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Stereoselective synthesis of microcarpalide

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Abstract—Microcarpalide is a strong microfilament disrupting agent. The convergent and stereoselective synthesis of microcarpalide was succeeded via Julia olefination and macrolactonization.

1. Introduction

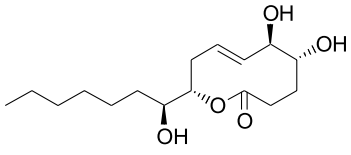
Microcarpalide, a 10-membered lactone, was isolated from the fermentation broth of an unidentified endophytic fungus by Hemscheidt and co-workers in 2001.[1] This compound acts as a strong microfilament disrupting agent and shows weak cytotoxicity to mammalian cells. Because of the large difference between the effective concentration for the antimicrofilament activity and the cytotoxicity, it is thought that this compound will be an effective tool for the studies of cell motility and metastasis. Then, we started the synthesis of microcarpalide. We have already published a rapid communication,[2] and here, we wish to report a full account of our work (Fig. 1).

2. Results and discussion

Our retrosynthesis is shown in Scheme 1. We selected lactonization as a ring-closing step. The precursor for the lactonization **A** would be prepared from aldehyde **B** and sulfone **C** via one-pot Julia coupling.[3] The aldehyde and the sulfone would be obtained by Sharpless asymmetric dihydroxylation[4] of olefins **D** and **E**, respectively. During our work in progress, other groups[5–10] also reported the total synthesis of microcarpalide, all of them using ring-closing metathesis as a key step.

The synthesis of the sulfone unit is shown in Scheme 2. The known olefinic alcohol **2**[11] was protected with PMB group and subjected to Sharpless asymmetric dihydroxylation[4,12] to give diol **4** (95% ee) as colorless crystals. Purification of the desired enantiomer could be realized by two times of recrystallization, affording **4** with >99% ee (determined by chiral HPLC). This diol was converted to *p*-methoxybenzylideneacetal **5** and the residual secondary alcohol was protected by MOM group. After removal of *p*-methoxybenzylidene group, the primary hydroxyl group of **7** was converted to corresponding 1-phenyl-1*H*-tetrazol-5-yl sulfone[13] **8** by Mitsunobu reaction and subsequent Mo(VI) catalyzed oxidation.[14] Preparation of the sulfone unit **9** was achieved by protection of the secondary alcohol.

On the other hand, synthesis of the aldehyde unit **16** is shown in Scheme 3. Starting from diol **10**,[15] olefinic ester **11** was prepared by Claisen rearrangement.[16,17] In our previous report,[2] ester **11** was temporarily hydrolyzed into carboxylic acid **12**, which was subjected to Sharpless asymmetric dihydroxylation[4] to afford the desired diol. This unstable diol was protected immediately together with re-esterification of the carboxyl group to give **13**. But the enantiomeric purity of this compound was determined to be only 60% ee. Therefore, we revised the synthetic route to intermediate **13** for the better enantiomeric purity. Direct dihydroxylation of **11** gave exclusively γ-lactone **14**, instead of the desired diol, as colorless crystals (95% ee). Purification of the desired enantiomer could be achieved by recrystallization, affording **14** with >99% ee (determined by chiral HPLC). Although,



Microcarpalide (**1**)

Figure 1.

Keywords: Microcarpalide; Microfilament disrupting agent; Macrolactonization; Julia olefination; Sharpless asymmetric dihydroxylation.
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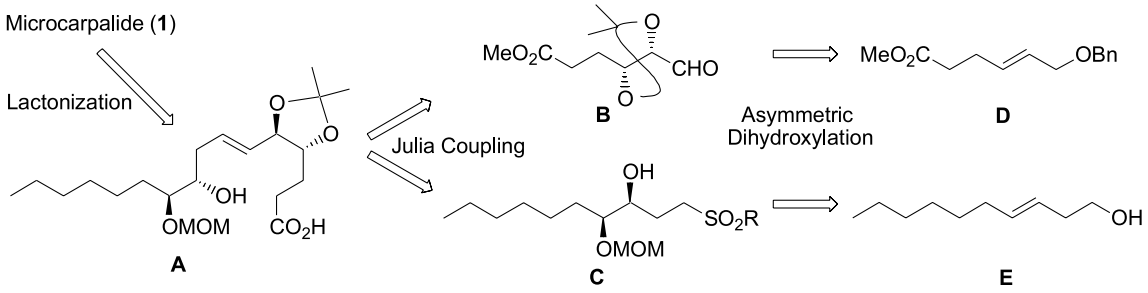
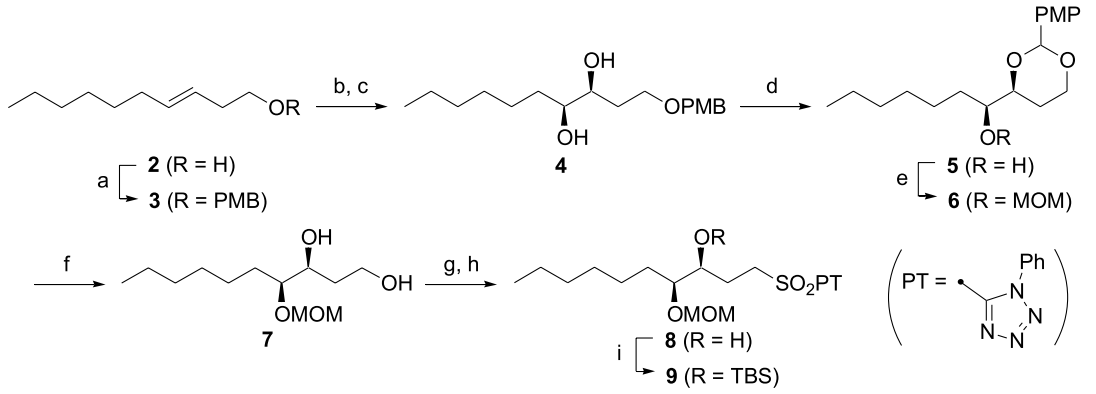
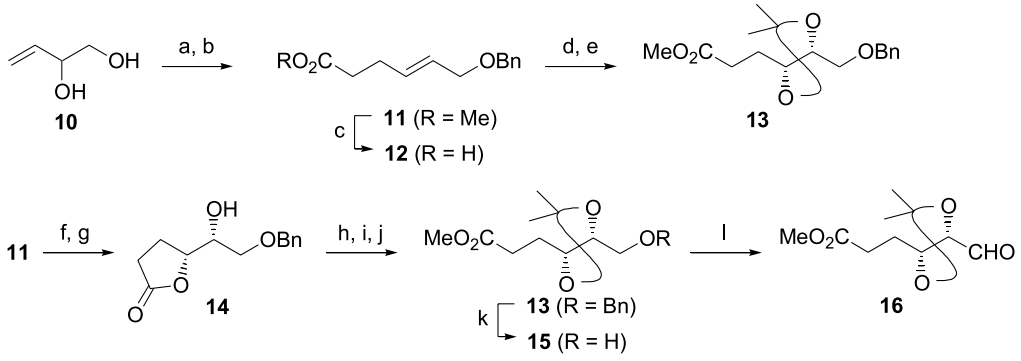


Scheme 1. Synthetic plan.



Scheme 2. Reagents and conditions: (a) PMBCl, NaH, TBAB, THF, reflux, quant.; (b) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 95% ee; (c) recrystn., >99% ee, 74% in two steps; (d) DDQ, CH_2Cl_2; (e) MOMCl, *i*-Pr_2EtN, CH_2Cl_2; (f) AcOH, H_2O, THF, 82% in three steps; (g) PTSH, PPh_3, DIAD, THF; (h) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH; (i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 91% in three steps.



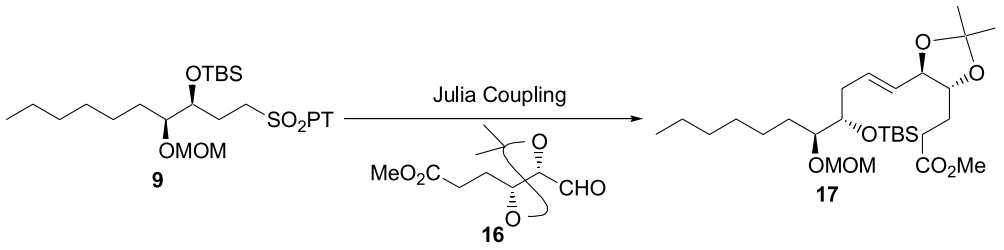
Scheme 3. Reagents and conditions: (a) BnBr, NaH, TBAI, THF; (b) $MeC(OMe)_3$, $EtCO_2H$, 140 °C, 48% in two steps; (c) LiOH, THF, H_2O, 95%; (d) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O; (e) 2,2-dimethoxypropane, HCl, acetone, 74% in two steps; (f) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH, H_2O, 95% ee, 83%; (g) recrystn., >99% ee, 86%; (h) LiOH, THF, H_2O; (i) 2,2-dimethoxypropane, acetone; (j) CH_2N_2, Et_2O, EtOAc, 88% in three steps; (k) H_2, 10% Pd/C, *i*-PrOH, quant.; (l) 4-MeO-TEMPO, KBr, NaOCl, $NaHCO_3$, CH_2Cl_2, H_2O, ca. 70%.

the yield in methanolysis of the lactone **14** was low (<40%), hydrolysis and subsequent protection afforded **13** in much better yield. After hydrogenolysis, **15** was successfully oxidized to the corresponding aldehyde **16** mediated by oxoammonium salt.[18]

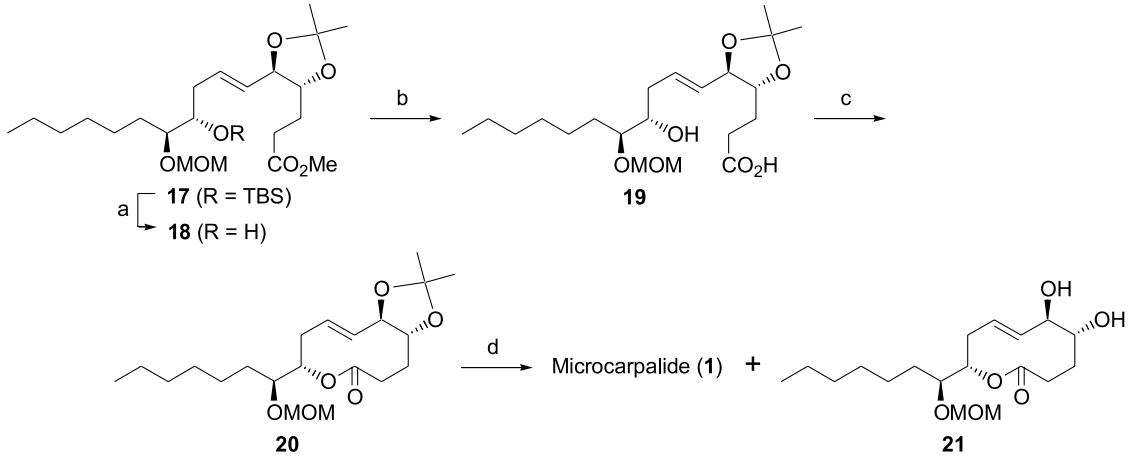
Now that both of the two units were obtained enantioselectively, we tried one-pot Julia coupling[3,13,19] in several conditions (Table 1). The reaction employing LiHMDS as a base gave the desired olefin **17** in poor yield (entries 1 and 2). On the other hand, good yield was realized when KHMDS was used as a base, but *E*/*Z* selectivity was not so high (entries 3 and 4). Because the low selectivity seemed to be caused by some chelation effects of oxygen functional groups in the sulfone **9** and the aldehyde **16** with potassium cation, we tried other conditions employing additives to prevent this chelation. When 18-c-6 was added (entry 6), *trans*-olefin **17** was successfully obtained in good yield and high selectivity. Separation of **17** from *cis*-isomer was easily succeeded by silica gel column chromatography.

Final steps including lactonization are shown in Scheme 4. The *trans*-olefin **17** was treated with TBAF and hydrolyzed to give hydroxy acid **19**, a lactonization precursor. It was subjected to Yamaguchi's method[20] to afford 10-membered lactone **20** in excellent yield. Formation of dimeric lactone was observed in higher concentration, but not in 1 mmol/L. Deprotection of **20** was performed in the similar method as Marco et al.[5] to give microcarpalide (**1**) successfully together with small amount of partially deprotected

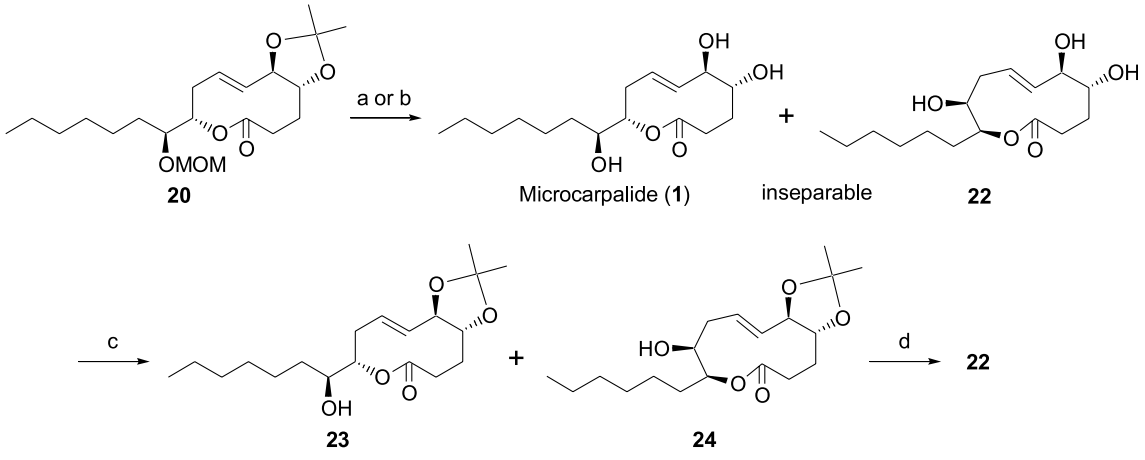
Table 1.



Entry	Base	Temperature (°C)	Additive	*E*:*Z*	Yield (%)
1	LiHMDS	−78	—	3:1	10
2	LiHMDS	−108	—	10:1	32
3	KHMDS	−78	—	2:1	64
4	KHMDS	−108	—	2:1	77
5	KHMDS	−108	HMPA	3:1	71
6	KHMDS	−108	18-c-6	10:1	72



Scheme 4. Reagents and conditions: (a) TBAF, THF, 99%; (b) LiOH, H_2O, THF; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, then DMAP, benzene, 94%; (d) $BF_3 \cdot OEt_2$, $(CH_2SH)_2$, CH_2Cl_2, −20 to −10 °C, 69% (**1**), 15% (**21**).



Scheme 5. Reagents and conditions: (a) DOWEX®-50W, MeOH, H_2O, 50 °C, 98%; (b) $BF_3 \cdot OEt_2$, $(CH_2SH)_2$, CH_2Cl_2, 0 °C, 70%; (c) 2,2-dimethoxypropane, PPTS, acetone; separation, 74% (**23**), 14% (**24**); (d) PPTS, MeOH, 85%.

compound **21**. The analytical and spectroscopic data of synthesized **1** were identical to the reported data.[1,5–10] As reported, the NMR spectra of **1** was observed as a mixture of two conformers in the ratio about 3.5:1.

Interestingly, acid-catalyzed isomerization of microcarpalide was clarified in the course of our examination of deprotection conditions as shown in Scheme 5. Treating **20** with DOWEX-50W (MeOH, H_2O, 50 °C, 4 days) or $BF_3 \cdot OEt_2$ and $(CH_2SH)_2$ (CH_2Cl_2, 0 °C, 2 h) gave inseparable mixture of microcarpalide (**1**) and small amount of unknown compound **22**. For structural determination of

22, this mixture was treated with 2,2-dimethoxypropane and PPTS to afford the corresponding acetonides, expected 10-membered lactone **23** and another lactone **24**. These compounds were easily separated and the structure of **24** was confirmed to be 11-membered lactone by ^{1}H-COSY spectrum. Deprotection of the isolated **24** gave **22** as a single product and its ^{1}H NMR spectrum was identical with that of the previous minor component in the inseparable mixture (**1** and **22**). Similarly, microcarpalide (**1**) was found to be partially isomerized affording the mixture of **1** and **22** by treatment with TsOH. ^{1}H NMR spectrum (in CD_3CN, 24 °C) showed this mixture comprised the major conformer of **1**, the minor conformer of **1** and 11-memberd lactone **22** (5:1.5:1).

In conclusion, we have accomplished a convergent and stereoselective synthesis of microcarpalide. All of the four chiral centers were introduced by Sharpless asymmetric dihydroxylation. One-pot Julia olefination gave the desired *trans*-olefin in good yield and high selectivity in the presence of crown ether and Yamaguchi's macrolactonization was also successful in excellent yield. The total yield was 23% in 13 steps. We also observed an interesting acid-catalyzed isomerization of microcarpalide.

3. Experimental

3.1. General

Optical rotations were recorded with a JASCO DIP-1000 polarimeter. IR spectra were measured with a JASCO FT/IR-230 spectrophotometer. ^{1}H and ^{13}C NMR were recorded on JEOL JNM AL300. Mass spectra were recorded on JEOL JMS-700T. Column chromatography was performed using Merck silica gel 60 (0.060–0.200 mm). TLC was carried out on Merck glass plates precoated with silica gel 60 F_{254} (0.25 mm). HPLC was performed using SHOWA DENKO shodex DS-4. Melting points are uncorrected values.

3.2. Synthetic studies

3.2.1. (*E*)-1-(4-Methoxybenzyloxy)-3-decene (3). To a solution of alcohol (**2**, 8.8 g, 56 mmol) in THF (160 mL) were added NaH (60%, 3.0 g, 78 mmol), PMBCl (9.0 mL, 66 mmol) and tetra-*n*-butylammonium bromide (100 mg, 0.31 mmol). The reaction mixture was heated under reflux for 2 days, poured into saturated NH_4Cl solution and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (10:1) gave **3** (15.5 g, quant.) as a colorless oil. $n_D^{25}=1.4957$. IR (film): $\nu=1613$, 1514, 1464, 1248, 1099, 1038 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=0.88$ (3H, t, $J=6.5$ Hz,), 1.2–1.4 (8H, m), 1.98 (2H, br q, $J=6.0$ Hz), 2.30 (2H, br q, $J=6.5$ Hz), 3.45 (2H, t, $J=7.0$ Hz), 3.81 (3H, s), 4.45 (2H, s), 5.41 (1H, dt, $J=15.0$, 6.0 Hz), 5.47 (1H, dt, $J=15.0$, 6.0 Hz), 6.88 (2H, d, $J=8.5$ Hz), 7.26 (2H, d, $J=8.5$ Hz). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.00; H, 10.12.

3.2.2. (3*S*,4*S*)-1-(4-Methoxybenzyloxy)decane-3,4-diol (4). A mixture of AD-mix-α (70 g) and methanesulfonamide (4.8 g, 50.5 mmol) in Bu^{t}OH (240 mL) and water (240 mL) was stirred at room temperature for 30 min. The mixture was cooled down to 0 °C and then, **3** (13.8 g, 50 mmol) was added to it. Stirred at 4 °C overnight, Na_2SO_3 (100 g) was added to the mixture. After stirring at room temperature for 30 min, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (3:1) gave crude **4** (95% ee) as colorless crystals. Crude product was recrystallized from hexane/EtOAc (20:1) to yield pure **4** (11.5 g, 74% recovery, >99% ee) as colorless crystals. HPLC [column: Daicel Chiralcel OD (0.46 cm×25 cm), eluent: hexane/ethanol (98:2), flow rate: 1.0 mL/min, detection: UV (254 nm)]: $t_R=21$ min [0.3%, (*R*,*R*)-isomer], 25 min [99.7%, (*S*,*S*)-isomer]. Mp=49.5–50.0 °C. $[\alpha]_D^{29}$ −2.2 (*c* 1.1, $CHCl_3$). IR (KBr): $\nu=3464$, 3374, 1513, 1249, 1086 cm^{-1}. ^{1}H NMR ($CDCl_3$): $\delta=0.88$ (3H, t, $J=6.6$ Hz,), 1.2–1.6 (10H, m), 1.7–1.9 (2H, m), 2.47 (1H, d, $J=5.5$ Hz), 3.17 (1H, d, $J=4.5$ Hz), 3.42 (1H, br m), 3.6–3.75 (3H, m), 3.81 (3H, s), 4.46 (2H, s), 6.89 (2H, d, $J=9.0$ Hz), 7.24 (2H, d, $J=9.0$ Hz). Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.69; H, 9.81.

3.2.3. (1*S*)-1-[(4*S*)-2-(4-Methoxyphenyl)-1,3-dioxan-4-yl] heptan-1-ol (5). DDQ (5.8 g, 19 mmol) was added to a solution of diol (**4**) in CH_2Cl_2 (120 mL) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous sodium sulfate and concentrated in vacuo to provide *p*-methoxybenzylidene acetal **5** (5.8 g) as a yellow oil. This crude product was used in the next reaction without further purification. ^{1}H NMR (C_6D_6): $\delta=0.91$ (3H, t, $J=6.6$ Hz), 1.2–1.5 (10H, m), 1.6–1.8 (2H, m), 2.30 (1H, d, $J=4.0$ Hz), 3.26 (3H, s), 3.35–3.5 (3H, m), 3.96 (1H, ddd, $J=1.0$, 5.0, 11.0 Hz), 5.34 (1H, s), 6.82 (2H, d, $J=11.0$ Hz), 7.54 (2H, d, $J=11.0$ Hz).

3.2.4. (1*S*)-1-Methoxymethoxy-1-[(4*S*)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]heptane (6). To a solution of crude *p*-methoxybenzylidene acetal (5.8 g) in CH_2Cl_2 (180 mL) was added Pr^i_2EtN (9.0 mL, 52 mmol) and MOMCl (3.0 mL, 40 mmol). This solution was stirred at room temperature overnight, poured into water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous sodium sulfate and concentrated in vacuo to give MOM ether **6** (5.9 g) as a yellow oil. This crude product was used in the next reaction without further purification. ^{1}H NMR (C_6D_6): $\delta=0.90$ (3H, t, $J=6.6$ Hz,), 1.07 (1H, d, $J=13.0$ Hz), 1.2–1.85 (11H, m), 3.24 (6H, s), 3.56 (1H, dt, $J=2.5$, 12.0 Hz), 3.69 (1H, br m), 3.83 (1H, ddd, $J=2.5$, 6.0, 12.0 Hz), 4.02 (1H, br dd, $J=5.0$, 12.0 Hz), 4.66 (1H, d, $J=6.5$ Hz), 4.81 (1H, d, $J=6.5$ Hz), 5.42 (1H, s), 6.80 (2H, d, $J=8.5$ Hz), 7.61 (2H, d, $J=8.5$ Hz).

3.2.5. (3*S*,4*S*)-4-(Methoxymethoxy)decane-1,3-diol (7). A mixture of crude **6** (5.9 g), acetic acid (5.0 mL), water (5.0 mL) and THF (15 mL) was refluxed for 2 h. The reaction mixture was poured into saturated $NaHCO_3$

solution and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (1:1–1:3) gave **7** (3.6 g, 82% in three steps) as a colorless oil. $n_D^{23}=1.4527$. $[\alpha]_D^{22}$ +24 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3400$, 1468, 1152, 1100, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.86$ (3H, t, $J=6.9$ Hz,), 1.25–1.6 (10H, m), 1.65–1.75 (2H, m), 2.81 (1H, t, $J=$ 5.5 Hz), 3.37 (1H, ddd, $J=4.5$, 6.5, 6.5 Hz), 3.43 (3H, s), 3.48 (1H, d, $J=3.0$ Hz), 3.7–1.8 (1H, m), 3.85 (2H, q, $J=$ 5.5 Hz), 4.69 (1H, d, $J=7.0$ Hz), 4.73 (1H, d, $J=7.0$ Hz). FAB-HRMS *m/z* calcd for $C_{12}H_{27}O_4$ $[M+H]^+$ 235.1909, found 235.1906.

3.2.6. (3*S*,4*S*)-4-(Methoxymethoxy)-1-(1-phenyl-1*H*-tetrazole-5-sulfonyl)decan-3-ol (8). The 40% solution of diisopropyl azodicarboxylate in toluene (5.8 mL, 11 mmol) was added to a solution of diol **7** (2.0 g, 8.5 mmol), PPh_3 (2.3 g, 8.8 mmol) and 1-phenyl-5-mercapto-1*H*-tetrazole (1.9 g, 11 mmol) in THF (60 mL) at −20 °C. Stirred at 0 °C for 20 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (2:1) gave crude sulfide as a colorless oil. To the solution of crude sulfide in ethanol (100 mL) was added the mixture of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.5 g, 1.2 mmol) and 30% H_2O_2 solution (6.0 mL, 53 mmol) at 0 °C. Stirred at room temperature for 6 h, the reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous sodium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (4:1) gave crude **8** as a colorless oil. This crude product was used in the next reaction without further purification. ^1H NMR ($CDCl_3$): $\delta=0.88$ (3H, t, $J=$ 6.6 Hz), 1.2–1.6 (10H, m), 2.0–2.2 (2H, m), 3.17 (1H, d, $J=$ 5.0 Hz), 3.35 (1H, dt, $J=6.5$, 5.5 Hz), 3.41 (3H, s), 3.5–3.7 (1H, m), 3.8–4.1 (2H, m), 4.68 (1H, d, $J=6.5$ Hz), 4.70 (1H, d, $J=6.5$ Hz), 7.6–7.7 (5H, m).

3.2.7. (3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(methoxymethoxy)-1-(1-phenyl-1*H*-tetrazole-5-sulfonyl)decane (9). To a solution of crude **8** in CH_2Cl_2 (80 mL) was added TBSOTf (2.6 mL, 11 mmol) and 2,6-lutidine (1.7 mL, 15 mmol). The reaction mixture was stirred at room temperature for 30 min, poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (20:1) gave **9** (4.2 g, 91% in three steps) as a colorless oil. $n_D^{24}=1.4951$. $[\alpha]_D^{24}$ −18 (*c* 1.0, $CHCl_3$). IR (film): $\nu=1344$, 1151, 1097, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.10$ (3H, s), 0.11 (3H, s), 0.88 (3H, t, $J=$ 6.5 Hz), 0.90 (9H, s), 1.25–1.7 (10H, m), 2.01 (1H, m), 2.24 (1H, m), 3.38 (3H, s), 3.45 (1H, m), 3.82 (2H, m), 3.95 (1H, ddd, $J=4.2$, 4.2, 8.4 Hz), 4.61 (1H, d, $J=7.0$ Hz), 4.67 (1H, d, $J=7.0$ Hz), 7.6–7.7 (5H, m). FAB-HRMS *m/z* calcd for $C_{25}H_{45}N_4O_5SSi$ $[M+H]^+$ 541.2880, found 541.2877.

3.2.8. (*E*)-6-Benzyloxyhex-4-enoic acid methyl ester (11). According to the reported manner,[15,21] diol **10** (32 g, 0.36 mol) was treated with benzyl bromide to give monobenzyl ether as the mixture of primary and secondary alcohols. Propionic acid (1.6 mL) was added to the solution of this mixture in trimethyl orthoacetate (280 mL). The reaction mixture was refluxed for 2 h with absorbing generated methanol by molecular sieves 4 Å. After cooling, the reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (5:1) gave **11** (41 g, 48% in two steps) as a colorless oil. $n_D^{26}=1.5042$. IR (film): $\nu=$ 1739, 1437, 1362, 1166, 1116 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=$ 2.35–2.45 (4H, m), 3.68 (3H, s), 3.97 (2H, d, $J=5.0$ Hz), 4.50 (2H, s), 5.6–5.8 (2H, m), 7.25–7.35 (5H, m). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.27; H, 7.77.

3.2.9. (5*R*)-5-[(1*R*)-2-Benzyloxy-1-hydroxyethyl]tetrahydrofuran-2-one (14). The mixture of AD-mix-β (160 g) and methanesulfonamide (11 g, 0.12 mol) in Bu^tOH (550 mL) and water (550 mL) was stirred at room temperature for 30 min. The mixture was cooled down to 0 °C and then **11** (27 g, 0.12 mol) was added to it. Stirred at 4 °C overnight, Na_2SO_3 (50 g) was added to the mixture. After stirring at room temperature for 30 min, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (2:1–1:1) gave crude **14** (22.5 g, 83%, 95% ee) as a colorless crystal. Crude product was recrystallized from hexane–EtOAc to yield pure **14** (19.3 g, 86% recovery, >99% ee) as colorless crystals. HPLC [column: Daicel Chiralcel OD-H (0.46 cm×25 cm), eluent: hexane/Pr^iOH (9:1), flow rate: 1.0 mL/min, detection: UV (254 nm)]: $t_R=19.4$ min [99.9%, (*R*,*R*)-isomer], 22.3 min [0.1%, (*S*,*S*)-isomer]. Mp=105.0–106.5 °C. $[\alpha]_D^{27}$ −47 (*c* 1.0, $CHCl_3$). IR (KBr): $\nu=3469$, 1759, 1197, 1083 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=2.2$–2.3 (2H, m), 2.4–2.7 (3H, m), 3.60 (2H, d, $J=6.0$ Hz), 3.83 (1H, m), 4.56 (2H, s), 4.55–4.6 (1H, m), 7.3–7.4 (5H, m). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.11; H, 6.84.

3.2.10. 3-[(4*R*,5*R*)-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid methyl ester (13). Lithium hydroxide monohydrate (4.0 g, 95 mmol) was added to the mixture of lactone **14** (10 g, 43 mmol), THF (100 mL) and water (100 mL). Stirred at room temperature for 1 h, the reaction mixture was poured into 0.3 N HCl and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was dissolved in 2,2-dimethoxypropane (50 mL) and acetone (100 mL) and stirred at room temperature overnight. After evaporation, the residue was dissolved in ethyl acetate (100 mL) and treated with a solution of CH_2N_2 in ether. The reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (5:1) gave

13 (11 g, 88%) as a colorless oil. $n_D^{25}=1.4879$. $[\alpha]_D^{26}$ +15 (*c* 1.5, $CHCl_3$). IR (film): $\nu=1739$, 1449, 1373, 1081 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=1.39$ (3H, s), 1.40 (3H, s), 1.8–2.05 (2H, m), 2.4–2.6 (2H, m), 3.5–3.6 (2H, m), 3.67 (3H, s), 3.8–3.9 (2H, m), 4.59 (2H, s), 7.3–7.4 (5H, m). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.90; H, 7.66.

3.2.11. 3-[(4*R*,5*R*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid methyl ester (15). To a solution of **13** (5.0 g, 17 mmol) in Pr^iOH (135 mL) was added 10% Pd/C (400 mg) and the mixture was stirred overnight under H_2 atmosphere. The mixture was filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (2:1) gave **15** (3.7 g, quant.) as a colorless oil. $n_D^{27}=1.4472$. $[\alpha]_D^{24}$ +29 (*c* 1.0, $CHCl_3$). IR (film): $\nu=3476$, 1739, 1441, 1375, 1250, 1166, 1073 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=1.40$ (6H, s), 1.8–2.1 (3H, m), 2.4–2.6 (2H, m), 3.6–3.85 (3H, m), 3.69 (3H, s), 3.91 (1H, dt, $J=3.3$, 8.1 Hz). FAB-HRMS *m/z* calcd for $C_{10}H_{19}O_5$ $[M+H]^+$ 219.1233, found 219.1237.

3.2.12. 3-[(4*R*,5*S*)-5-Formyl-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid methyl ester (16). 4-Methoxy-2,2,6,6-tetramethylpiperidine 1-oxyl (750 mg, 4.0 mmol) was added to a mixture of alcohol **15** (2.8 g, 13 mmol), 0.8 M NaOCl solution (19 mL, 15 mmol), KBr (750 mg, 6.3 mmol), $NaHCO_3$ (1.6 g, 19 mmol), CH_2Cl_2 (160 mL) and water (80 mL) at 0 °C and the mixture was stirred at 0 °C for 15 min. The reaction mixture was poured into 10% $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (2:1–1:1) gave crude **16** (1.95 g, ca. 70%) as a colorless oil. This crude product was used in the next reaction without further purification. ^1H NMR ($CDCl_3$): $\delta=1.41$ (6H, s), 1.85–2.15 (2H, m), 2.4–2.6 (2H, m), 3.69 (3H, s), 3.98 (1H, dd, $J=2.0$, 7.5 Hz), 4.10 (1H, dt, $J=4.5$, 7.5 Hz), 9.74 (1H, d, $J=2.0$ Hz).

3.2.13. 3-[(4*R*,5*R*)-5-{(1*E*,4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-5-(methoxymethoxy)undec-1-enyl}-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid methyl ester (17). To a solution of sulfone **9** (1.0 g, 1.9 mmol) and 18-crown-6 (740 mg, 2.8 mmol) in THF (40 mL) was added 0.5 M solution of KHMDS in toluene (4.4 mL, 2.2 mmol) at −100 °C. Stirred at −100 °C for 30 min, a solution of aldehyde **16** (600 mg, 2.78 mmol) in THF (10 mL) was dropped into this solution. The reaction mixture was allowed to warm to room temperature during 2 h and poured into saturated NH_4Cl solution. This mixture was extracted with ethyl acetate and the organic layer was washed with saturated $NaHCO_3$ solution and brine. After drying with anhydrous magnesium sulfate, solvent was removed in vacuo and the residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (10:1) gave **17** (645 mg, 66%) and *cis*-isomer (62 mg, 6%) as colorless oils. $n_D^{25}=1.4550$. $[\alpha]_D^{25}$ −20 (*c* 0.60, $CHCl_3$). IR (film): $\nu=1743$, 1252, 1162, 1044 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.05$ (6H, s), 0.89 (9H, s), 0.85–0.95 (3H, m), 1.25–1.5 (9H, m), 1.39 (6H, s), 1.5–1.7 (1H, m), 1.75–2.0 (2H, m), 2.15 (1H, ddd, $J=7.5$, 8.5, 15.0 Hz), 2.3–2.6 (3H, m), 3.37 (3H, s), 3.35–3.45 (1H, m), 3.6–3.7 (1H, m), 3.67 (3H, s), 3.75 (1H, dt, $J=8.5$, 4.3 Hz), 3.98 (1H, t, $J=7.5$ Hz), 4.62 (1H, d, $J=6.6$ Hz), 4.69 (1H, d, $J=6.6$ Hz), 5.46 (1H, dd, $J=7.5$, 15.0 Hz), 5.85 (1H, dt, $J=15.0$, 7.5 Hz). Anal. Calcd for $C_{28}H_{54}O_7Si$: C, 63.36; H, 10.25. Found: C, 63.36; H, 10.31.

3.2.14. 3-[(4*R*,5*R*)-5-{(1*E*,4*S*,5*S*)-4-Hydroxy-5-methoxymethoxyundec-1-enyl}-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid methyl ester (18). To a solution of **17** (530 mg, 1.0 mmol) in THF (10 mL) was added 1.0 M TBAF solution in THF (2.0 mL, 2 mmol) and the solution was stirred at room temperature for 2 h. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (4:1) gave **18** (412 mg, 99%) as a colorless oil. $n_D^{27}=1.4621$. $[\alpha]_D^{27}$ +13 (*c* 0.90, $CHCl_3$). IR (film): $\nu=3482$, 1740, 1441, 1373, 1221, 1163, 1037 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.88$ (3H, t, $J=6.6$ Hz), 1.25–1.65 (10H, m), 1.34 (6H, s), 1.75–2.0 (2H, m), 2.2–2.6 (4H, m), 2.75 (1H, d, $J=4.8$ Hz), 3.38 (1H, m), 3.41 (3H, s), 3.59 (1H, m), 3.67 (3H, s), 3.6–3.7 (1H, m), 4.01 (1H, t, $J=8.0$ Hz), 4.69 (2H, s), 5.52 (1H, dd, $J=8.0$, 15.3 Hz), 5.90 (1H, dt, $J=15.3$, 7.5 Hz). FAB-HRMS *m/z* calcd for $C_{22}H_{41}O_7$ $[M+H]^+$ 417.2852, found 417.2866.

3.2.15. 3-[(4*R*,5*R*)-5-{(1*E*,4*S*,5*S*)-4-Hydroxy-5-methoxymethoxyundec-1-enyl}-2,2-dimethyl-1,3-dioxolan-4-yl]propionic acid (19). A mixture of **18** (368 mg, 0.88 mmol), $LiOH\cdot H_2O$ (75 mg, 1.8 mmol), THF (7 mL) and water (5 mL) was stirred at room temperature for 2 h. The reaction mixture was poured into 10% tartaric acid solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was suspended in $CHCl_3$, filtered through Celite® and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (1:1) gave crude **19** (400 mg) as a colorless oil. This crude product was used in the next reaction without further purification. IR (film): $\nu=3446$, 3300–2500 (br), 1714, 1377, 1219, 1157, 1101, 1038 cm^{-1}. ^1H NMR ($CDCl_3$): $\delta=0.89$ (3H, t, $J=6.6$ Hz), 1.25–1.65 (10H, m), 1.40 (6H, s), 1.8–2.05 (2H, m), 2.2–2.6 (4H, m), 3.35–3.45 (1H, m), 3.42 (3H, s), 3.6–3.75 (2H, m), 4.03 (1H, t, $J=8.0$ Hz), 4.70 (2H, s), 5.53 (1H, m), 5.90 (1H, dt, $J=15.0$, 7.2 Hz).

3.2.16. 4,5-*O*-Isopropylidene-10-*O*-methoxymethylmicrocarpalide (20). Triethylamine (280 μL, 2.0 mmol) and 2,4,6-trichlorobenzoyl chloride (200 μL, 1.3 mmol) were added to a solution of the crude hydroxy acid **19** (400 mg) in THF (7 mL). The reaction mixture was stirred at room temperature for 5 h and then filtered through Celite® under argon. The resultant solution was slowly added over 22 h using syringe pump to a refluxing solution of DMAP (2.2 g, 18 mmol) in dry benzene (1000 mL). After the addition was complete, the reaction mixture was stirred for additional 2 h and then concentrated in vacuo. The residue was dissolved in ethyl acetate and washed with 1 N HCl, saturated

$NaHCO_3$ solution and brine. The organic layer was dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with hexane/ethyl acetate (6:1) gave **20** (320 mg, 94%) as a colorless oil. $n_D^{26}=1.4742$. $[\alpha]_D^{24}$ −37 (*c* 0.60, $CHCl_3$). IR (film): $\nu=1735$, 1456, 1372, 1236, 1163, 1063 cm^{-1}. ^1H NMR (CD_3CN, observed as a mixture of two conformers in a ratio of 3:1) Major conformer: $\delta=0.89$ (3H, t, $J=6.6$ Hz), 1.25–1.65 (10H, m), 1.41 (6H, s), 1.9–1.25 (2H, m), 2.25–2.7 (4H, m), 3.41 (3H, s), 3.6–3.7 (2H, m), 3.93 (1H, t, $J=9.0$ Hz), 4.68 (1H, d, $J=7.2$ Hz), 4.71 (1H, d, $J=7.2$ Hz), 4.93 (1H, dt, $J=8.7$, 3.5 Hz), 5.33 (1H, dd, $J=9.0$, 15.0 Hz), 5.74 (1H, ddd, $J=4.5$, 11.0, 15.0 Hz). Minor conformer: $\delta=0.89$ (3H, t, $J=6.6$ Hz), 1.25–1.65 (11H, m), 1.41 (6H, s), 2.25–2.7 (5H, m), 3.41 (3H, s), 3.6–3.7 (1H, m), 3.76 (1H, dt, $J=2.5$, 9.5 Hz), 3.8–3.9 (1H, m), 4.68 (1H, d, $J=7.2$ Hz), 4.71 (1H, d, $J=7.2$ Hz), 5.09 (1H, br m), 5.7–5.8 (1H, m), 5.90 (1H, dt, $J=16.0$, 8.0 Hz). FAB-HRMS *m/z* calcd for $C_{21}H_{37}O_6$ $[M+H]^+$ 385.2590, found 385.2596.

3.2.17. Microcarpalide (1). To a solution of **20** (89 mg, 0.23 mmol) and 1,2-ethanedithiol (90 μL, 1.1 mmol) in CH_2Cl_2 (10 mL) was added $BF_3\cdot OEt_2$ (55 μL, 0.43 mmol) at −20 °C and the mixture was stirred at −20–−10 °C for 40 min. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with $CHCl_3$/MeOH (20:1) gave **1** (46 mg, 66%) and MOM ether **21** (12 mg, 15%) both as colorless oils. $n_D^{19}=1.4965$. $[\alpha]_D^{26}$ −29 (*c* 0.67, MeOH). IR (film): $\nu=3438$, 2929, 2857, 1712, 1225, 1155, 1065 cm^{-1}. ^1H NMR (CD_3CN, observed as a mixture of two conformers in a ratio of 3.5:1) Major conformer: δ (ppm) 0.88 (3H, t, $J=6.9$ Hz), 1.2–1.4 (8H, m), 1.3–1.5 (2H, m), 1.7–1.8 (1H, m), 2.0–2.2 (2H, m), 2.1–2.3 (2H, m), 2.4–2.6 (1H, m), 2.8–2.9 (2H, br m), 3.12 (1H, br d), 3.54 (1H, br m), 3.77 (1H, br), 4.10 (1H, br), 4.81 (1H, ddd, $J=3.3$, 4.8, 11.1 Hz), 5.49 (1H, dddd, $J=2.1$, 5.1, 9.9, 15.6 Hz), 5.69 (1H, dd, $J=2.4$, 15.6 Hz). Minor conformer: δ (ppm) 0.88 (3H, t, $J=6.9$ Hz), 1.2–1.4 (8H, m), 1.3–1.5 (2H, m), 1.7–1.8 (1H, m), 2.0 (1H, m), 2.0–2.2 (1H, m), 2.2–2.4 (1H, m), 2.4–2.6 (2H, m), 2.8–2.9 (2H, br m), 3.2–3.3 (2H, br m), 3.5–3.6 (2H, m), 4.60 (1H, ddd, $J=2.7$, 4.5, 8.1 Hz), 5.05 (1H, dd, $J=9.3$, 15.6 Hz), 5.6–5.7 (1H, m). ^{13}C NMR (CD_3CN, observed as a mixture of two conformers): δ (ppm) 14.4, 23.3, 26.1, 26.3, 26.3, 26.4, 29.0, 29.9, 32.1, 32.2, 32.5, 33.8, 34.1, 35.9, 36.7, 72.4, 72.8, 73.4, 73.8, 76.4, 76.9, 79.5, 79.7, 126.6, 130.0, 133.7, 134.5, 173.5, 176.4. FAB-HRMS *m/z* calcd for $C_{16}H_{29}O_5$ $[M+H]^+$ 301.2015, found 301.2003.

3.2.18. 4,5-*O*-Isopropylidene-microcarpalide (23) and (4*R*,5*R*,6*E*,9*S*,10*S*)-4,5-Isopropylidenedioxy-9-hydroxy-6-hexadecen-10-olide (24). To a solution of **20** (112 mg, 0.29 mmol) in MeOH (6 mL) and water (1.2 mL) was added DOWEX®-50W X8 (1.0 g) and the mixture was stirred at 50 °C for 5 days. The reaction mixture was diluted with ethyl acetate and filtered through Celite®. After concentration, the residue was chromatographed over silica gel. Elution with $CHCl_3$/MeOH (20:1) gave a mixture of **1** and **22** (86 mg, 98%) as a colorless oil. This mixture (45 mg, 0.15 mmol) was dissolved in 2,2-dimethoxypropane (1 mL) and acetone (1 mL) and treated with PPTS (10 mg, 0.04 mmol). Stirred at room temperature overnight, the reaction mixture was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC [hexane/ethyl acetate (3:1)] to give **23** (38 mg, 74%) and **24** (7 mg, 14%) both as colorless oils.

Compound **23**. $[\alpha]_D^{27}$ −36 (*c* 0.40, $CHCl_3$). ^1H NMR ($CDCl_3$, observed as a mixture of two conformers in a ratio of 3.5:1) Major conformer: δ (ppm) 0.88 (3H, t, $J=6.5$ Hz), 1.2–1.5 (10H, m), 1.41 (6H, s), 1.97 (1H, dddd, $J=3.5$, 8.0, 12.0, 15.0 Hz), 2.09 (1H, br ddd, $J=4.5$, 5.5, 15.0 Hz), 2.32 (1H, ddd, $J=4.5$, 12.0, 13.5 Hz), 2.42 (1H, br ddd, $J=2.5$, 4.5, 12.0 Hz), 2.54 (1H, ddd, $J=3.5$, 5.5, 13.5 Hz), 2.67 (1H, ddd, $J=9.0$, 11.0, 12.0 Hz), 3.6–3.7 (2H, m), 3.92 (1H, t, $J=9.0$ Hz), 4.71 (1H, ddd, $J=2.5$, 4.5, 9.0 Hz), 5.33 (1H, dd, $J=9.5$, 15.5 Hz), 5.78 (1H, ddd, $J=4.5$, 11.0, 15.5 Hz). Minor conformer: δ (ppm) 0.88 (3H, t, $J=6.5$ Hz), 1.2–1.7 (11H, m), 1.41 (6H, s), 2.0–2.7 (5H, m), 3.6–3.65 (1H, m), 3.77 (1H, br dt, $J=4.0$, 10.0 Hz), 3.8–3.9 (1H, m), 4.94 (1H, br m), 5.65–5.75 (1H, m), 5.85–5.95 (1H, m). FAB-HRMS *m/z* calcd for $C_{19}H_{33}O_5$ $[M+H]^+$ 341.2328, found 341.2301.

Compound **24**. ^1H NMR ($CDCl_3$): $\delta=0.87$ (3H, t, $J=6.5$ Hz), 1.2–1.8 (10H, m), 1.39 (3H, s), 1.40 (3H, s), 2.05–2.55 (6H, m), 3.63 (1H, m), 3.87 (1H, dt, $J=9.0$, 5.0 Hz), 3.97 (1H, t, $J=8.5$ Hz), 4.92 (1H, dd, $J=5.0$, 9.0 Hz), 5.53 (1H, dd, $J=8.5$, 16.0 Hz), 5.84 (1H, dt, $J=16.0$, 8.0 Hz). FAB-HRMS *m/z* calcd for $C_{19}H_{33}O_5$ $[M+H]^+$ 341.2328, found 341.2301.

3.2.19. (4*R*,5*R*,6*E*,9*S*,10*S*)-4,5,9-Trihydroxy-6-hexadecen-10-olide (22). To a solution of **24** (6.0 mg, 0.018 mmol) in MeOH (1.5 mL) was added PPTS (1 mg, 0.004 mmol) and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous magnesium sulfate and concentrated in vacuo. The residue was purified by preparative TLC [$CHCl_3$/MeOH (10:1)] to give **22** (4.5 mg, 85%) as a colorless oil. $[\alpha]_D^{26}$ −17 (*c* 0.32, MeOH). ^1H NMR (CD_3CN): δ (ppm) 0.87 (3H, t, $J=6.5$ Hz), 1.2–1.35 (8H, m), 1.60 (2H, m), 1.8–1.9 (2H, m), 2.1–2.2 (2H, m), 2.3–2.4 (2H, m), 2.97 (1H, d, $J=7.0$ Hz), 3.11 (1H, d, $J=3.5$ Hz), 3.20 (1H, d, $J=3.5$ Hz), 3.40 (1H, m), 3.63 (1H, dt, $J=3.5$, 7.0 Hz), 3.88 (1H, tt, $J=2.5$, 7.0 Hz), 4.81 (1H, dt, $J=2.5$, 7.0 Hz), 5.47 (1H, ddt, $J=7.0$, 15.0, 1.0 Hz), 5.76 (1H, dt, $J=15.0$, 7.0 Hz). FAB-HRMS *m/z* calcd for $C_{16}H_{29}O_5$ $[M+H]^+$ 301.2015, found 301.2036.

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