, 115.8, 76.8, 45.5, 43.6; IR (Neat Film, NaCl) 3193, 2917, 2850, 1722, 1613, 1598, 1515, 1442, 1223, 1175, 1116, 838, 774 cm^{-1}; HRMS (ESI/APCI) m/z calcd for $C_{11}H_{11}O_6$ $[M-H]^-$: 239.0561, found 239.0563.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.02.059.

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