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Efficient syntheses of *trans*-(+)-laurediol from carbohydrate precursors

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Abstract—Two routes for the synthesis of the marine natural product *trans*-laurediol **6** are described. In the first approach **6** is obtained in ten steps and 21% overall yield from monoacetone D-glucose. The second route provides the target in eleven steps and 13% yield from D-mannose. Both routes are more efficient, both in terms of number of steps and overall yield, than previously reported syntheses.

1. Introduction

A rich variety of halogenated nonisoprenoid sesquiterpenes have been isolated from the widely distributed red algae of the genus *Laurencia*.[1] The structures of these natural products are diverse and include *trans*-kumausyne **1**, *trans*-deacetylkumausyne **2**, srilankenyne **3**, *trans*-obtusenyne **4**, and obtusine **5**. The biosynthesis of these compounds has been proposed to occur via the electrophilic cyclization of the linear glycols, *trans*-laurediol **6** and *cis*-laurediol **7**, which have been isolated from *Laurencia nipponica* (Fig. 1).[2]

A recent synthesis[3] of **2** involved, as the key step, a bromonium ion-promoted cyclization of **7** and thus these linear diols represent useful starting materials for the preparation of **1**–**5** and related compounds. Consequently, the development of efficient routes for the preparation of **6** and **7** have been the subject of a number of investigations. The first synthesis of **6**, by Masamune and co-workers was accomplished in 21 steps from (2*R*,3*R*)-(+)-tartaric acid.[4] Immediately following their report was another by Martín and co-workers who synthesized **6** and **7** from propargylic alcohol in 28 steps.[5] Later work by the Martín group led to a 12-step synthesis of **6** from 1,4-butanediol using a Sharpless asymmetric dihydroxylation reaction as the key step.[6] We describe herein two alternative syntheses of **6**, which employ readily available carbohydrate derivatives as the source of the chirality.

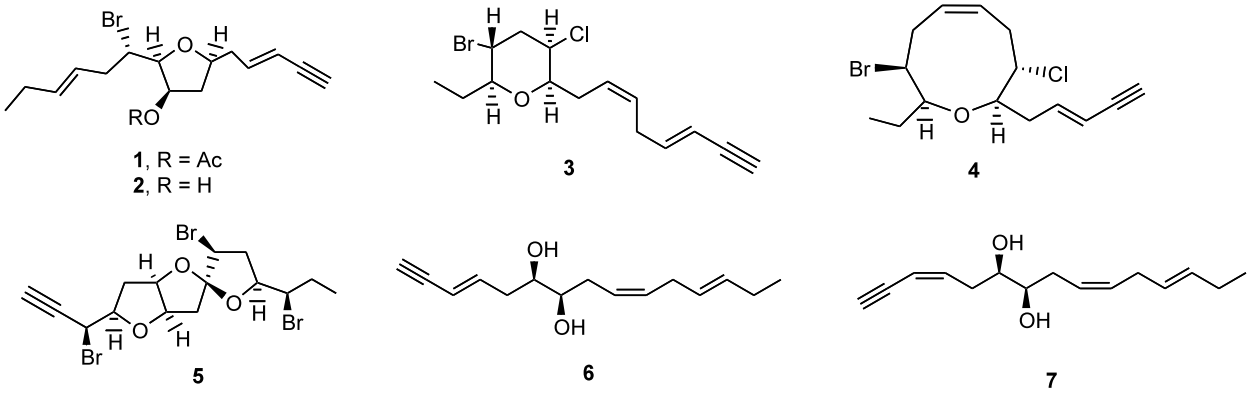

Figure 1. Structures of *trans*-kumausyne **1**, *trans*-deacetylkumausyne **2**, srilankenyne **3**, *trans*-obtusenyne **4**, obtusine **5**, *trans*-laurediol **6** and *cis*-laurediol **7**.

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2. Results and discussion

The retrosynthetic analysis of our first approach to **6** is provided in Fig. 2. We envisaged that this diol could be obtained from **16** by reaction with the appropriate Wittig reagent followed by debenzoylation. Lactol **16** could be prepared from **10** by a sequence of reactions including a stereoselective Wittig olefination and deoxygenation at C-2. In turn, hemiacetal **10** could be synthesized from the hydroxy alkene **9** through a regiocontrolled Pd(II) mediated Wacker oxidation.[7] The synthesis of **9** from commercially available monoacetone glucose **8** has been previously reported.[8]

Thus, monoacetone-D-glucose **8** was converted into **9** in 82% yield upon treatment[8] with iodine, triphenylphosphine, and imidazole in refluxing THF (Scheme 1). This alkene was subsequently reacted[7] under standard Wacker oxidation conditions to provide lactol **10** as a 2:1 diastereomeric mixture in 83% yield. Wittig reaction of **10** with the ylide derived from (E)-CH_3CH_2-$CH{=}CHCH_2CH_2P^+Ph_3I^-$ resulted in its stereoselective conversion into diene **11**, which was then protected as the corresponding benzoate ester **12** in 81% yield over the two steps.

With **12** in hand, all that remained was the deoxygenation at C-2 and introduction of the enyne side chain at C-1. To this end, the isopropylidene acetal was cleaved with dry 0.1 M HCl in refluxing methanol to give a 1:1 α:β mixture of methyl furanosides **13** in 89% yield. Deoxygenation at C-2 was accomplished via a two-step protocol. Alcohol **13** was converted to the corresponding 2-phenoxythiocarbonate **14** in 95% yield by treatment with PhOC(S)Cl and pyridine and this product was then deoxygenated upon reaction with n-Bu_3SnH and AIBN in refluxing toluene.[9] Methyl glycoside **15** was obtained in 78% yield and subsequent hydrolysis yielded **16** in 88% yield. This hemiacetal was then reacted with the ylide obtained upon reaction of the commercially available 3-(trimethylsilyl-2-propynyl)-triphenyl phosphonium bromide with freshly sublimed t-BuOK. The product of this Wittig reaction was not purified;[10] rather, following workup and concentration, the reaction mixture was treated with NaOH in methanol to yield **6** in 65% yield from **16**. This route provides **6** in ten steps from **8** in 21% overall yield.

We also explored another route to **6**, which is illustrated in Scheme 2. This synthesis makes use of lactone **18**, which can be prepared[11] in two steps from D-man-

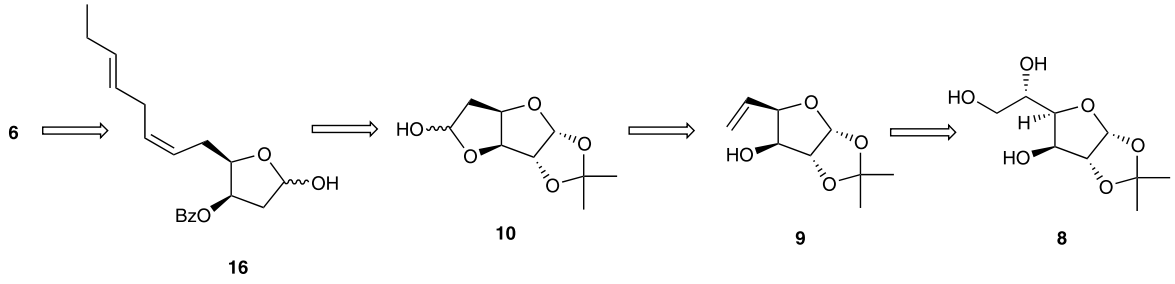
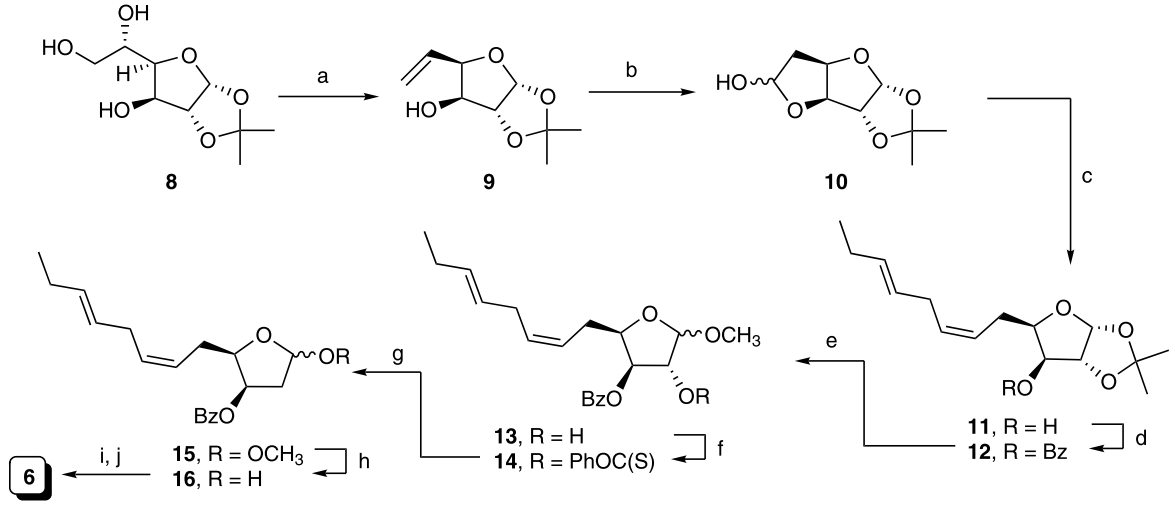
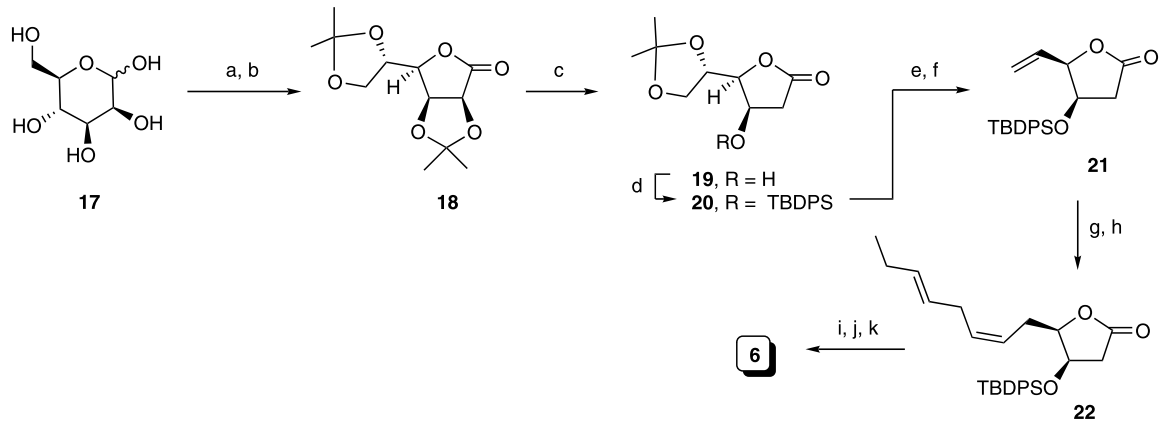


Figure 2. Retrosynthetic analysis for the synthesis of **6** from monacetone glucose **8**.



Scheme 1. *Reagents and conditions*: (a) I_2, Ph_3P, imidazole, THF, reflux, 3 h, 82%; (b) $PdCl_2$ (cat), CuCl, O_2, DMF:water (4:1), rt, 4 h, 83%; (c) (E)-EtCH=$CHCH_2CH_2PPh_3I$, $KN(TMS)_2$, THF, –20°C, 2 h, 85%; (d) BzCl, pyridine, CH_2Cl_2, 0°C, 1 h, 95%; (e) AcCl, CH_3OH, reflux, 12 h, 89%; (f) PhOC(S)Cl, pyridine, DMAP, CH_2Cl_2, 0°C, 1 h, 95%; (g) n-Bu_3SnH, AIBN (cat), toluene, reflux, 2 h, 78%; (h) 30% aq. AcOH, 1N HCl, 60°C, 3 h, 88%; (i) $TMSCCCH_2PPh_3Br$, t-BuOK, Et_2O, –10°C, 1 h; (j) NaOH, CH_3OH, rt, 2 h, 65% (two steps).



Scheme 2. *Reagents and conditions*: (a) acetone, H_2SO_4, $CuSO_4$, rt, 12 h, 82%; (b) PCC, CH_2Cl_2, reflux, 3 h, 81%; (c) SmI_2, THF, rt, 5 min, 91%; (d) TBDPSCl, imidazole, DMF, rt, 3 h, 88%; (e) HOAc:H_2O, (3:2), rt, 8 h; (f) I_2, Ph_3P, imidazole, THF, reflux, 3 h, 66% (from **20**); (g) $PdCl_2$ (cat), CuCl, O_2, DMF:water (8:2), rt, 5 h; (h) (*E*)-EtCH=CHCH$_2$CH$_2$PPh$_3$I, KN(TMS)$_2$, THF, −20°C, 2 h, 67% (from **21**); (i) DIBAL-H, toluene, −20°C, 1 h; (j) TMSCCCH$_2$PPh$_3$Br, *t*-BuOK Et$_2$O, −10°C, 1 h; (k) *n*-Bu$_4$NF, THF, rt, 2 h, 55% (from **22**).

nose **17**. Treatment of **18** with samarium iodide[12] gave, in 91% yield, alcohol **20**, which was then protected as its *t*-butyldiphenylsilyl ether in 88% yield. Cleavage of the 5,6-isopropylidene acetal and subsequent deoxygenation of the product diol with triphenylphosphine and iodine afforded alkene **21** in 66% yield. Wacker oxidation of **21** followed by Wittig reaction with (*E*)-$CH_3CH_2CH{=}CHCH_2CH{=}PPh_3$ afforded the known lactone **22**[6b] in 67% yield over two steps. Diol **6** was obtained in three steps from **20** as previously reported.[6b] The route illustrated in Scheme 2 afforded **6** in eleven steps from **17** in 13% overall yield.

In summary, we have developed two efficient routes for the synthesis of *trans*-laurediol **6**, a marine natural product that is proposed to be the biosynthetic precursor of a number of halogenated nonisoprenoid sesquiterpene natural products. In one approach the product is obtained in ten steps from monoacetone glucose **8**. In the other approach, **6** can be obtained in eleven steps from D-mannose **17**. Both routes give the product in fewer number of steps and higher overall yield than earlier syntheses.[4–6]

3. Experimental

3.1. General

Solvents were distilled from the appropriate drying agents before use. Unless stated otherwise, all reactions were carried out under a positive pressure of argon and were monitored by TLC on silica gel 60 F_{254} (0.25 mm, E. Merck). Spots were detected under UV light or by charring with 10% H_2SO_4 in ethanol. Solvents were evaporated under reduced pressure and below 40°C (bath). Organic solutions of crude products were dried over anhydrous Na_2SO_4. Column chromatography was performed on silica gel 60 (40–60 μM). The ratio between silica gel and crude product ranged from 100 to 50:1 (w/w). Optical rotations were measured at 21± 2°C. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 250, 400 or 500 MHz, and chemical shifts are referenced to either TMS (0.0, $CDCl_3$). ^{13}C NMR spectra were recorded at 62.5, 100, or 125 MHz, and ^{13}C chemical shifts are referenced to $CDCl_3$ (77.00, $CDCl_3$). Electrospray mass spectra were recorded on samples suspended in THF or CH_3OH.

3.2. (2*S*,3*S*,4*R*,5*R*)-2,2-Dimethyl-hexahydrofuro[2′,3′:4,5]-furo[2,3-*d*][1,3]dioxol-5-ol, 10

To a solution of alkene **9**[8] (0.70 g, 3.76 mmol) in 20% aq. DMF (15 mL) was added $PdCl_2$ (0.13 g, 0.73 mmol) and CuCl (0.56 g, 5.6 mmol) in one portion. Air was bubbled through the solution for 4 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (100 mL), and the resulting mixture was filtered through Celite and rinsed with CH_2Cl_2 (2×50 mL). The organic layers were combined and washed with 1 M aq. HCl solution (100 mL) and water (2×100 mL). The organic phase was separated, dried, filtered, and concentrated. Purification of the resulting residue by chromatography (5:1, hexanes/EtOAc) afforded the title compound **10** (0.63 g, 83%) as a white solid as a 2:1 mixture of diastereomers: R_f 0.41 (2:1, hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 6.03 (d, 0.43H, J=3.8 Hz), 5.88 (d, 0.56H, J=3.8 Hz), 5.64 (ddd, 0.56H, J=5.3, 5.3, 3.9 Hz), 5.47 (dd, 0.43H, J=8.4, 5.5 Hz), 4.97–4.92 (m, 1H), 4.78 (d, 0.43H, J=3.8 Hz), 4.65–4.63 (m, 1.13H), 4.52 (d, 0.43H, J=3.7 Hz), 3.80 (d, 0.56H, J=3.9 Hz), 3.71 (d, 0.43H, J=8.5 Hz), 2.42 (dd, 0.56H, J=14.7, 5.4 Hz), 2.28 (d, 0.43H, J=14.5 Hz), 2.12–1.96 (m, 1.12H), 1.51–1.49 (m, 4.65H), 1.34 (s, 1.29H), 1.32 (s, 1.81H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 112.6, 112.2, 106.9 (2), 100.6, 100.4, 87.9, 85.8, 85.3, 84.0, 83.4, 83.1, 41.0, 40.7, 27.6, 27.5, 27.1, 27.0. HRMS (ESI) calcd for $[C_9H_{14}O_5]Na^+$ 225.0733, found 225.0725.

3.3. (2*S*,3*S*,4*R*,5*R*)-2,2-Dimethyl-5-[octa-2(*Z*),5(*E*)-dienyl]-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-ol, 11

To a slurry of (*E*)-$CH_3CH_2CH{=}CHCH_2CH_2PPh_3I$ (3.50 g, 7.41 mmol), 4 Å molecular sieves in dry THF (30 mL) at −20°C was added 0.5 M $KN(TMS)_2$ solution (14.8 mL, 7.41 mmol) in toluene. After stirring for 30 min, a solution of **10** (0.6 g, 2.97 mmol) in dry THF (10 mL) was added dropwise and the resulting mixture was allowed to stir for 2 h. A satd. aq. solution of ammonium chloride (50 mL) was added the resulting mixture was subsequently extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (30 mL), dried, filtered, and concentrated to give an oily residue, which was purified via column chromatography (6:1 hexanes/EtOAc) to provide **11** (0.74 g, 85%) as a colorless oil: R_f 0.50 (2:1, hexanes/EtOAc); $[\alpha]_D$ +29.3 (*c* 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$, δ_H) 5.91 (d, 1H, $J=3.8$ Hz), 5.62–5.34 (m, 4H), 4.51 (d, 1H, $J=3.8$ Hz), 4.16 (ddd, 1H, $J=8.3$, 8.3, 2.4 Hz), 4.06 (br s, 1H), 2.83–2.70 (m, 2H), 2.51–2.39 (m, 2H), 2.06–1.95 (m, 2H), 1.88 (br s, 1H), 1.50 (s, 3H), 1.31 (s, 3H), 0.96 (t, 3H, $J=7.5$ Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$, δ_C) 133.1, 131.2, 127.3, 124.8, 111.9, 104.8, 85.6, 80.3, 75.4, 30.9, 27.0, 26.5, 26.2, 25.9, 14.2. HRMS (ESI) calcd for $[C_{15}H_{24}O_5]Na^+$ 291.1566, found 291.1576.

3.4. (2*S*,3*S*,4*R*,5*R*)-Benzoic acid 2,2-dimethyl-5-[octa-2(*Z*),5(*E*)-dienyl]-tetrahydro-furo[2,3-*d*][1,3]dioxol-6-yl ester, 12

To a solution of **11** (0.6 g, 2.24 mmol) in CH_2Cl_2 (10 mL) and pyridine (2 mL) at 0°C was added benzoyl chloride (0.31 mL, 3.0 mmol) dropwise over 20 min. The reaction mixture was subsequently warmed to rt and stirred for 1 h before being diluted with CH_2Cl_2 (25 mL). This solution was washed successively with a 2% aq. HCl solution (1×50 mL), a satd aq. $NaHCO_3$ solution (1×50 mL), and water (1×50 mL). The organic layer was dried, filtered, and concentrated to afford the crude product, which was purified via chromatography (10:1, hexanes/EtOAc) to give **12** (0.79 g, 95%) as a colorless oil: R_f 0.43 (3:1, hexanes/EtOAc); $[\alpha]_D$ +36.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.14 (d, 2H, $J=7.1$ Hz), 8.05 (d, 2H, $J=7.1$ Hz), 7.64 (dd, 2H, $J=7.5$, 7.5 Hz), 7.57 (dd, 1H, $J=7.4$, 7.4 Hz), 7.51 (dd, 2H, $J=8.0$, 7.6 Hz), 7.44 (dd, 2H, $J=7.9$, 7.5 Hz), 5.98 (d, 1H, $J=3.8$ Hz), 5.47–5.26 (m, 5H), 4.63 (d, 1H, $J=3.9$ Hz), 4.39 (ddd, 1H, $J=7.3$, 7.3, 2.8 Hz), 2.68–2.48 (m, 4H), 1.93–1.88 (m, 2H), 1.55 (s, 3H), 1.32 (s, 3H), 0.90 (t, 3H, $J=7.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 165.8, 133.9, 133.0, 131.5, 130.2, 129.8, 128.9, 127.0, 124.4, 112.3, 105.0, 84.0, 79.5, 77.3, 30.8, 27.0, 26.6, 26.0, 25.9, 14.1. HRMS (ESI) calcd for $[C_{22}H_{28}O_5]Na^+$ 395.1834, found 395.1821.

3.5. (3*S*,4*R*,5*R*)-Benzoic acid 4-hydroxy-5-methoxy-2-octa-[2(*Z*),5(*E*)-dienyl]-tetrahydro-furan-3-yl ester, 13

To a solution of dry methanol (10 mL) was added acetyl chloride (0.1 mL) at 0°C followed by the addition of **12** (0.7 g, 1.91 mmol). The resulting solution was refluxed for 12 h under argon before being cooled and neutralized with pyridine (0.5 mL). The solution was then concentrated to an oily residue, which was purified via chromatography (6:1 hexanes/EtOAc) to yield **13** (0.53 g, 89%) as a colorless oil as a 1:1 α:β mixture: R_f 0.21 (1:1, hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$, δ_H) 8.07–8.03 (m, 2.00H), 7.59 (dd, 1.17H, $J=7.4$, 7.4 Hz), 7.45 (dd, 2.34H, $J=7.9$, 7.9 Hz), 5.54–5.28 (m, 4.99H), 5.19 (dd, 0.77H, $J=5.3$, 2.1 Hz), 5.05 (d, 0.41H, $J=4.7$ Hz), 4.90 (d, 0.72H, $J=1.6$ Hz), 4.49–4.27 (m, 2.34H), 2.74–2.42 (m, 4.85H), 1.97–1.92 (m, 2.59H), 0.95–0.90 (m, 3.44H); ^{13}C NMR (100 MHz, $CDCl_3$, δ_C) 167.2, 166.6, 133.9, 133.8, 133.0, 131.1, 130.9, 130.2, 130.0, 129.9, 128.9 (2), 127.2, 127.1, 125.4, 125.0, 109.5, 101.8, 81.1, 80.4, 80.3, 80.1, 77.8 (2), 77.4, 77.1, 56.2, 56.1, 30.9, 28.9, 27.7, 25.9, 14.2. HRMS (ESI) calcd for $[C_{20}H_{26}O_5]Na^+$ 369.1678, found 369.1661.

3.6. (3*S*,4*R*,5*R*)-Benzoic acid 5-methoxy-2-octa-[2(*Z*),5(*E*)-dienyl]-4-phenoxythiocarbonyloxy-tetrahydro-furan-3-yl ester, 14

To a solution of **13** (0.4 g, 1.16 mmol) in dry CH_2Cl_2 (5 mL) under an argon atmosphere was added pyridine (2 mL), followed by the subsequent addition of DMAP (10 mg) and phenyl chlorothionoformate (0.19 mL, 1.4 mmol) at 0°C. The reaction was allowed to stir for 1 h and then a satd. aq. $NaHCO_3$ solution (2 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (2×25 mL) and the combined organic phases were dried, filtered, and concentrated to afford an oily residue, which was purified by chromatography (12:1 hexanes/EtOAc) to provide **14** (0.5 g, 95%) as a pale yellow oil: R_f 0.61 (2:1, hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 8.15–8.13 (m, 2H), 7.54–7.46 (m, 5H), 7.35–7.31 (m, 2H), 7.19–7.18 (m, 2H), 5.90 (m, 0.37H), 5.75–5.72 (m, 1H), 5.56–5.42 (m, 3H), 5.35–5.32 (m, 1H), 5.22 (s, 0.63H), 4.62 (ddd, 0.63H, $J=5.8$, 2.4, 2.4 Hz), 4.54 (dd, 0.37H, $J=6.2$, 6.2 Hz), 3.56–3.54 (m, 3H), 2.76–2.48 (m, 4H), 2.02–1.98 (m, 2H), 1.00–0.96 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ_C) 195.1, 194.0, 166.2, 165.8, 154.0 (2), 153.9, 133.9, 133.1, 131.2, 130.2, 130.3, 130.1 (2), 130.0, 129.8, 129.0 (2), 127.2, 127.1, 127.0, 125.1, 124.8, 122.3, 122.2 (2), 106.9, 100.1, 89.3, 86.0, 82.1, 77.1, 76.6, 75.6, 56.2, 56.1, 31.0 (2), 28.9, 27.6, 25.9, 14.2. HRMS (ESI) calcd for $[C_{27}H_{30}O_6]Na^+$ 489.1712, found 489.1701.

3.7. (4*R*,5*R*)-Benzoic acid 5-methoxy-2-octa-[2(*Z*),5(*E*)-dienyl]-tetrahydro-furan-3-yl ester, 15

To a solution of **14** (0.4 g, 0.85 mmol) in toluene (5 mL) was added tri-*n*-butyltin hydride (0.29 g, 1.0 mmol) and AIBN (12 mg, 0.1 mmol) at rt. The resulting mixture was heated at reflux for 2 h, cooled, and the solvent evaporated. The resulting residue was purified by chromatography (10:1 hexanes/EtOAc) to yield **15** (0.31 g, 78%) as a colorless oil: R_f 0.53 (3:1, hexanes/EtOAc); $[\alpha]_D$ +59.1 (*c* 0.9, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$, δ_H) 8.07 (dd, 2H, $J=8.2$, 1.2 Hz), 7.53 (dd, 1H, $J=7.9$, 1.2 Hz), 7.43 (dd, 2H, $J=6.4$, 6.4 Hz),

5.52–5.30 (m, 5H), 5.11 (dd, 1H, $J=5.7$, 1.2 Hz), 4.21 (ddd, 1H, $J=5.8$, 1.9, 1.9 Hz), 3.44 (s, 3H), 2.69 (dd, 2H, $J=5.7$, 5.2 Hz), 2.62–2.40 (m, 3H), 2.27–2.21 (m, 1H), 1.96–1.90 (m, 2H), 0.95–0.88 (m, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$, δ_C) 167.1, 156.2, 133.8, 133.0, 131.1, 130.3, 130.1, 128.9, 127.2, 125.4, 121.0, 115.8, 104.8, 82.4, 73.7, 55.8, 40.0, 31.0, 29.0, 25.9, 18.0, 14.2. HRMS (ESI) calcd for $[C_{20}H_{26}O_4]Na^+$ 353.1729, found 353.1705.

3.8. (4*R*,5*R*)-Benzoic acid 5-hydroxy-2-octa-[2(*Z*),5(*E*)-dienyl]-tetrahydro-furan-3-yl ester, 16

A solution of compound **15** (0.25 g, 0.76 mmol) in 30% aqueous acetic acid (10 mL) and 1N HCl (2 mL) was stirred for 3 h at 60°C. The reaction mixture was subsequently neutralized with a satd aq. $NaHCO_3$ solution (5 mL) and extracted into CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (10 mL), dried, filtered, and concentrated. The crude product was purified by chromatography (6:1, hexanes/EtOAc) to yield the title compound **16** (0.21 g, 88%) as a colorless oil: R_f 0.15 (1:1, hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 8.12–8.08 (m, 2.00H), 7.61 (dd, 1.01H, $J=7.4$, 7.4 Hz), 7.48 (dd, 2.02H, $J=7.9$, 7.9 Hz), 5.81 (br s, 0.75H), 5.64–5.59 (m, 1.26H), 5.54–5.39 (m, 3.05H), 5.33–5.29 (m, 0.96H), 4.40 (ddd, 0.76H, $J=7.0$, 7.0, 3.6 Hz), 4.16 (ddd, 0.21H, $J=7.1$, 7.1, 4.0 Hz), 3.85 (br s, 0.72H), 3.61 (d, 0.19H, $J=6.4$ Hz), 2.74–2.48 (m, 4.29H), 2.43 (dd, 1.53H, $J=4.0$, 4.0 Hz), 2.01–1.94 (m, 2.02H), 0.94 (t, 3.00H, $J=7.5$ Hz); (125 MHz, $CDCl_3$, δ_C) 166.3, 166.2, 133.7, 133.6, 133.0, 131.2 (2), 130.4, 130.3, 130.1 (2), 129.0, 128.9, 127.1, 125.1, 98.4, 97.8, 82.5, 80.0, 75.4, 74.0, 42.2, 41.3, 30.9 (2), 28.9, 27.4, 25.9, 14.2. HRMS (ESI) calcd for $[C_{19}H_{24}O_4]Na^+$ 339.1572, found 339.1566.

3.9. Synthesis of *trans*-laurediol 6 from 16

To a suspension of $TMSCCCH_2PPh_3Br$ (0.37 g, 0.82 mmol) in anhydrous Et_2O (5 mL) under an argon atmosphere at −10°C was added potassium *tert*-butoxide (92 mg, 0.82 mmol) and the reaction mixture was stirred for 30 min. A solution of lactol **16** (0.2 g, 0.63 mmol) in Et_2O (5 mL) was added dropwise over the course of 30 min, and the resulting mixture was allowed to stir for 1 h. A satd. aq. solution of ammonium chloride was added followed by Et_2O (20 mL). The organic layer was separated, dried, filtered, and concentrated to obtain the crude protected product. The crude product was dissolved in CH_3OH (10 mL), followed by the addition of NaOH (0.1 g, 2.5 mmol) and the mixture was allowed to stir for 2 h at rt. The reaction mixture was then neutralized with acetic acid (0.2 mL) and concentrated to an oily residue, which was purified by chromatography (6:1 hexanes/EtOAc) to afford target compound **6** (0.13 g, 65% over two steps) as a colorless oil: $[\alpha]_D^{23}$ +22.1 (*c* 1.0, CCl_4); lit:[6b] $[\alpha]_D^{25}$ +19.8 (*c* 1.2, CCl_4); lit:[2] $[\alpha]_D$ +27.2 (no concentration or temperature data reported). The ^{1}H and ^{13}C NMR spectral data for this compound matched those previously reported for 6.[2,6b] HRMS (ESI) calcd for $[C_{15}H_{22}O_2]Na^+$ 257.1512, found 257.1535.

3.10. (5*R*,4*R*)-5-(2,2-Dimethyl-[1,3]dioxolan-4(*R*)-yl)-4-hydroxy-dihydro-furan-2-one, 19

To a solution of **18**[11] (2.57 g, 10 mmol) in anhydrous ethylene glycol (7.2 g, 120 mmol) and deoxygenated anhydrous THF (10 mL) was added dropwise a solution of 0.1 M SmI_2 in THF (30 mL, 30 mmol) at rt under an argon atmosphere. After stirring for 5 min, a satd. aq. $NaHCO_3$ solution was added and then the mixture was extracted with EtOAc. The organic layer was washed with a sat. aq. $Na_2S_2O_3$ solution, water, and brine before being dried, filtered, and evaporated. The product was purified by chromatography (8:1 hexanes/EtOAc) to yield **19** (1.83 g, 91%) as a white solid. R_f 0.63 (2:1 hexanes/EtOAc); $[\alpha]_D$ +39.9 (*c* 0.9, $CHCl_3$), mp = 63–65°C; ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 4.70–4.65 (m, 2H), 4.30–4.27 (m, 2H), 4.08 (dd, 1H, $J=5.4$, 10.9 Hz), 2.37 (dd, 1H, $J=4.8$, 17.3 Hz), 2.25 (br s, 1H), 2.22 (d, 1H, $J=17.3$ Hz), 1.48 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125.7 MHz, $CDCl_3$ δ_C) 110.1, 84.7, 72.3, 70.2, 67.6, 39.3, 27.2, 25.5. HRMS (EI) calcd for (M+Na) $C_9H_{14}O_5$ 225.0739, found 225.0721.

3.11. (5*R*,4*R*)-4-(*t*-Butyldiphenylsilanyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4(*R*)-yl)-dihydro-furan-2-one, 20

To a solution of **19** (1.0 g, 8.9 mmol) in DMF (10 mL) was added imidazole (1.4 g, 24 mmol) followed by the addition of *t*-butyldiphenylchlorosilane (1.4 mL, 16 mmol). The resulting solution was stirred at rt for 3 h. The reaction mixture was subsequently partitioned between H_2O (10 mL) and ether (20 mL) and the organic layer was washed with water (3×10 mL), dried, filtered and concentrated. The crude product was purified by chromatography (10:1 hexanes/EtOAc) to give **20** (3.45 g, 88%) as a colorless oil. R_f 0.43 (4:1 hexanes/EtOAc); $[\alpha]_D$ +49.1 (*c* 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, δ_H) 7.80–7.69 (m, 4H), 7.52–7.30 (m, 6H), 4.72–4.64 (m, 2H), 4.30–4.22 (m, 2H), 4.08 (dd, 1H, $J=5.4$, 10.9 Hz), 2.37 (dd, 1H, $J=4.8$, 17.3 Hz), 2.22 (d, 1H, $J=17.3$ Hz), 1.48 (s, 3H), 1.43 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$ δ_C) 175.3, 136.5, 136.1, 135.2, 133.6, 132.6, 130.6, 130.5, 128.4, 128.1, 109.9, 84.9, 72.3, 70.2, 67.6, 39.3, 27.2, 25.6, 19.6. HRMS (EI) calcd for (M+Na) $C_{25}H_{32}O_5Si$ 463.1917, found 463.1901.

3.12. (4*R*,5*R*)-4-(*t*-Butyldiphenylsilanoxy)-5-vinyl-dihydro-furan-2-one, 21

A mixture of compound **20** (2.0 g, 4.5 mmol) and 60% aq. acetic acid (50 mL) was stirred at rt for 8 h. The resulting solution was azeotropically distilled with toluene in vacuo to obtain the crude product. The diol (4.5 mmol) was redissolved in THF (50 mL) containing triphenylphosphine (4.7 g, 18 mmol) and imidazole (1.2 g, 18 mmol) and the solution was heated to 50°C. To this mixture was added iodine (4.5 g, 18 mmol) and the solution was heated at reflux for 3 h. The reaction mixture was then cooled and evaporated and the resulting syrup was dissolved in EtOAc and successively washed with 5% aq. NaOH, a sat. aq. $Na_2S_2O_3$ solution, and water. The organic layer was dried, filtered

and concentrated. The product was purified by chromatography (10:1 hexanes/EtOAc) to yield **21** (1.09 g, 66%, two steps). R_f 0.65 (3:1 hexanes/EtOAc); $[\alpha]_D$ +36.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.77–7.65 (m, 4H), 7.52–7.30 (m, 6H), 5.49–5.43 (m, 2H), 4.77 (dd, 1H, $J=5.6$, 5.6 Hz), 4.61 (dd, 1H, $J=4.8$, 8.8 Hz), 2.45–2.43 (m, 1H), 1.12 (s, 9H); ^{13}C NMR (125.7 MHz, $CDCl_3$ δ) 175.2, 136.2, 136.1, 133.3, 132.9, 132.2, 130.6, 130.5, 128.3 (2), 120.4, 89.2, 717.7, 38.7, 27.3, 19.6. HRMS (EI) calcd for (M+Na) $C_{22}H_{26}O_3Si$ 389.1549, found 389.1530.

3.13. (4*R*,5*R*)-4-(*t*-Butyldiphenylsilanoxy)-5-[octa-2(*Z*),5(*E*)-dienyl]-dihydro-furan-2-one, 22

To a solution of **21** (1.40 g, 3.8 mmol) in 20% aq. DMF (15 mL) was added $PdCl_2$ (0.13 g, 0.73 mmol) and CuCl (0.56 g, 5.6 mmol) in one portion. Air was bubbled through the solution for 5 h at rt. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and the resulting mixture was filtered through Celite and rinsed with CH_2Cl_2 (2×50 mL). The organic layers were combined and washed with 1 M aq. HCl solution (100 mL) and water (2×100 mL). The organic phase was separated, dried, filtered, and concentrated. This crude product was used in the next step without further purification. To a slurry of the (*E*)-$CH_3CH_2CH{=}CHCH_2CH_2PPh_3I$ (2.14 g, 4.6 mmol), 4 Å molecular sieves in dry THF (30 mL) at −20°C was added 0.5 M $KN(TMS)_2$ solution (9.4 mL, 4.71 mmol) in toluene. After stirring for 30 min a solution of the crude aldehyde (1.45 g, 3.8 mmol) in dry THF (10 mL) was added dropwise and the resulting mixture was allowed to stir for 2 h. A sat. aq. solution of ammonium chloride (50 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were washed with water (30 mL) dried, filtered, and concentrated. The product was purified by chromatography (8:1; hexanes/EtOAc) to provide **22** (1.14 g, 67%) as a colorless oil. R_f 0.35 (4:1 hexanes/EtOAc); $[\alpha]_D$ +76.1 (*c* 0.8, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$, δ_H) 7.68–7.60 (m, 4H), 7.51–.29 (m, 6H), 5.57–5.31 (m, 4H), 4.55 (ddd, 1H, $J=4.3$, 4.3, 4.6 Hz), 4.29 (ddd, 1H, $J=4.3$, 4.3, 8.4 Hz), 2.76–2.71 (m, 2H), 2.68–2.63 (m, 1H), 2.48–2.43 (m, 1H), 2.42 (d, 2H, $J=4.3$ Hz), 2.00–1.95 (m, 2H), 1.07 (s, 9H), 1.00 (dd, 3H, $J=8.3$ Hz); ^{13}C NMR (125.7 MHz, $CDCl_3$ δ_C) 174.1, 135.4, 132.7, 132.4, 131.8, 130.8, 129.9, 128.8, 127.4, 126.1, 124.0, 84.7, 70.1, 38.5, 30.8, 26.8, 25.8, 25.3, 18.9, 14.0. HRMS (EI) calcd for (M+Na) $C_{28}H_{36}O_3Si$ 471.2331, found 471.2317.

3.14. Synthesis of *trans*-Laurediol 6 From 22

To a solution of **22** (1.0 g, 2.2 mmol) in toluene at −20°C was added a solution of 1 M DIBAL-H (2.15 mL, 2.15 mmol) in hexanes, and the mixture was stirred for 1 h while warming to rt. The solution was diluted with sat. aq. solution of sodium potassium tartarate (10 mL) and allowed to stir for 3 h at rt. The resulting mixture was extracted with Et_2O (3×25 mL) and the combined organic phases were dried, filtered, and concentrated to afford the lactol which was used immediately without further purification. To a suspension of $TMSCCCH_2PPh_3Br$ (1.29 g, 3.0 mmol) in anhydrous Et_2O (5 mL) under an argon atmosphere at −10°C was added potassium *t*-butoxide (335 mg, 3.0 mmol) and the reaction was stirred for 30 min. A solution of the lactol (1.0 g, 2.2 mmol) in Et_2O (5 mL) was added dropwise over the course of 30 min, and the resulting mixture was allowed to stir for 1 h, before a satd. aq. solution of ammonium chloride (10 mL) and Et_2O (20 mL) were added. The organic layer was separated, dried, filtered, and concentrated. This crude product was dissolved in THF (10 mL) followed by addition of *n*-Bu_4NF (1 M solution in THF, 2.5 mL, 2.5 mmol) and the mixture was allowed to stir for 2 h at rt. The reaction mixture was then concentrated and the residue purified by column chromatography (6:1, hexanes/EtOAc) to provide **6** (0.28 g, 55% over three steps) as a colorless oil: $[\alpha]_D$ +21.4 (*c* 0.9, CCl_4), The ^1H and ^{13}C spectral data for this compound matched those previously reported for **6**.[2,6b] HRMS (ESI) calcd for $[C_{15}H_{22}O_2]Na^+$ 257.1512, found 257.1522.

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