Synthesis Y. Kurogome et al. Paper

Synthesis of Decytospolide A, B and Their C-3 Epimers Using Stereoselective Oxypalladation

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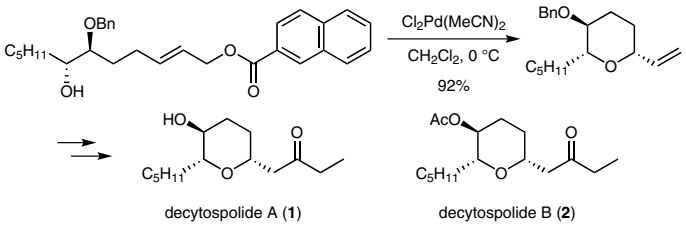

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Abstract Stereoselective synthesis of decytospolide A and B and their C-3 epimers, which have a 2,6-*cis*-tetrahydropyran ring, has been achieved in high stereoselectivity and yield. The oxypalladation of single diastereomers of 6-(benzyloxy)-7-hydroxydodec-2-enyl 2-naphthoates was optimized to give products with a 2,6-*cis*-tetrahydropyran ring with high diastereoselectivity and yield.

Key words natural products, palladium, antitumor agents, cyclization, total synthesis

Tetrahydropyrans (THPs) are widely distributed in nature and most of them show interesting biological activities. So far, great efforts have been devoted toward the total synthesis of natural products that contain a THP ring, such as (–)-apicularen A, (–)-diospongine A, pyranicin, and so on (Figure 1).[1] Recently, Zhang and co-workers isolated decytospolide A (**1**) and B (**2**) from *Cytospora* sp., an endophytic fungus from *Ilex canariensis*.[2] Decytospolide A has significant antitumor activity against A549 tumor cell lines. In the last four years, effort has been devoted to the total synthesis of decytospolides. Since the first total syntheses of decytospolide, reported by Reddy and co-workers[3] and Krishna and co-workers[4] independently, eight reports have been published. Liu and co-workers used the palladium-catalyzed decarboxylative allylation of 3,4-dihydro-2*H*-pyran to form the THP ring.[5] Quite recently, Prins reaction,[6] regioselective reduction of the carbonyl group,[7] and olefin metathesis,[8] intramolecular oxa-Michael reaction,[9] and 3,3-sigmatropic rearrangement[10] were applied to the synthesis of decytospolides. We have developed a palladium(II)-catalyzed diastereoselective cyclization (oxypalladation and azapalladation) for the construction of THP,[11] piperidine,[12] and pyrrolidine[13] rings. But there is room for improvement in the

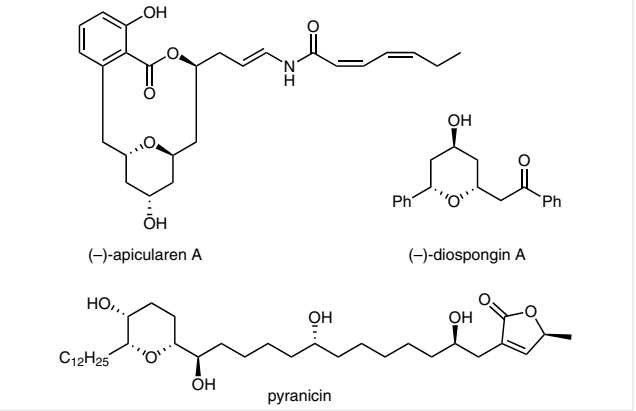


Figure 1 Examples of natural products that possess the tetrahydropyran ring

diastereoselectivity and yield of 2,6-*cis*-tetrahydropyran formation. Here, we wish to report the further optimization of the diastereoselectivity of tetrahydropyran ring formation and its application to the stereoselective synthesis of decytospolide A (**1**) and B (**2**) using oxypalladation (Figure 2).

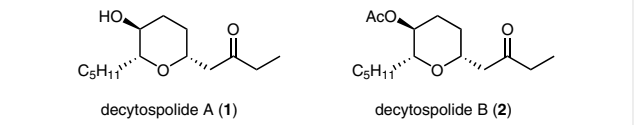
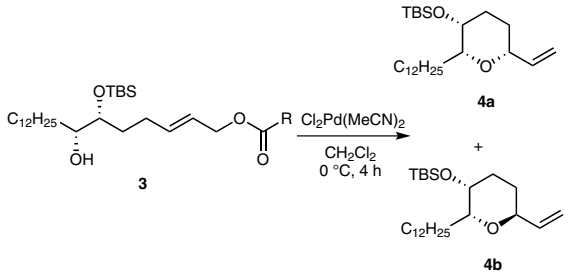


Figure 2 The structures of decytospolide A (**1**) and B (**2**) isolated from *Ilex canariensis*

At first, we examined the diastereoselective oxypalladation of aromatic allylic esters as a model study. Although we found in a previous report that $Cl_2Pd(MeCN)_2$ as the catalyst and CH_2Cl_2 as the solvent gave good stereoselectivity, the chemical yield was only 74%.[11] Thus we focused on the

structures of aromatic allylic esters to obtain high yields. We examined the reaction condition using various allylic esters **3** (Table 1).

Table 1 Diastereoselective Oxypalladation of Aromatic Allyl Esters **3**



R	Yield (%)	Ratio **4a**/**4b**[a]
mesityl	78	84:16
Ph	55	91:9
biphenyl-4-yl[11]	74	93:7[b]
2,4,6-triisopropylphenyl	50	95:5
1-naphthyl	98	85:15
2-naphthyl	99	95:5

[a] The ratio of **4a**/**4b** was determined by ^{1}H NMR analysis.
[b] The reaction was carried out –10 °C.

As a result, the 2-naphthoate ester gave good stereoselectivity and yield, respectively. A chairlike transition state with equatorial orientation of substituents at the 2- and 6-positions can explain the favorable formation of the desired stereoisomer **4a** (**A**) as we reported previously.[11b] Steric factors, such as the 2-naphthyl group, which has 'planar' bulkiness, seem to be necessary to obtain high selectivity (Figure 3).

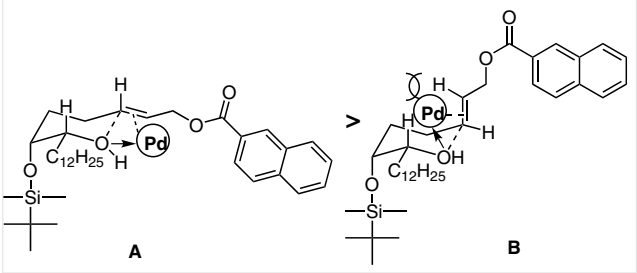
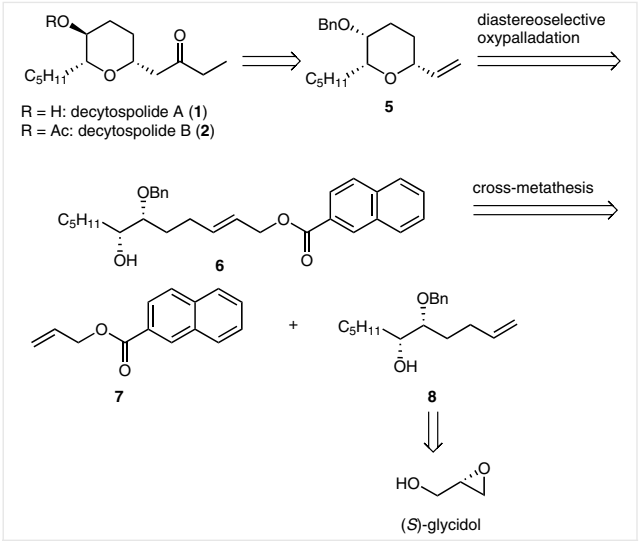


Figure 3 Proposed mechanism of diastereoselective oxypalladation

Next we focused on its application to the synthesis of decytospolide A (**1**) and B (**2**). Our synthetic strategy is outlined in Scheme 1. The key step is diastereoselective oxypalladation of aromatic allylic ester **6**. Compound **6** would be synthesized from **7** and **8** using Grubbs cross-metathesis. Alcohol **8** could be synthesized from commercially available (*S*)-glycidol (Scheme 1).



Scheme 1 Synthetic strategy for decytospolide A (**1**) and B (**2**)

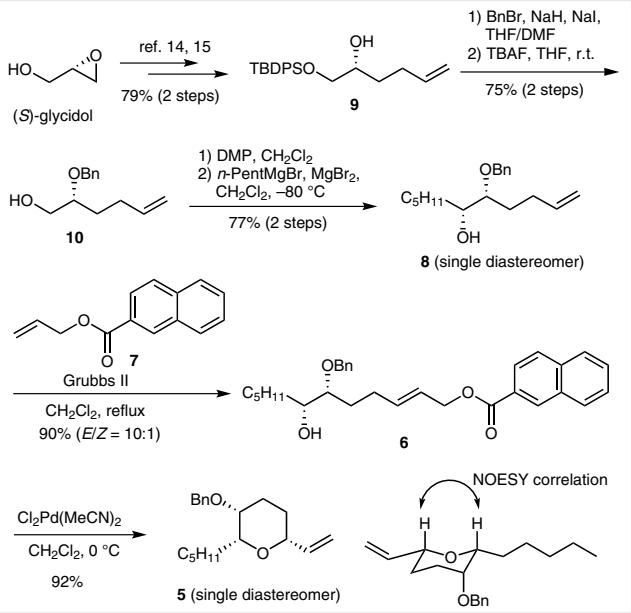
As shown in Scheme 2, the cyclization precursor **6** was prepared as follows. The alcohol **9** was prepared from (*S*)-glycidol using reported procedures.[14,15] The secondary hydroxy group of **9** was protected as a benzyl group followed by deprotection of the TBDPS group to afford primary alcohol **10**. The primary hydroxy group of **10** was oxidized with Dess–Martin periodinane followed by treatment with *n*-pentylmagnesium bromide in the presence of $MgBr_2$ to give **8** as a single diastereomer.[16] Determination of the absolute configuration of the newly formed chiral center was not performed at this stage. Cross-metathesis reaction of **8** with 5 equivalents of allyl 2-naphthoate (**7**) afforded cyclization precursor **6** in 90% yield (*E*/*Z* = 10:1).[17] When this reaction was performed using Hoveyda–Grubbs 2nd generation catalyst the yield of desired product was only 12%. Using Grubbs 1st generation catalyst furnished **6** in 42% yield (Scheme 2,Table 2). The absolute configuration of **6** was confirmed using advanced Mosher methodology (see the Supporting Information).[18] The *E*/*Z* geometrical isomers of **6** were not separated.

Table 2 Cross-Metathesis Reaction of **8** with Naphthoate Ester **7**[a]

Catalyst (5 mol%)	Yield (%)
Hoveyda–Grubbs 2nd	12
Grubbs 1st	42
Grubbs 2nd	90

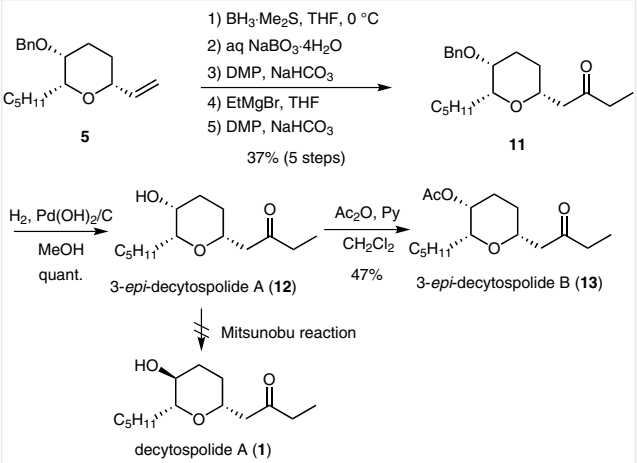
[a] The reaction was carried out in CH_2Cl_2 (0.05 mol/L) for 12 h under reflux; catalyst 5 mol% calculated from **8**.

Oxypalladation of **6** using $Cl_2Pd(MeCN)_2$ as a catalyst gave tetrahydropyran **5** as a single diastereomer. The geometry of the double bond did not affect the diastereoselectiv-



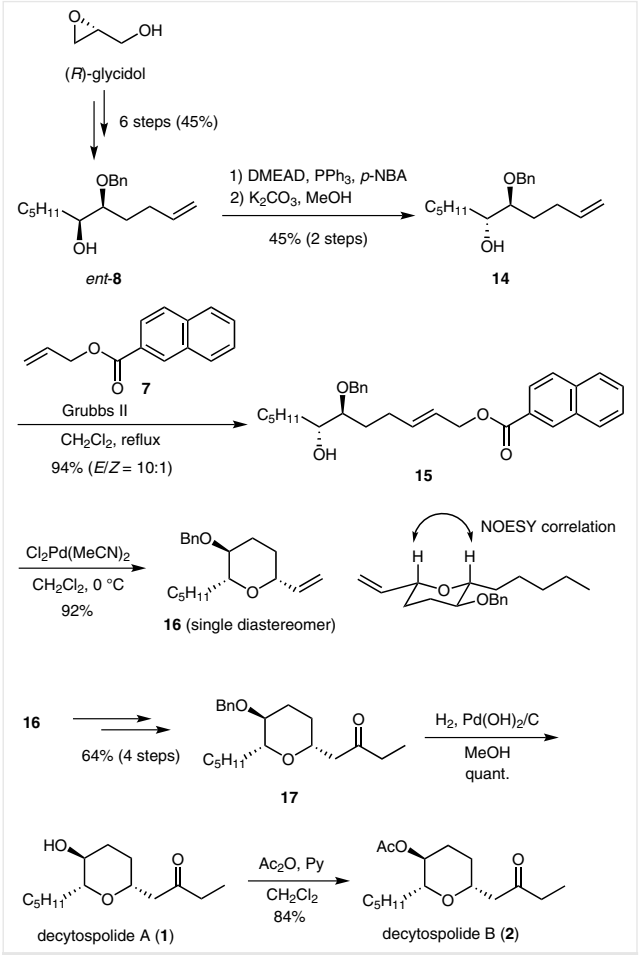
Scheme 2 Synthesis of THP moiety of decytospolides

ity. The relative stereochemistry of **5** was determined by a 2D-NOESY experiment. Hydroboration of **5** using borane–dimethyl sulfide complex, oxidation of the resulting primary hydroxy group with Dess–Martin periodinane, treatment of the aldehyde with ethylmagnesium bromide, and subsequent oxidation with Dess–Martin periodinane gave **11**. These four steps did not require any purification. Hydrogenolysis of the benzyl ether of **11** afforded 3-*epi*-decytospolide A (**12**). Finally, we tried to invert the secondary hydroxy group at the C-3 position using the Mitsunobu reaction. However, Mitsunobu inversion did not proceed using various reaction conditions. 3-*epi*-Decytospolide A (**12**) was converted into 3-*epi*-decytospolide B (**13**) (Scheme 3).



Scheme 3 First attempt to synthesize decytospolide A (**1**)

Because the Mitsunobu reaction of **12** did not work, we modified our synthetic plan as shown in Scheme 4. We decided to invert the secondary hydroxy group at the C-3 position before cyclization. The synthesis started from (*R*)-glycidol, using the same procedure as described before, to afford *ent*-**8**. Mitsunobu inversion of *ent*-**8** using di-2-methoxyethyl azodicarboxylate (DMEAD), PPh_3, and *p*-nitrobenzoic acid followed by treatment with K_2CO_3 in MeOH afforded **14**. Cross-metathesis reaction of **14** with 2-naphthoate ester **7** afforded cyclization precursor **15** in 94% yield (*E*/*Z* = 10:1). The *E*/*Z* geometrical isomers of **15** could not be separated. Oxypalladation of **15** using $Cl_2Pd(MeCN)_2$ as a catalyst gave **16** as a single diastereomer. The stereochemistry at benzyloxy group and the geometry of double bond did not affect the diastereoselectivity. The relative stereochemistry of **16** was determined by a 2D-NOESY experiment. Compound **16** was successfully converted into decytospolide A (**1**) and B (**2**) as described in the synthesis of 3-



Scheme 4 Synthesis of decytospolide A (**1**) and B (**2**)

epi-decytospolides. The physical and spectral data of the synthetic decytospolide A (**1**) and B (**2**) were consistent with those of the reported values (Scheme 4).[2,10]

In conclusion, we have improved the stereoselectivity and chemical yield of oxypalladation of 6-(benzyloxy)-7-hydroxydodec-2-enyl 2-naphthoates to form the 2,6-*cis*-tetrahydropyran ring. This methodology was applied to the stereoselective synthesis of decytospolide A (**1**) and B (**2**). Decytospolide A (**1**) and B (**2**) were synthesized from (*R*)-glycidol through 15 steps in 12% overall yield and 16 steps in 10% yield, respectively.

CH_2Cl_2 was distilled from CaH_2, THF was distilled from sodium benzophenone ketyl; Silica gel and other materials were used as received. All reactions were carried out under argon. ^1H and ^{13}C NMR spectra were obtained at r.t. on a Bruker Avance 500 MHz instrument. Chemical shifts were relative to TMS as an internal standard. Mass spectra were obtained on JEOL GC-mate II mass spectrometer. IR spectra were recorded with JASCO FT-IR 480 Plus infrared spectrophotometer. Optical rotations were determined with a JASCO DIP-1000 polarimeter.

(*R*)-2-(Benzyloxy)hex-5-en-1-ol (10)

To a solution of NaH (60% dispersion in mineral oil, 2.5 g, 63.5 mmol) in THF/DMF (5:1, 120 mL) was added **9** (9.0 g, 25.4 mmol) in THF (7 mL) at 0 °C and the mixture was stirred for 10 min. BnBr (6.0 mL, 50.8 mmol) in THF (6 mL) was added to the mixture over 10 min followed by NaI (370 mg, 2.5 mmol). The mixture was stirred for 7 h at r.t., the reaction was quenched with MeOH (5 mL), and the mixture was stirred for 1 h, diluted with sat. aq NH_4Cl, and extracted with hexane/EtOAc (3:1). The organic layer was dried ($MgSO_4$) and concentrated. The residue was dissolved in THF (120 mL) and TBAF (1.0 M in THF, 50 mL, 50 mmol) was added to the solution. The mixture was stirred for 12 h at r.t., and the reaction was quenched with sat. aq NH_4Cl and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to afford **10** (3.9 g, 75%, 2 steps) as a colorless oil. The physical and spectral data were identical with those of the reported values.[19]

(5*R*,6*R*)-5-(Benzyloxy)undec-1-en-6-ol (8)

To a solution of **10** (3.71 g, 18 mmol) and $NaHCO_3$ (3.6 g, 43.2 mmol) in CH_2Cl_2 (90 mL) was added Dess–Martin periodinane (9.2 g, 21.6 mmol) at 0 °C. The mixture was stirred for 1 h at r.t., the reaction was quenched with sat. aq $NaHCO_3/Na_2S_2O_3$ (1:1, 20 mL), and the mixture was stirred until the organic layer was clear. The mixture was extracted with Et_2O (60 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude aldehyde was used for the next step without further purification. Next the crude aldehyde was diluted with CH_2Cl_2 (300 mL) and $MgBr_2$ (993 mg, 5.4 mmol) was added to the solution. To this mixture was added *n*-pentylmagnesium bromide (2.0 M in Et_2O, 27 mL, 54 mmol) at –80 °C and the mixture was stirred for 8 h at this temperature. When the reaction was complete, the reaction was quenched with sat. aq NH_4Cl and the mixture was vigorously stirred. The mixture was extracted with Et_2O and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified with silica gel column chromatography (hexane/EtOAc = 8:1) to afforded **8** (3.84 g, 77%, 2 steps) as a colorless oil; $[\alpha]_D^{20}$ –6.32 (*c* 1.17, $CHCl_3$).

IR (film): 3446, 3065, 3031, 2930, 2858, 1640, 1496, 1454, 1376, 1207, 1071, 1027, 995, 911, 734, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 5.85–5.80 (m, 1 H), 5.05–4.97 (m, 2 H), 4.66 (d, *J* = 6.5 Hz, 1 H), 4.51 (d, *J* = 6.5 Hz, 1 H), 3.56–3.53 (m, 1 H), 3.30–3.33 (m, 1 H), 2.24–2.14 (m, 3 H), 1.78–1.20 (m, 10 H), 0.89 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.39, 138.33, 128.47, 127.84, 127.79, 114.83, 81.66, 72.67, 72.56, 33.46, 31.88, 29.60, 29.34, 25.44, 22.62, 14.06.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{18}H_{28}O_2$; 276.2089, found: 276.2083.

(6*R*,7*R*,2*E*)-6-(Benzyloxy)-7-hydroxydodec-2-enyl 2-Naphthoate (6); Typical Procedure

To a solution of **8** (878 mg, 3.2 mmol) and allyl 2-naphthoate (**7**) (3.4 g, 15.8 mmol) in CH_2Cl_2 (320 mL) was added Grubbs 2nd catalyst (131 mg, 0.16 mmol) and the reaction mixture was heated under reflux for 40 h. When the reaction was complete, the solvent was removed under reduced pressure to give an oily residue. To this residue Et_2O/hexane (7 mL; 2:5) were added and the resulting white precipitate was removed by filtration. The filtrate was concentrated and the residue was purified with silica gel column chromatography ($CHCl_3$/EtOAc = 40:1 to 20:1) to afford **6** (1.31 g, 90%) as a colorless oil; $[\alpha]_D^{20}$ +0.400 (*c* 1.89, $CHCl_3$). *E*/*Z* = 10:1.

IR (film): 3500, 3061, 3029, 2930, 2857, 1715, 1455, 1375, 1353, 1281, 1226, 1195, 1130, 1092, 1027, 960, 865, 826, 762, 735, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.07 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.89–7.87 (m, 2 H), 7.61–7.53 (m, 2 H), 7.37–7.27 (m, 5 H), 5.92–5.88 (m, 1 H), 5.78–5.74 (m, 1 H), 4.84–4.82 (m, 2 H), 4.65 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 3.57–3.55 (m, 1 H), 3.35–3.32 (m, 1 H), 2.23–2.20 (m, 3 H), 1.80–1.20 (m, 10 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.55, 138.24, 135.85, 132.45, 131.05, 129.33, 128.47, 128.21, 128.11, 127.83, 127.81, 127.74, 127.50, 126.61, 125.24, 124.43, 81.57, 72.64, 72.59, 65.68, 33.42, 31.87, 29.56, 27.93, 25.45, 22.61, 14.05.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{30}H_{36}O_4$; 460.2614, found: 460.2618.

(2*R*,3*R*,6*R*)-3-(Benzyloxy)-2-pentyl-6-vinyltetrahydropyran (5); Typical Procedure

To a solution of **6** (46 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) was added $Cl_2Pd(MeCN)_2$ (1.3 mg, 5 μmol) at 0 °C. The mixture was stirred for 2 h at this temperature, and the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified with preparative TLC (hexane/EtOAc = 5: 1) to afford **5** (26 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ –20.6 (*c* 1.70, $CHCl_3$).

IR (film): 3029, 2929, 2857, 1455, 1339, 1311, 1204, 1085, 989, 919, 732, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H), 5.94–5.87 (m, 1 H), 5.24 (d, *J* = 17.5 Hz, 1 H), 5.08 (d, *J* = 10.5 Hz, 1 H), 4.68 (d, *J* = 12.5 Hz, 1 H), 4.41 (d, *J* = 12.5 Hz, 1 H), 3.87–3.84 (m, 1 H), 3.34–3.29 (m, 2 H), 2.20–2.17 (m, 1 H), 1.81–1.45 (m, 5 H), 1.32–1.20 (m, 5 H), 1.12–1.08 (m, 1 H), 0.85 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.23, 138.66, 128.18, 128.10, 127.50, 114.77, 79.85, 78.76, 71.08, 70.48, 31.90, 31.62, 26.27, 26.16, 25.20, 22.56, 14.06.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{19}H_{28}O_2$; 288.2089, found: 288.2087.

1-[(2*R*,5*R*,6*R*)-5-(Benzyloxy)-6-pentyltetrahydropyran-2-yl]butan-2-one (11); Typical Procedure

To a solution of **5** (107 mg, 0.37 mmol) in THF (20 mL) was added borane–dimethyl sulfide complex (1.0 M in THF, 3.7 mL, 3.7 mmol) at 0 °C. The mixture was stirred for 6 h at the same temperature, the reaction was diluted with water and $NaBO_3·4H_2O$ (113 mg, 0.74 mmol) and the resulting mixture was stirred for 1 h at r.t. The mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water, brine, dried ($MgSO_4$), and concentrated. The crude primary alcohol was used for the next step without purification. The crude alcohol was diluted with CH_2Cl_2 (10 mL) and Dess–Martin periodinane (170 mg, 0.4 mmol) and $NaHCO_3$ (67 mg, 0.8 mmol) were added to the mixture at 0 °C. The mixture was stirred for 1 h at r.t., the reaction was quenched with sat. aq $NaHCO_3$/$Na_2S_2O_3$ (1:1, 10 mL), and the mixture was stirred until the organic layer was clear. The mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude aldehyde was used for the next step without purification. The crude aldehyde was diluted with THF (10 mL) and EtMgBr (3.0 M in Et_2O, 1.0 mL, 1.0 mmol) was added to the solution dropwise at –80 °C. The mixture was stirred for 3 h at 0 °C, and the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The crude product was used for the next step without purification. The crude material was diluted with CH_2Cl_2 (5 mL) and Dess–Martin periodinane (81 mg, 0.19 mmol) and $NaHCO_3$ (32 mg, 0.38 mmol) were added to the mixture at 0 °C. The mixture was stirred for 1 h at r.t., the reaction was quenched with sat. aq $NaHCO_3$/$Na_2S_2O_3$ (1:1, 10 mL), and the mixture was stirred until the organic layer was clear. The mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified with preparative TLC (hexane/EtOAc = 4:1) to give **11** (46 mg, 37%, 4 steps) as a colorless oil; $[\alpha]_D^{19}$ –49.7 (*c* 1.52, $CHCl_3$).

IR (film): 3029, 2934, 2857, 1714, 1496, 1455, 1411, 1375, 1344, 1274, 1205, 1081, 1027, 923, 732 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 4.67 (d, *J* = 12.5 Hz, 1 H), 4.41 (d, *J* = 12.0 Hz, 1 H), 3.81–3.78 (m, 1 H), 3.29–3.25 (m, 2 H), 2.80 (dd, *J* = 15.0, 8.0 Hz, 1 H), 2.57–2.40 (m, 2 H), 2.36 (dd, *J* = 15.0, 4.5 Hz, 1 H), 2.13 (dd, *J* = 14.0, 2.5 Hz, 1 H), 1.68–1.61 (m, 2 H), 1.52–1.37 (m, 3 H), 1.28–1.17 (m, 5 H), 1.11–1.06 (m, 1 H), 1.02 (t, *J* = 6.8 Hz, 3 H), 0.85 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.48, 138.49, 128.15, 128.11, 127.52, 127.49, 79.92, 74.80, 71.36, 70.55, 48.63, 37.34, 31.70, 31.52, 26.27, 26.15, 25.11, 22.51, 13.96, 7.41.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{21}H_{32}O_3$; 332.2352, found: 332.2354.

3-*epi*-Decytospolide A (12); Typical Procedure

A solution of **11** (41 mg, 0.12 mmol) in MeOH (6 mL) was hydrogenated over a catalytic amount of $Pd(OH)_2/C$ (4 mg) for 1 h. The mixture was filtered and the filtrate was concentrated to afford **12** (30 mg, quant) as a colorless oil; $[\alpha]_D^{19}$ –11.9 (*c* 1.07, $CHCl_3$).

IR (film): 3450, 2935, 2857, 1713, 1457, 1376, 1274, 1078, 1037, 994, 920 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.84–3.81 (m, 1 H), 3.60 (s, 1 H), 3.33 (dd, *J* = 8.3, 5.3 Hz, 1 H), 2.71 (dd, *J* = 15.0, 8.0 Hz, 1 H), 2.55–2.43 (m, 2 H), 2.41 (dd, *J* = 15.3, 4.8 Hz, 1 H), 1.98–1.93 (m, 2 H), 1.72–1.56 (m, 1 H), 1.61–1.23 (m, 10 H), 1.04 (t, *J* = 7.3 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.95, 80.05, 74.80, 65.89, 48.71, 37.14, 31.68, 31.55, 30.78, 25.72, 25.10, 22.52, 13.96, 7.46.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{14}H_{26}O_3$; 242.1882, found: 242.1887.

3-*epi*-Decytospolide B (13); Typical Procedure

To a solution of **12** (11 mg, 0.046 mmol) and pyridine (0.013 mL, 0.18 mmol) in CH_2Cl_2 (3 mL) were added Ac_2O (0.08 mL, 0.09 mmol) and a catalytic amount of DMAP (2 mg) at 0 °C. The mixture was stirred for 9 h at r.t., and the reaction was quenched with water. After removal of the solvent under reduced pressure, the residue was purified with preparative TLC (hexane/EtOAc = 4:1) to afford **13** (6.2 mg, 47%) as a colorless oil; $[\alpha]_D^{20}$ –36 (*c* 0.39, $CHCl_3$).

IR (film): 2937, 2857, 1736, 1716, 1459, 1371, 1242, 1083, 1024, 962, 730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.81 (s, 1 H), 3.88–3.83 (m, 1 H), 3.43–3.41 (m, 1 H), 2.76 (dd, *J* = 15.5, 7.5 Hz, 1 H), 2.55–2.40 (m, 3 H), 2.11 (s, 3 H), 2.01 (dd, *J* = 6.3, 2.8 Hz, 1 H), 1.77–1.71 (m, 1 H), 1.64 (br s, 1 H), 1.56–1.48 (m, 2 H), 1.37–1.24 (m, 7 H), 1.04 (t, *J* = 7.3 Hz, 3 H), 0.86 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.77, 170.82, 78.45, 74.36, 68.22, 48.63, 37.10, 31.59, 31.48, 28.28, 26.21, 24.99, 22.47, 13.95, 7.50.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{16}H_{28}O_4$: 284.1988, found: 284.1990.

(5*S*,6*S*)-5-(Benzyloxy)undec-1-en-6-ol (*ent*-8)

This compound was synthesized as described in the synthesis of **8**. Using *ent*-**10** (9.0 g, 25.4 mmol) afforded *ent*-**8** in 76% yield (2 steps).

(5*S*,6*R*)-5-(Benzyloxy)undec-1-en-6-ol (14)

To a solution of *ent*-**8** (2.95 g, 10.7 mmol) and triphenylphosphine (4.2 g, 16 mmol) and *p*-nitrobenzoic acid (2.7 g, 16 mmol) in toluene (50 mL) was slowly added di-2-methoxyethyl azodicarboxylate (3.8 g, 16 mmol) at r.t. The mixture was stirred for 5 h, and the reaction was quenched with sat. aq NH_4Cl. The reaction mixture was extracted with Et_2O (20 mL × 2) and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was roughly purified with silica gel flash chromatography (hexane/EtOAc = 10:1) to give the *p*-nitrobenzoate of *ent*-**8**. This compound was dissolved in MeOH (5 mL) and K_2CO_3 (1.5 g, 10.9 mmol) was added to the solution. The mixture was stirred for 2 h, the mixture was diluted with hexane and insoluble material was removed by filtration. The filtrate was concentrated and the residue was purified silica gel column chromatography (hexane/EtOAc = 10:1) to afford **14** (1.32 g, 45%, 2 steps) as a colorless oil; $[\alpha]_D^{20}$ –10.6 (*c* 1.74, $CHCl_3$).

IR (film): 3447, 3030, 2931, 2857, 1639, 1508, 1496, 1455, 1339, 1071, 1027, 911, 734, 697, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 5 H), 5.84–5.76 (m, 1 H), 5.03–4.95 (m, 2 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.5 Hz, 1 H), 3.86–3.82 (m, 1 H), 3.38–3.35 (m, 1 H), 2.28–2.24 (m, 1 H), 2.12–2.05 (m, 2 H), 1.76–1.70 (m, 1 H), 1.57–1.25 (m, 9 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.53, 138.37, 128.43, 127.84, 127.74, 114.79, 81.47, 71.83, 71.49, 32.02, 31.88, 29.89, 27.69, 25.87, 22.59, 14.03.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{18}H_{28}O_2$: 276.2089, found: 276.2091.

(6*S*,7*R*,2*E*)-6-(Benzyloxy)-7-hydroxydodec-2-enyl 2-Naphthoate (15)

This compound was synthesized as described in the synthesis of **6**. Compound **14** (721 mg, 2.61 mmol) and allyl 2-naphthoate (**7**) (2.7 g, 13 mmol) afforded **15** (1.13 g, 94%) as a colorless oil; $[\alpha]_D^{20}$ –16.2 (*c* 1.11, $CHCl_3$); *E*/*Z* = 10:1

IR (film): 3500, 3061, 3029, 2931, 2857, 1715, 1455, 1353, 1281, 1227, 1196, 1130, 1092, 960, 865, 826, 779, 762, 735, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.61 (s, 1 H), 8.06 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.94 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 8.5 Hz, 2 H), 7.61–7.52 (m, 2 H), 7.35–7.26 (m, 5 H), 5.90–5.85 (m, 1 H), 5.75–5.70 (m, 1 H), 4.81 (d, *J* = 6.0 Hz, 2 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 4.52 (d, *J* = 11.0 Hz, 1 H), 3.86–3.84 (m, 1 H), 3.39–3.35 (m, 1 H), 2.40–2.20 (m, 1 H), 2.15–2.07 (m, 1 H), 2.06 (d, *J* = 2.5 Hz, 1 H), 1.78–1.74 (m, 1 H), 1.60–1.25 (m, 9 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.54, 138.29, 136.04, 135.49, 132.46, 131.04, 129.33, 128.46, 128.20, 128.10, 127.88, 127.80, 127.74, 127.54, 126.60, 125.25, 124.42, 81.33, 71.79, 71.42, 65.73, 32.09, 31.89, 28.47, 27.65, 25.89, 22.59, 14.04.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{30}H_{36}O_4$; 460.2614, found: 460.2620.

(2*R*,3*S*,6*R*)-3-(Benzyloxy)-2-pentyl-6-vinyltetrahydropyran (16)

This compound was synthesized as described in the synthesis of **5**. Compound **15** (413 mg, 0.90 mmol) afforded **16** (238 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ +82.7 (*c* 1.98, $CHCl_3$).

IR (film): 3088, 3065, 3030, 2932, 2859, 1496, 1455, 1435, 1353, 1292, 1205, 1099, 1082, 989, 921, 734, 697, 635 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 5.86–5.81 (m, 1 H), 5.22 (dt, *J* = 17.5, 1.5 Hz, 1 H), 5.08 (d, *J* = 11.0 Hz, 1 H), 4.63 (d, *J* = 11.5 Hz, 1 H), 4.47 (d, *J* = 11.5 Hz, 1 H), 3.80–3.78 (m, 1 H), 3.25–3.22 (m, 1 H), 3.12–3.09 (m, 1 H), 2.29–2.25 (m, 1 H), 1.90–1.81 (m, 1 H), 1.79–1.76 (m, 1 H), 1.52–1.25 (m, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.73, 138.51, 128.34, 127.76, 127.59, 114.71, 80.67, 77.51, 77.12, 70.93, 32.24, 32.07, 30.89, 29.28, 25.05, 22.67, 14.11.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{19}H_{28}O_2$; 288.2089, found: 288.2082.

1-{(2*R*,5*S*,6*R*)-5-(Benzyloxy)-6-pentyltetrahydropyran-2-yl}butan-2-one (17)

This compound was synthesized as described in the synthesis of **11**. Compound **16** (84 mg, 0.39 mmol) afforded **17** (62 mg, 64%, 4 steps) as a colorless oil; $[\alpha]_D^{20}$ +53.6 (*c* 0.99, $CHCl_3$).

IR (film): 3030, 2932, 2858, 1715, 1496, 1455, 1411, 1375, 1348, 1205, 1083, 1027, 989, 736 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 5 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.45 (d, *J* = 12.0 Hz, 1 H), 3.75–3.73 (m, 1 H), 3.08–3.04 (m, 1 H), 2.63 (dd, *J* = 15.0, 8.0 Hz, 1 H), 2.50–2.43 (m, 2 H), 2.36 (dd, *J* = 15.0, 5.0 Hz, 1 H), 2.24 (dd, *J* = 12.3, 3.8 Hz, 1 H), 1.87–1.75 (m, 3 H), 1.50–1.20 (m, 9 H), 1.03 (t, *J* = 7.3 Hz, 3 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.03, 138.43, 128.30, 127.71, 127.57, 80.76, 77.19, 74.09, 70.85, 48.39, 37.00, 32.07, 31.80, 29.14, 24.96, 22.62, 14.01, 7.45.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{21}H_{32}O_3$; 332.2352, found: 332.2358.

Decytospolide A (1)

This compound was synthesized as described in the synthesis of **12**. Compound **17** (60 mg, 0.18 mmol) afforded **1** (44 mg, quant.) as a colorless oil; $[\alpha]_D^{19}$ +23.8 (*c* 1.01, $CHCl_3$) {Lit.[10] $[\alpha]_D^{22}$ +15.3 (*c* 0.500, $CHCl_3$)}.

IR (film): 3431, 2933, 2857, 1713, 1457, 1375, 1273, 1078, 1024, 988, 935 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 3.75–3.72 (m, 1 H), 3.26–3.25 (m, 1 H), 3.03 (dd, *J* = 9.0, 2.0 Hz, 1 H), 2.65 (dd, *J* = 15.0, 7.8 Hz, 1 H), 2.55–2.41 (m, 2 H), 2.38 (dd, *J* = 15.3, 4.8 Hz, 1 H), 2.10–2.06 (m, 1 H), 1.83–1.65 (m, 3 H), 1.51–1.20 (m, 9 H), 1.04 (t, *J* = 7.3 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.17, 82.10, 74.06, 70.41, 48.32, 37.04, 32.86, 31.89, 31.75, 31.21, 24.95, 22.58, 13.99, 7.46.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{14}H_{26}O_3$; 242.1882, found: 242.1879.

Decytospolide B (2)

This compound was synthesized as described in the synthesis of **13**. Compound **1** (22 mg, 0.09 mmol) afforded **2** (22 mg, 84%) as a colorless oil; $[\alpha]_D^{20}$ +34.5 (*c* 1.11, $CHCl_3$) {Lit.[10] $[\alpha]_D^{22}$ +21.9 (*c* 0.50, $CHCl_3$)}.

IR (film): 2938, 2859, 1739, 1716, 1458, 1373, 1239, 1081, 1040, 940, 727 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.48–4.42 (m, 1 H), 3.79–3.75 (m, 1 H), 3.26–3.21 (m, 1 H), 2.67 (dd, *J* = 15.0, 8.0 Hz, 1 H), 2.55–2.42 (m, 2 H), 2.38 (dd, *J* = 15.3, 4.8 Hz, 1 H), 2.16–2.12 (m, 1 H), 2.04 (s, 3 H), 1.77–1.72 (m, 1 H), 1.54–1.20 (m, 10 H), 1.04 (t, *J* = 7.3 Hz, 3 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.85, 170.29, 79.25, 74.15, 72.00, 48.14, 37.16, 31.87, 31.65, 30.75, 29.29, 24.77, 22.55, 13.97, 7.45.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{16}H_{28}O_4$: 284.1988, found: 284.1992.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561114.

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